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| | |

**TITLE**

# Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU).

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## ABSTRACT

**Introduction:** Methenamine hippurate is a urinary antiseptic used as preventive treatment for recurrent urinary tract infections (UTIs) in some Scandinavian countries. However, the scientific evidence for the preventive effect and safety for longer-term use is limited. The aim of this study is to assess whether methenamine hippurate can reduce the incidence of UTIs in older women with recurrent UTIs.

**Methods and analysis**: The ImpresU-consortium is a collaboration between Norway, Sweden, Poland and the Netherlands. The study is a randomised, controlled, triple-blind phase IV clinical trial. Women ≥70 years with recurrent UTIs are screened for eligibility in a general practice setting. We aim to include 400 women in total, with 100 recruited from each collaborating country. The participants are randomised to treatment with methenamine hippurate 1g or placebo tablets twice daily for a treatment period of six months, followed by a drug-free follow-up period of six months. The primary outcome is number of antibiotic treatments for UTIs during the treatment period. The secondary outcomes include number of antibiotic treatments for UTIs during the follow-up period and self-reported symptom of severity and duration of UTI episodes. Differences in complications between the treatment groups are measured as safety outcomes. We also aim to investigate whether strain characteristics or phylogenetic subgroups of *E. coli* present in the urine culture at inclusion have a modifying effect on the outcomes.

**Ethics and dissemination:** Ethical approvals are obtained in all participating countries. The results will be communicated in peer-reviewed journals and at scientific conferences.

**Trial registrations**: ClinicalTrials: NCT04077580 (04.09.19), EudraCT: 2018-002235-15

**KEYWORDS:** Infectious diseases, primary care, preventive medicine, clinical trials, urinary tract infections

## ARTICLE SUMMARY

**Strengths and limitations of this study:**

● This is the first study to examine the preventive effect of methenamine hippurate using a randomized, placebo-controlled clinical trial design with a long-term follow-up.

● The study investigates the effect of a potentially highly relevant non-antibiotic preventive treatment for recurrent UTIs.

● Diagnosis and treatment of UTIs are left to the physicians. Individual interpretations of definition of UTI and adherence to guidelines may impact the registration of UTI episodes.

## INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections in humans [1]. Women are more prone to develop UTIs than men, and the incidence of UTIs peaks in young sexually active women and again in postmenopausal women [2, 3]. Approximately half of all women will experience at least one episode of UTI in their lifetime, with half of them experiencing recurrence within 6-12 months [4, 5]. The prevalence of UTIs in women over 65 years is almost double the rate seen in the overall female population [6], and recurrent UTIs in older women are consequently a major driver of antibiotic prescriptions. Repeated antibiotic exposure over decades has altered the susceptibility of uropathogens showing increasing antimicrobial resistance (AMR). AMR is considered by World Health Organization(WHO) to be one of the largest threats to global health [7]. Older age, previous UTI and antibiotic exposure are all risk factors for development of AMR [8-10]. Studies have shown that reducing antibiotic prescribing at the level of primary care is associated with decreased local AMR [11]. Both rational prescribing of antibiotics and feasible and appropriate non-antibiotic preventive measures are important to reduce antibiotic pressure and slow the progression of AMR [12].

### Methenamine hippurate

Methenamine was first used as a urinary antiseptic more than 100 years ago [13]. In Norway and Sweden the combination drug methenamine hippurate has been used as a preventive treatment for recurrent UTIs for nearly 50 years [14]. Despite its popularity in the Nordic countries, the drug is hardly used outside of Scandinavia. Methenamine hippurate is absorbed from the gastrointestinal tract and excreted by the kidneys to form methenamine and hippuric acid. Methenamine is hydrolyzed to formaldehyde and ammonia in acidic urine. Formaldehyde acts as a bacteriostatic agent, denaturizing the enzymes of the bacteria [15]. The hippuric acid ensures that the pH in the urine to stay acidic, but has limited bacteriostatic effect itself [16]. Despite evidence suggesting carcinogenic effect of formaldehyde when inhaled in high dosages, the Scientific Committee on Health and Environmental Risks (SCHER) assessment report on methenamine from 2007 concludes that formation of low-dose formaldehyde from cleavage of methenamine in body compartments should be of no concern with respect to carcinogenity [17-19]. Being an antiseptic, formaldehyde has not yet been shown to cause AMR [20, 21]. In an era of increasing AMR, methenamine hippurate represents a potentially highly relevant non-antibiotic preventive treatment in women with recurrent UTIs [22] .

However, non-antibiotic treatment options for UTIs like methenamine hippurate have not yet yielded conclusive evidence of effect [23-25]. Recent years' progression of AMR has led to a growing interest in exploring methenamine hippurate as preventive alternative for recurrent UTIs. A recent study comparing long term methenamine hippurate treatment with trimethoprim found similar rates of recurrence and adverse effects in the two groups [26]. Also, a large multicenter study demonstrated non-inferiority of methenamine hippurate compared to prophylactic antibiotics [27].

Focusing on methenamine as preventive treatment in older adults, a review from 2019 concluded that methenamine appeared to be a safe and effective treatment option in this patient population although randomized controlled trials with placebo are lacking [28]. Further, a retrospective observational study in women ≥60 years found longer time to first UTI after initiating methenamine treatment compared to average time between UTIs pre-initiation. The effect appeared to be similar regardless of kidney function, making it a promising non-antibiotic preventive treatment option in this age group [29].

**Escherichia coli**

Escherichia coli (*E. coli*) is a part of the human gastrointestinal microbiota [30]. Uropathogenic *E. coli* from fecal reservoirs are the predominant causative microbes in uncomplicated UTIs [31-33]. Strains of *E. coli* can be divided into phylogenetic subgroups (A, B1, B2, C, D, E and F). Subgroup B2 and D are the most prevalent types associated with extra-intestinal infections [34-36]. The management of UTIs is complicated by increasing prevalence of antibiotic-resistant strains of *E. coli* [37]. Persistent or re-lapsing UTIs are often associated with *E. coli* strains of subtype B2, and recent research indicates that recurrences often are caused by the same strain as the first UTI episode [38, 39]. Our hypothesis is that the phylogenetic subgroups or other strain characteristics of *E. coli* present in the urine cultures at inclusion could have a modifying role on the preventive effect of methenamine hippurate.

**Unresolved issues and objectives**

To our knowledge, the preventive effect of methenamine hippurate has never been tested against placebo in a large prospective RCT with long-time follow-up among older women in primary care. The primary objective of this study is to investigate whether methenamine hippurate reduces the need for antibiotic use due to recurrent UTIs. As re-lapsing UTIs seems to be associated with certain subgroups of *E. coli,* we also aim to explore whether the effect of methenamine hippurate is influenced by strain type or phylogenetic subgroup of *E. coli* present at baseline.

**Risk/Benefit evaluation**

The benefit of the study is potentially large for older women with recurrent UTIs, resulting in fewer UTI episodes, reduced antibiotic usage and increased quality of life. Subsequent reduction of urinary antibiotic use may contribute to slowing the progression of AMR in the population. Methenamine hippurate is a well-tolerated drug and adverse effects are uncommon and generally mild [15]. The risk of the study is considered to be very small, and the possible benefits greatly outweigh the potential risk.

## METHODS

**Study Design and Procedures**

This study is a triple blind, randomised, controlled phase IV trial in women ≥70 years with recurrent UTIs. Recurrent UTIs are defined as ≥3 episodes of antibiotic treated UTIs during

the last twelve months or ≥ 2 episodes during the last six months [40]. The participants will be recruited from general practice, and the included patients will be randomised to active intervention (1 gr methenamine hippurate x 2, standard recommended dose [15]), or control (one placebo tablet twice daily) for six months. To evaluate if there is a prolonged effect of treatment, another six months follow-up will be performed. A total of 400 patients will be randomized, approximately 100 patients in each participating country. Study visits and procedures are listed in table 1.

**Table 1**. Study visits and procedures. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure for the ImpresU clinical trial.

| | STUDY PERIOD | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Treatment period | | | | Follow-up period | | |
| **TIMEPOINT:** | *Screening* | Baseline | *At time of UTI* Day 2-180 | *Follow-up UTI** Day 2-180 | *Monthly follow-up* Day 2-180 | *End of IMP*** Day 180 | *At time of UTI* Day 180-360 | *Follow-up UTI** Day 180-360 | *End of study* Day 360 |
| **ENROLMENT:** | | | | | | | | | |
| **Eligibility screen** | X | X | | | | | | | |
| **Informed consent** | | X | | | | | | | |
| ***Demography*** | | X | | | | | | | |
| ***Medical history*** | | X | | | | | | | |
| ***Physical examination*** | | X*** | | | | | | | |
| ***Concomitant medication*** | | X**** | | | | | | | |
| ***Randomisation*** | | X | | | | | | | |
| ***CRF-completion*** | | X | X | X | X | X | X | X | X |
| **Dispensing of trial drugs** | | X | | | | | | | |
| **INTERVENTIONS:** | | | | | | | | | |
| ***Methenamine hippurate*** | | ← | — | — | — | → | | | |
| ***Placebo*** | | ← | — | — | — | → | | | |
| ***Compliance*** | | | | | X | X | | | X |
| ***Midstream urine dipstick/culture*** | | X | X***** | | | | X***** | X***** | |

| ASSESSMENTS: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *UTI Record* | | | X | X | | | X | X | |
| *Patient Reported Outcome* | | | X | X | X | X | X | X | X |
| *Adverse event assessment* | | | X | X | X | X | X | X | X***** |

* Every episode of acute UTI both in intervention period and follow-up period will be followed with registrations every 7 day until the patient is restored.
** Investigational medicinal product.
*** If needed to determine eligibility or complete baseline data.
**** After baseline visit concomitant medication will only be registered in case of Serious Adverse Event (SAE).
***** If taken by the GP.
****** In case of SAE present and not resolved by day 360, this will be followed until resolution.

**Study assessments**

*Visit 1 – Screening, inclusion and randomisation*

Eligible patients will be found through a screening procedure of the Electronic Patient Record. Signed and dated informed consent will be collected by the research team prior to any study-related activity. Demography, level of care, concomitant medication, and medical history will be registered, including risk factors for recurrent UTIs (i.e., urinary bladder dysfunction, diabetes mellitus, obesity (BMI >30), local treatment with oestrogen, sexual activity or abnormality of the urogenital tract). A voided urine specimen will be collected for dipstick analysis of pH, nitrite and leukocyte esterase and subsequently sent for culturing with examination of resistance pattern and urease-production.

We will freeze any isolates of *E. coli* found and send them to the Department of Clinical Microbiology at Sahlgrenska University Hospital in Sweden for analysis of strain type and phylogenetic subgroup.

*Telephone follow-up in case of acute UTI episode(s)*

Any episodes of acute UTIs during the study period (day 2-360) will be handled by regular health services. The study team will follow up on each UTI episode by telephone every seven days until resolved. We will register UTI symptoms using Patient Reported Outcome, table 2. We will register the antibiotic prescribed for the episode (name of drug, dosage and duration), results of urine analysis (dipstick and urine culture, if taken), and any complications of the UTI (i.e., pyelonephritis, urosepsis or hospital admissions). Relevant SAEs will be registered.

**Table 2.** Patient Reported Outcome form used at every UTI episode in the ImpresU clinical trial.

| Patient Reported Outcome | |
|---|---|
| 1. Degree of pain at urination (scale 0-6)*_____ | |
| 2. Urgency (scale 0-6)*_____ | |
| 3. Frequent urination (scale 0-6)*_____ | |
| 4. Visible blood in urine? | Yes □ No □ |
| 5. Abdominal pain not related to urination | Yes □ No □ |
| 6. Has the patient had fever? (>38° rectal OR, >37,5 axillae OR > 37,8 tympanic) | Yes □ No □ |
| 7. Side effect of study drug?<br>If yes, what side effect: _____ | Yes □ No □ |
| 8. Feeling unwell? | Yes □ No □ |
| 9. Flank pain? | Yes □ No □ |
| 10. Other symptom(s): _____ | |
| 11. I feel restored | Yes □ No □ |

*Telephone contacts every 30 days during the first six months and day 360*

The study participants will be contacted by telephone every 30 days in the six months treatment period, at the end of treatment (day 180) and at end of study (day 360). Any symptoms/side effects from the trial medication will be recorded, as well as relevant SAEs. Participants will be asked if they have forgotten to contact the study team in case of any UTI-related health care contacts. If so, the study team will follow up the episodes retrospectively with registration of relevant data. Compliance with study medication will also be registered.

**Study population**

There are several inclusion and exclusion criteria (table 3).

**Table 3.** Inclusion/exclusion criteria in the ImpresU clinical trial.

| **Inclusion criteria** |
|---|
| Woman.<br>Age ≥70 years.<br>Recurrent UTIs (≥3 episodes of antibiotic treated acute cystitis the last twelve months or ≥2 episodes the last 6 months).<br>Able and willing to comply with all trial requirements.<br>Able and willing to give informed consent. |
| **Exclusion criteria** |
| Intake of methenamine hippurate within the last 12 months.<br>Allergy for methenamine hippurate.<br>Current antibiotic prophylaxis for UTI.<br>Urinary catheter (chronic indwelling catheters as well as intermittent urinary catheterisation).<br>Known severe chronic renal failure or estimated creatinine glomerular filtration rate ≤30 ml/min (known = registered in GP' clinical records).<br>A known condition or treatment associated with significant impaired immunity (e.g., long-term oral steroids, chemotherapy, or immune disorder).<br>Known severe hepatic impairment.<br>Severe dehydration.<br>Any previous episode of gout (uric acid)<br>Need for long term use of antacids such as magnesium hydroxide, magnesium carbonate, aluminum hydroxide.<br>Life expectancy estimated by a clinician to be less than six months.<br>Involvement in, including completion of, follow-up procedures, in another clinical trial of an investigational medicinal product in the last 90 days.<br>Incontinence too severe to be able to provide a voided urine specimen.<br>Participation in ImpresU Work Package 2*.<br>Significant known abnormal renal tract anatomy/physiology (i.e., single kidney, persistent urinary tract stone disease, severe vesicoureteral reflux) or neuropathic bladder disorders.<br>Lactose intolerance. |

* *An antibiotic stewardship intervention to improve antibiotic prescribing for urinary tract infections in frail elderly.*

### Subject enrolment and randomisation

Four sets of 100 random numbers, one set for each participating country, will be created using Research Randomizer. A block randomization will be performed. Block size will be concealed to prevent functional un-blinding. The outcome will be transferred to a separate Excel spreadsheet for each country, and each country will follow their randomisation list

strictly sequentially as subjects are eligible for randomisation. If a subject discontinues from the study, the subject number will not be re-used, and the subject will not be allowed to re-enter the study. The inclusion will stop when a total of 400 participants are included in the study.

**Discontinuation and withdrawal of subjects**

Subjects are free to discontinue their participation at any time without prejudice to further treatment. Participants developing SAEs possibly due to methenamine hippurate will discontinue study medication. Alkalizing antacids can potentially reduce the effect of methenamine hippurate and should be avoided. Study participants requiring long-term use of antacids during the first six months of study will discontinue study medication. Participants developing serious illness, making it impossible for them to continue taking the study tablets or comply with study requirements, will discontinue study medication and/or withdraw from study participation. Other reasons for discontinuing treatment or withdrawing a subject are incorrect enrolment and subjects lost to follow-up. Participants who prematurely discontinue treatment, except for patients' withdrawing their consent, will be followed up in the same framework as participants receiving study medication.

**Patient and Public Involvement**

The concept and patient information material was presented for a group of users prior to study start to ensure readability and comprehension. Input from participating patients and clinicians early in the study will be used to adapt and improve study implementation.

**STUDY TREATMENTS**

**Identity of investigational medicinal products (IMP)**

IMP will be purchased from the pharmaceutical company Mylan A/S. The IMP and corresponding placebo will be sent to Kragerø Tablet factory AS for packing and labelling according to the randomisation list. Kragerø Tablet factory AS will deliver the IMP to a designated pharmacy in each country, which in turn will distribute to participating sites. The IMP will be handed out consecutively to participants for six months' use. Boxes with active substance consist of tablets with methenamine hippurate 1 gram. Boxes with placebo will contain tablets with the equivalent dose of lactose. The boxes will have identical labelling with corresponding labels for each participating country in local language. Only the participants' study ID on the label will be linked to the randomisation list, revealing the content of the IMP.

**Storage and handling**

One pharmacy/medical distributor will be responsible for delivering the IMP to the relevant sites in each country. The medication will be stored at each site in a locked cupboard in a secure access room together with the sealed code envelopes. IMPs will be stored with a controlled temperature not exceeding 30 °C. A member of the research team will collect and count any remaining IMP by the end of 180 days of the trial to report treatment compliance. Any unused IMP will be sent to the designated pharmacy for drug count and destruction.

**Blinding**

Participants, GPs meeting patients, pharmacists dispensing drugs, the investigators and persons involved in statistical analysis will not be aware of group allocation until all statistical analyses are done (triple blind).

**Breaking the blinding in an emergency situation**

The study code should only be broken for valid medical or safety reasons. There will be one sealed opaque envelope for each medication ID available at the study sites, revealing the identity of the IMP. On patient/physician information cards, there will be a telephone number provided by the Sponsor to be used in emergency situations. The coordinating center (or the Sponsor) provides the treating physician with treatment allocation details, and the treating physician deals with the participant's medical emergency accordingly.

**Study Objectives and Variables**

The primary objective of this study is to investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTIs (table 4). The remaining objectives are considered secondary. Pyelonephritis, hospitalization and death will be registered as safety endpoints.

**Table 4.** Study objectives and variables in the ImpresU clinical trial.

| Objectives | | Outcome Measures / variables / endpoints | Time point(s) of evaluation of this outcome measure (if applicable) |
|---|---|---|---|
| **Primary Objective** | | | |
| **1** | To investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTIs (measured as number of antibiotic courses). | Number of UTI antibiotic treatments during the six months of treatment. If the participant receives >1 antibiotic course for UTI without symptom relief, it is regarded as one episode and counted as one antibiotic treatment. If there has been an asymptomatic period of at least 14 days in-between two UTI antibiotic courses, this is regarded as a new antibiotic treatment. | After six months of treatment. |
| **Secondary Objectives** | | | |
| **2a** | To investigate if methenamine hippurate will have a prolonged | Number of UTI antibiotic treatments during the six months following completion of treatment. If the participant receives >1 antibiotic | Six months after completing (12 months after |

| | | | |
|---|---|---|---|
| | effect on antibiotic usage even after discontinuation. | course for UTI without symptom relief, it is regarded as one episode and counted as one antibiotic treatment. If there has been an asymptomatic period of at least 14 days in-between two UTI antibiotic courses, this is regarded as a new antibiotic treatment. | commencing) treatment. |
| **2b** | To investigate if methenamine hippurate reduces the incidence of UTIs. | Number of UTIs (acute symptoms specific/related to the urinary tract) during the six months of treatment. If the participant has had >1 UTI episode without symptom relief, it is regarded as one episode. If there has been an asymptomatic period of at least 14 days in-between two UTI episodes, this is regarded as a new episode. | After six months of treatment. |
| **2c** | To investigate if methenamine hippurate can reduce severity of UTI symptoms. | Registration of symptom severity when initiating treatment for UTI. | After six months of treatment. |
| **2d** | To investigate if methenamine hippurate can reduce duration of UTI episodes. | Registration of number of days of symptoms during UTI episodes. | After six months of treatment. |
| **2e** | To investigate if number of complications such as pyelonephritis and hospital admission for UTIs differ between methenamine hippurate and placebo. | Registration of number of pyelonephritis and hospital admission for UTI. | Six and 12 months after commencing treatment. |
| **2f** | To investigate if strain characteristics/phylogenetic subgroups of *E. coli* found at inclusion is an effect modifier in all the above outcomes. | (See above) | (See above) |



**Handling, storage and destruction of biological samples**

At inclusion, a urine specimen will be collected for culture and dipstick urinalysis. After analysis, the urine specimen will be destroyed. However, we will freeze isolates of *E. coli* from the inclusion urine culture. Bacteria are not regarded human material and do not need biobank registration. The study team will order copies of medical records from acute UTI episodes including laboratory urinalysis results.

## SAFETY

Methenamine hippurate is a well-tolerated drug, and the adverse effects are generally mild [24]. Anticipated adverse drug reactions in the study includes gastric irritation, irritation of the bladder, nausea and vomiting (all uncommon), diarrhoea and abdominal pain (incidence unknown). Skin and subcutaneous disorders like rash and pruritus are both registered as uncommon [15]. Participants developing clinically significant dehydration or receiving a course of sulphonamide antibiotics, will pause IMP due to theoretical increased risk of crystalluria. The participants will continue with study treatment when dehydration is clinically resolved and/or the sulphonamide antibiotic treatment is completed.

### Adverse Events (AE)

As methenamine hippurate has been in clinical use for decades, non-serious adverse events will not be recorded for the purpose of this study - except in The Netherlands, where the Medical Ethical Committee required registration of all AEs. It will be left to the Investigator's clinical judgment to decide whether a symptom or side effect is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily discontinue treatment due to intolerable symptoms or side effects.

### Serious Adverse Event (SAE)

All SAEs that are life threatening or results in death will be reported. SAEs requiring inpatient hospitalization or prolongation of existing hospitalization, and SAEs resulting in persistent or significant disability/incapacity will only be reported if relationship with IMP cannot be excluded or the SAE is a complication of a UTI. SAEs representing expected events in a frail older population will not be reported. If relationship with IMP cannot be excluded, these SAEs are possibly, probably or definitely related to the trial medication. These adverse events will be reported as SAR (Serious Adverse drug Reaction) if expected and included in SmPC or as SUSAR (Suspected Unexpected Serious Adverse Reaction) if unexpected and not included in SmPC (Figure 1). SAEs will be registered throughout the whole study period. In case of a SAE not resolved by day 360, this SAE will be followed until resolution.

**[Insert Figure 1: Safety reporting flowchart for the ImpresU clinical trial.]**

### Premature termination of the study

A data safety monitoring committee (a statistician and two external researchers with experience from clinical trials and UTI infections in primary care) will meet every six months to ensure data safety. The difference between groups in SAEs deemed to be linked to methenamine hippurate, will be continuously monitored. The study will be terminated if there is a significant difference between the two trial arms regarding SAE, SAR and SUSAR probably or definitely related to the trial medication or UTI. This will be evaluated by comparing the two groups without breaking the code. The code will be broken if the difference between groups is statistically significant ($p<0.05$). The study will be prematurely terminated if the statistical difference is to the disadvantage of active IMP. SAE, SAR and SUSAR possibly related to the trial medication or UTI will be registered but not used for decision-making.

## STATISTICS

### Sample size calculation

The sample size calculation is made for the primary objective described in table 1. We assume these selected older women will have an average of two courses of antibiotics for suspected UTIs every six months (4). We assume a 25% reduction of antibiotic prescriptions during the first six-month after introduction of methenamine hippurate. This means that the intervention group would have an average of 1.5 prescriptions while the control group is assumed to remain around 2.0. We assume the standard deviation in each group to be 1.5. This will result in an effect size of 0.33 (small effect). We assume the level of significance being 0.05, the power to be 0.80 and that a two-tailed test is explored. We use Student's t-test as the statistical analysis but also calculate for Mann-Whitney test (if the outcome variable is not normally distributed). The planned statistical method will be multivariable linear regression. Student's t-test and Mann-Whitney test are used as surrogate methods to estimate sample size. Under the assumptions given above, an effective sample size of 286 patients (143+143) is required if t-test can be used. However, if Mann-Whitney's test is required we need 298 (149+149) patients. To achieve an effective sample size of at least 298, after considering a 25% loss to follow-up, we aim to include 400 patients.

### Statistical analysis

We will adjust all analysis for confounding variables obtained at visit 1 (table 5).

**Table 5.** Confounding variables to be adjusted for in the analysis in the ImpresU clinical trial.

| **Confounding variables obtained at visit 1** |
|---|
| Patient's age.<br>Urine acidity (pH).<br>Number of antibiotic courses for UTIs in the 12 months preceding inclusion in the study.<br>Presence of urease/stone-producing bacteria in urine culture day 1 such as *Proteus spp*, *Klebsiella spp*, *Morganella morganii*, *Corynebacterium urealyticum* and *Providencia*.<br>Use of local oestrogen.<br>Patient has diabetes mellitus.<br>Obesity defined as BMI ≥30.<br>Presence of known mild abnormality of the urogenital tract.<br>If the patient is sexually active.<br>If the patient previously has experienced urinary tract stone.<br>Strain characteristics and phylogenetic subtype of *E. coli* in the urine culture at inclusion will be analysed in a separate analysis. |

Planned statistical analysis for primary and secondary objectives are listed in table 6.

**Table 6**. Study objectives and statistical analysis in the ImpresU clinical trial.

| Objectives | | Statistical analysis | Time point(s) of evaluation of this outcome measure (if applicable) |
|---|---|---|---|
| **Primary Objective** | | | |
| **1** | The primary objective of this study is to investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTI (measured as number of antibiotic courses). | Standard linear regression will be used where the number of UTI antibiotic treatments will be the dependent variable. Group allocation together with the confounding variables above will be independent variables. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p-value will be delivered, but no useful effect size if a rank transformation is used. | After six months of treatment. |
| **Secondary objectives** | | | |
| **2a** | To investigate if methenamine hippurate will have a prolonged effect on antibiotic usage even after discontinuation. | Will be analysed using the same statistical approach as objective 1. | Six months after completing (12 months after commencing) treatment. |
| **2b** | To investigate if methenamine hippurate reduces the incidence of UTI. | Will be analysed using the same statistical approach as objective 1. UTIs will be the dependent variable. | After six months of treatment. |
| **2c** | To investigate if methenamine hippurate can reduce severity of UTI symptoms. | The outcome variable is measured at first day of UTI using a six-grade ordinal scale. The median value of all UTIs will be used if the patient has more than one episode of UTI. The dependent variable will be transformed using a rank transformation and analysed with linear regression using the same covariates as when analysing objective 1. | After six months of treatment. |
| **2d** | To investigate if methenamine hippurate can reduce duration of UTI episodes. | Will be analysed using the same statistical approach as objective 1. Number of days with symptoms will be the dependent variable. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p- | After six months of treatment. |

| | | | |
|---|---|---|---|
| | | value will be delivered, but no useful effect size if a rank transformation is used. | |
| **2e** | To investigate if the number of complications such as pyelonephritis and hospital admission for UTI differ between methenamine hippurate and placebo. | Will be analysed using the same statistical approach as objective 1. Number of severe events such as pyelonephritis or hospital admission will be the dependent variable. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p-value will be delivered, but no useful effect size if a rank transformation is used. | Six and 12 months after commencing treatment. |
| **2f** | To investigate if strain characteristics/phylogenetic subgroups of *E. coli* found at inclusion is an effect modifier in all the above outcomes. | Phylogenetic subtype of pure cultures of *E. coli* in the inclusion urine culture will be analysed in a separate statistical analysis if the number of cultures available for typing is at least 60. All statistics above will be repeated adding phylotype as an extra independent variable. Purely descriptive statistics will be presented if the number is less than 60. | (See above) |

**Primary and secondary statistical analysis and management of missing data**

The primary statistical analysis is intention to treat. Patients who have completed only a part of the first six months, will contribute data up until they leave the study. Their data will be recalculated as if they had participated all six months. Patients leaving during the second six-month period will also contribute with data as above. Patients leaving the study before the second six-month period commence will have their value for this period set to be the median value for both groups. A complete case analysis and a per-protocol analysis will also be made as secondary analysis and reported.

## DATA MANAGEMENT

**Recording and management of data**

We will use the electronic data capture system Research Online (RO) for data collection. RO meets all requirements according to Good Clinical Practice for electronic data entry with respect to safeguarding data integrity and data security regulations. Web-based case report forms are implemented into the system to facilitate data collection. Participants will be identified by a unique trial specific number. All source data will be stored at the coordinating centers for a minimum period of fifteen years after termination of the trial. After the data of the last subject is entered, a clean file will be produced for further analysis and publication, and the database will close. Direct access to the data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections

**Study sponsor**

University of Oslo, Norway.

### Monitoring

A study monitor will be appointed by the sponsor to monitor the study in all four countries. The quality control will have a risk-based approach. The monitor will have regular contacts with the coordinating centers and sites, and the extent of monitoring will be defined in a separate monitoring plan. Authorized representatives of the sponsor or regulatory authorities may perform audits or inspections, including source data verification.

## DISCUSSION

AMR in urinary pathogens is on the rise. With increasing life expectancy and current antibiotic use, this trend will continue unless appropriate prescribing and feasible and effective non-antibiotic preventive measures are implemented. If methenamine hippurate is safe and effective in reducing UTI episodes in older women with frequent UTIs, it could potentially change the management of recurrent UTIs outside Scandinavia. Less use of urinary antibiotics will reduce antibiotic pressure and potentially slow the progression of AMR. If methenamine hippurate is not effective, the result will still be beneficial as many women can avoid unnecessary medication.

Including only women ≥70 experiencing the highest number of UTIs in the twelve months preceding inclusion increases the chance of a spontaneous reduction in episodes in the following twelve months – regardless of any intervention [41]. As a result, we expect a decrease in the number of UTIs in both the placebo and intervention groups in the intervention period. However, the RCT design compensates for the possible effect of regression to the mean.

Management of acute UTIs are handled by regular health services in this study. With four European countries participating, the guidelines differ slightly. The individual interpretation of diagnosis and treatment guidelines will probably also differ on a physician level. In case of acute UTIs, patient symptoms will be reported directly from the patient, making the data prone to recall bias. In cases where the study team are notified of a UTI the same day, the patient symptoms are recorded in real time minimizing bias. However, missed UTIs discovered at monthly follow-up or when checking the patient records at end of study will be recorded retrospectively.

### Ethics and dissemination

All participants will receive standard medical care in case of a UTI. The participants will receive written information with contact details to the PI, the study team and a study telephone manned at all hours during the study period. A data monitor committee will ensure data safety. The risk of the study is considered very small, and our risk/benefit analysis concludes that the possible benefits of this study greatly outweigh the potential risk. The study protocol has been approved by the Norwegian Medicines Agency (NoMA, 18/16628-15), the Regional Committee for Medical and Health Research Ethics, NO (REK south-east, 2018/2502 A), the Swedish Medical Product Agency (5.1-2019-103684, 5.1-2021-35901, 5.1- 2021-64842 and 5.1-2021-92970), the Swedish Ethical Review Authority (2019-02749, 2020-00360 and 2021-03992), Committee of Bioethics of the Medical University of Lodz, PL (RNN/311/19/KE), Office for Registration of Medicinal Products, Medical Devices

and Biocidal , PL (UR/DBL/D/417/2021), Centrale Commissie Mensgebonden Onderzoek, NL (NL71512.041.19.) and Medical Ethical Review Committee, METC Utrecht, NL (20/032).

Within one year after the end of the study, the sponsor will submit a study report with the results of the study to the accredited competent authority. In addition, the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

**Insurances**

The Norwegian study subjects are covered by "Legemiddelansvarsforsikringen". The Swedish study subjects are covered by "The Swedish Pharmaceutical Insurance", LFF Service AB. The Dutch study subjects are covered by CNA Insurance Company (Europe) S.A. The Polish study subjects are covered by Towarzystwo Ubezpieczeń i Reasekuracji "WARTA".

**Trial status**

Subject enrolment started in December 2019 and will be completed by end of June 2022. All follow-ups are expected to be completed by the end of June 2023.

**Author Contributions**

ML, PS, CH, TV and MGC conceptualized the ImpresU project and obtained funding. ML, PS, RG, SHO and ESA drafted the protocol for the RCT, and SH, NG, CÅ, WG, HVK, TP, AK, MGC, CH and TV revised the protocol. SHO drafted the manuscript. All authors critically revised the article draft and approved the final manuscript.

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**Competing interests statement**

None declared.

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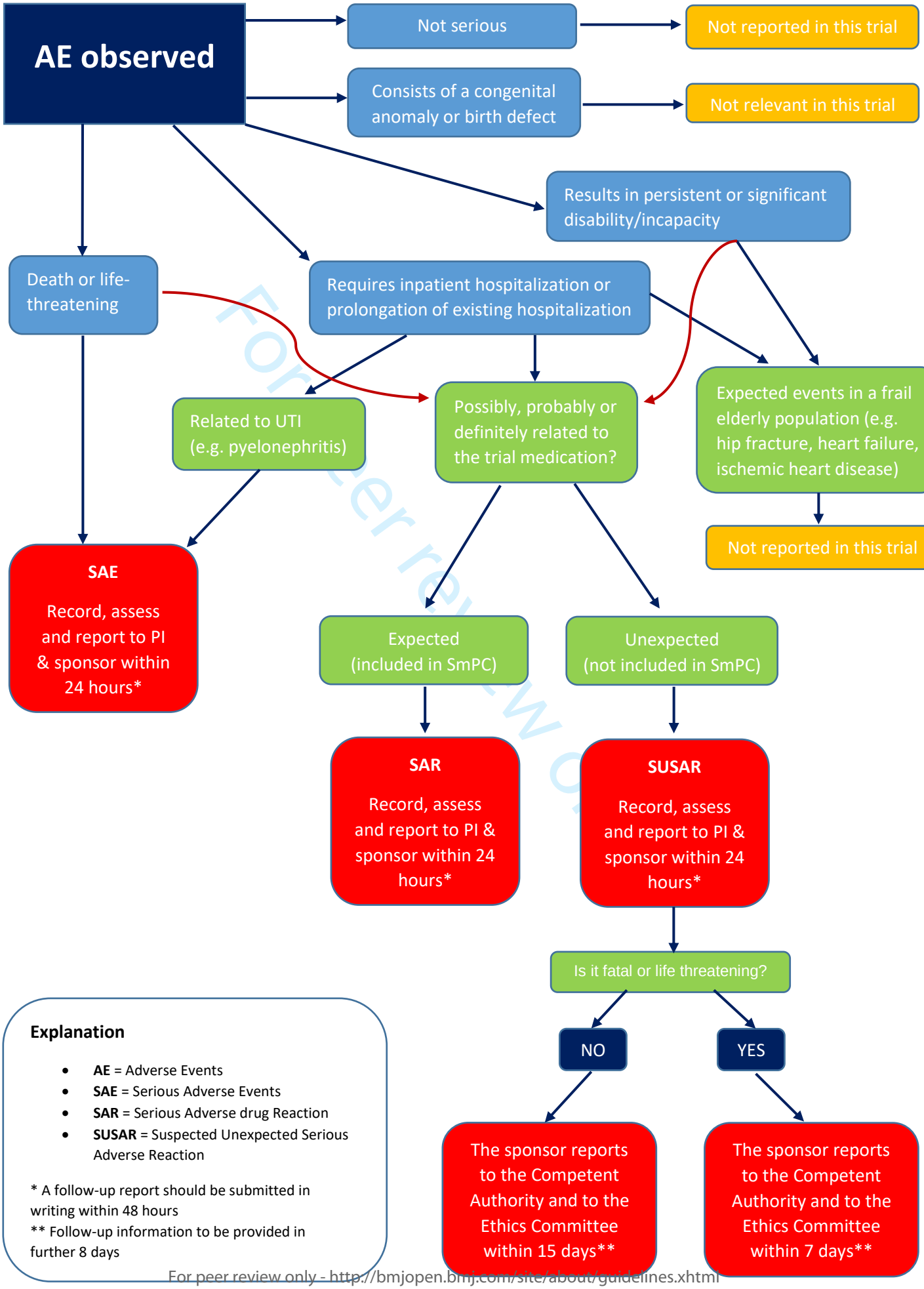
## Legends

**Figure 1.** Safety reporting flowchart for the ImpresU clinical trial.




SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | ___1_____ |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | ___2_____ |
| | 2b | All items from the World Health Organization Trial Registration Data Set | _____ |
| Protocol version | 3 | Date and version identifier | ___1_____ |
| Funding | 4 | Sources and types of financial, material, and other support | ___17_____ |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | ____17_____ |
| | 5b | Name and contact information for the trial sponsor | ____15_____ |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | ____N/A____ |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | _____12, 15_____ |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3-4 |
| | 6b | Explanation for choice of comparators | 4 |
| Objectives | 7 | Specific objectives or hypotheses | 4, 11 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4-5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5-7 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 4-9 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6-9 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 6 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 6-7, 11 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 5 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | N.A. |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8,9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8-10 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 10 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 10 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 5-7 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 5-7, 9 |

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| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 15 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13-15 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 15 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 12 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 6,7,12 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 16 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 16-17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | N.A |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N.A. |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 17 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 17 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 17 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 17 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N.A. |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | N.A, |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N.A. |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU).

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| | Life<br>Lindbaek, Morten; The Antibiotic Centre for Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo<br>Hoye, Sigurd; The Antibiotic Centre for Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo |
| Primary Subject Heading: | General practice / Family practice |
| Secondary Subject Heading: | Infectious diseases, Urology |
| Keywords: | INFECTIOUS DISEASES, PRIMARY CARE, PREVENTIVE MEDICINE, Clinical trials < THERAPEUTICS, Urinary tract infections < UROLOGY |
| | |

**TITLE**

# Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU).

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## ABSTRACT

**Introduction:** Methenamine hippurate is a urinary antiseptic used as preventive treatment for recurrent urinary tract infections (UTIs) in some Scandinavian countries. However, the scientific evidence for the preventive effect and safety for longer-term use is limited. The aim of this study is to assess whether methenamine hippurate can reduce the incidence of UTIs in older women with recurrent UTIs.

**Methods and analysis**: The ImpresU-consortium is a collaboration between Norway, Sweden, Poland and the Netherlands. The study is a randomised, controlled, triple-blind phase IV clinical trial. Women ≥70 years with recurrent UTIs are screened for eligibility in a general practice setting. We aim to include 400 women in total, with 100 recruited from each collaborating country. The participants are randomised to treatment with methenamine hippurate 1g or placebo tablets twice daily for a treatment period of six months, followed by a drug-free follow-up period of six months. The primary outcome is number of antibiotic treatments for UTIs during the treatment period. The secondary outcomes include number of antibiotic treatments for UTIs during the follow-up period and self-reported symptom of severity and duration of UTI episodes. Differences in complications between the treatment groups are measured as safety outcomes. We also aim to investigate whether strain characteristics or phylogenetic subgroups of *E. coli* present in the urine culture at inclusion have a modifying effect on the outcomes.

**Ethics and dissemination:** Ethical approvals are obtained in all participating countries. The results will be communicated in peer-reviewed journals and at scientific conferences.

**Trial registrations**: ClinicalTrials: NCT04077580 (04.09.19), EudraCT: 2018-002235-15

**KEYWORDS:** Infectious diseases, primary care, preventive medicine, clinical trials, urinary tract infections

## ARTICLE SUMMARY

**Strengths and limitations of this study:**

● This is the first study to examine the preventive effect of methenamine hippurate using a randomized, placebo-controlled clinical trial design with a long-term follow-up.

● The study investigates the effect of a potentially highly relevant non-antibiotic preventive treatment for recurrent UTIs.

● Diagnosis and treatment of UTIs are left to the physicians. Individual interpretations of definition of UTI and adherence to guidelines may impact the registration of UTI episodes.

## INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections in humans [1]. Women are more prone to develop UTIs than men, and the incidence of UTIs peaks in young sexually active women and again in postmenopausal women [2, 3]. Approximately half of all women will experience at least one episode of UTI in their lifetime, with half of them experiencing recurrence within 6-12 months [4, 5]. The prevalence of UTIs in women over 65 years is almost double the rate seen in the overall female population [6], and recurrent UTIs in older women are consequently a major driver of antibiotic prescriptions. Repeated antibiotic exposure over decades has altered the susceptibility of uropathogens showing increasing antimicrobial resistance (AMR). AMR is considered by World Health Organization(WHO) to be one of the largest threats to global health [7]. Older age, previous UTI and antibiotic exposure are all risk factors for development of AMR [8-10]. Studies have shown that reducing antibiotic prescribing at the level of primary care is associated with decreased local AMR [11]. Both rational prescribing of antibiotics and feasible and appropriate non-antibiotic preventive measures are important to reduce antibiotic pressure and slow the progression of AMR [12].

### Methenamine hippurate

Methenamine was first used as a urinary antiseptic more than 100 years ago [13]. In Norway and Sweden the combination drug methenamine hippurate has been used as a preventive treatment for recurrent UTIs for nearly 50 years [14]. Despite its popularity in the Nordic countries, the drug is hardly used outside of Scandinavia. Methenamine hippurate is absorbed from the gastrointestinal tract and excreted by the kidneys to form methenamine and hippuric acid. Methenamine is hydrolyzed to formaldehyde and ammonia in acidic urine. Formaldehyde acts as a bacteriostatic agent, denaturizing the enzymes of the bacteria [15]. The hippuric acid ensures that the pH in the urine stay acidic, but has limited bacteriostatic effect itself [16]. Despite evidence suggesting carcinogenic effect of formaldehyde when inhaled in high dosages, the Scientific Committee on Health and Environmental Risks (SCHER) assessment report on methenamine from 2007 concludes that formation of low-dose formaldehyde from cleavage of methenamine in body compartments should be of no concern with respect to carcinogenity [17-19]. Being an antiseptic, formaldehyde has not yet been shown to cause AMR [20, 21]. In an era of increasing AMR, methenamine hippurate represents a potentially highly relevant non-antibiotic preventive treatment in women with recurrent UTIs [22] .

However, non-antibiotic treatment options for UTIs like methenamine hippurate have not yet yielded conclusive evidence of effect [23-25]. The lack of conclusive evidence is manifested as an absence of clear official guidelines for initiation and duration of prophylactic treatment with methenamine hippurate [26]. Evaluation of treatment duration is especially challenging in the older population, often leading to prolonged or life-long treatment. Recent years' progression of AMR has led to a growing interest in exploring methenamine hippurate as preventive alternative for recurrent UTIs. A recent study comparing long term methenamine hippurate treatment with trimethoprim found similar rates of recurrence and adverse effects in the two groups [27]. The current pivotal study in

this field, the ALTAR study, recently demonstrated non-inferiority of methenamine hippurate compared to low-dose prophylactic antibiotics [28]. This trial recruited women ≥ 18 years of age with recurrent UTI from seconday urology and urogynaecology care. The participants were randomized to 12 months treatment with methenamine hippurate or low-dose antibiotics. The study was open-labeled, i.e. the participants were aware of their treatment allocation. Albeit the ALTAR study demonstrated non-inferiority, methodologically, the gold standard for demonstrating effect of a drug intervention is to compare the effect to no active treatment/placebo. Blinding the study to treatment allocation will further strengthen the outcome by reducing intentional and unintentional bias [29].

The vast majority of methenamine hippurate users are older women [30]. This is consistent with the gender distribution of UTIs and the increasing burden of UTIs with age. These patients are frequently attended in primary health care. Therefore, the ImpresU consortium set out to evaluate the prophylactic effect of methenamine hippurate on recurrent UTI in the patient population known to have the highest disease burden-utilizing a triple-blind, randomised, placebo-controlled trial design (RCT).



**Escherichia coli**

Escherichia coli (*E. coli*) is a part of the human gastrointestinal microbiota [31]. Uropathogenic *E. coli* from fecal reservoirs are the predominant causative microbes in uncomplicated UTIs [32-34]. Strains of *E. coli* can be divided into phylogenetic subgroups (A, B1, B2, C, D, E and F). Subgroup B2 and D are the most prevalent types associated with extra-intestinal infections [35-37]. The management of UTIs is complicated by increasing prevalence of antibiotic-resistant strains of *E. coli* [38]. Persistent or re-lapsing UTIs are often associated with *E. coli* strains of subtype B2, and recent research indicates that recurrences often are caused by the same strain as the first UTI episode [39, 40]. Our hypothesis is that the phylogenetic subgroups or other strain characteristics of *E. coli* present in the urine cultures at inclusion could have a modifying role on the preventive effect of methenamine hippurate.

**Unresolved issues and objectives**

To our knowledge, the preventive effect of methenamine hippurate has never been tested against placebo in a large prospective RCT with long-time follow-up among older women in primary care.

**Risk/Benefit evaluation**

The benefit of the study is potentially large for older women with recurrent UTIs, resulting in fewer UTI episodes, reduced antibiotic usage and increased quality of life. Subsequent reduction of urinary antibiotic use may contribute to slowing the progression of AMR in the population. Methenamine hippurate is a well-tolerated drug and adverse effects are uncommon and generally mild [15]. The risk of the study is considered to be very small, and the possible benefits greatly outweigh the potential risk.

## METHODS

### Study Design and Procedures

This study is a triple blind, randomised, controlled phase IV trial in women ≥70 years with recurrent UTIs. Recurrent UTIs are defined as ≥3 episodes of antibiotic treated UTIs during the last twelve months or ≥ 2 episodes during the last six months [41]. Antibiotic treatment is defined as receiving any course of urinary antibiotics for a suspected UTI regardless of dose regimen. The participants will be recruited from general practice, and the included patients will be randomised to active intervention (1 gr methenamine hippurate x 2, standard recommended dose [15]), or control (one placebo tablet twice daily) for six months. To evaluate if there is a prolonged effect of treatment, another six months follow-up will be performed. A total of 400 patients will be randomized, approximately 100 patients in each participating country. Study visits and procedures are listed in table 1.

**Table 1**. Study visits and procedures. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure for the ImpresU clinical trial.

| | STUDY PERIOD | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Treatment period | | | | Follow-up period | | |
| TIMEPOINT: | *Screening* | Baseline | *At time of UTI* Day 2-180 | *Follow-up UTI** Day 2-180 | *Monthly follow-up* Day 2-180 | *End of IMP*** Day 180 | *At time of UTI* Day 180-360 | *Follow-up UTI** Day 180-360 | *End of study* Day 360 |
| **ENROLMENT:** | | | | | | | | | |
| **Eligibility screen** | X | X | | | | | | | |
| **Informed consent** | | X | | | | | | | |
| ***Demography*** | | X | | | | | | | |
| ***Medical history*** | | X | | | | | | | |
| ***Physical examination*** | | X*** | | | | | | | |
| ***Concomitant medication*** | | X**** | | | | | | | |
| ***Randomisation*** | | X | | | | | | | |
| ***CRF-completion*** | | X | X | X | X | X | X | X | X |
| **Dispensing of trial drugs** | | X | | | | | | | |
| **INTERVENTIONS:** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***Methenamine hippurate*** | | ♦——— | ——— | ——— | ——— | ———♦ | | | |
| ***Placebo*** | | ♦——— | ——— | ——— | ——— | ———♦ | | | |
| ***Compliance*** | | | | | X | X | | | X |
| ***Midstream urine dipstick/culture*** | | X | X***** | | | | X***** | X***** | |
| **ASSESSMENTS:** | | | | | | | | | |
| ***UTI Record*** | | | X | X | | | X | X | |
| ***Patient Reported Outcome*** | | | X | X | X | X | X | X | X |
| ***Adverse event assessment*** | | | X | X | X | X | X | X | X****** |

* Every episode of acute UTI both in intervention period and follow-up period will be followed with registrations every 7 day until the patient is restored.
** Investigational medicinal product.
*** If needed to determine eligibility or complete baseline data.
**** After baseline visit concomitant medication will only be registered in case of Serious Adverse Event (SAE).
***** If taken by the GP.
****** In case of SAE present and not resolved by day 360, this will be followed until resolution.

## Study assessments

*Visit 1 – Screening, inclusion and randomisation*

Eligible patients will be found through a screening procedure of the Electronic Patient Record in the GP office. Patients living in nursing homes are not included in this study. Signed and dated informed consent will be collected by the research team prior to any study-related activity (Supplementary file 1), and the patient will be enrolled by the researcher with assistance from the GP. Demography, level of care, concomitant medication, and relevant medical history will be registered, including risk factors for recurrent UTIs (i.e., urinary bladder dysfunction, diabetes mellitus, obesity (BMI >30), local treatment with oestrogen, sexual activity or abnormality of the urogenital tract), as well as previous diagnosis of urinary tract stones, pyelonephritis and urosepis. A voided urine specimen will be collected for dipstick analysis of pH, nitrite and leukocyte esterase and subsequently sent for culturing with examination of resistance pattern and urease-production.

We will freeze any isolates of *E. coli* found and send them to the Department of Clinical Microbiology at Sahlgrenska University Hospital in Sweden for analysis of strain characteristics and phylogenetic subgroup.

*Telephone follow-up in case of acute UTI episode(s)*

Any episodes of acute UTIs during the study period will be handled by regular health services. The participants are instructed (both orally and written, see supplementary files 1,2) to contact the study team on a designated study phone each time they are prescribed a course of antibiotics/wait-and-see prescription for a suspected UTI. The study team will then follow up on the UTI episode by telephone consultations with the participant every seven days until resolved. We will register UTI symptoms using Patient Reported Outcome, table 2. We will register the antibiotic prescribed for the episode (name of drug, dosage and duration), results of urine analysis (dipstick and urine culture, if taken), and any complications of the UTI (i.e., pyelonephritis, urosepsis or hospital admissions). Relevant SAEs will be registered.

**Table 2.** Patient Reported Outcome form used at every UTI episode in the ImpresU clinical trial.

| **Patient Reported Outcome** | |
|---|---|
| 1. Degree of pain at urination (scale 0-6)*_____ | |
| 2. Urgency (scale 0-6)*_____ | |
| 3. Frequent urination (scale 0-6)*_____ | |
| 4. Visible blood in urine? | Yes □ No □ |
| 5. Abdominal pain not related to urination | Yes □ No □ |
| 6. Has the patient had fever? (>38° rectal OR, >37,5 axillae OR > 37,8 tympanic) | Yes □ No □ |
| 7. Side effect of study drug?<br>If yes, what side effect: _____ | Yes □ No □ |
| 8. Feeling unwell? | Yes □ No □ |
| 9. Flank pain? | Yes □ No □ |
| 10. Other symptom(s): _____ | |
| 11. I feel restored | Yes □ No □ |

*Telephone contacts every 30 days during the first six months and at the end of study*

The study participants will be contacted by telephone every 30 days in the six months treatment period, at the end of treatment and at the end of study. Any symptoms/side effects from the trial medication will be recorded, as well as relevant SAEs. Participants will be asked if they have forgotten to contact the study team in case of any UTI-related health care contacts. If so, the study team will follow up the episodes retrospectively with registration of relevant data. Compliance with study medication will also be registered.

**Study population**

There are several inclusion and exclusion criteria (table 3).

**Table 3.** Inclusion/exclusion criteria in the ImpresU clinical trial.

| **Inclusion criteria** |
|---|
| Woman.<br>Age ≥70 years.<br>Recurrent UTIs (≥3 episodes of antibiotic treated acute cystitis the last twelve months or ≥2 episodes the last 6 months).<br>Able and willing to comply with all trial requirements.<br>Able and willing to give informed consent. |
| **Exclusion criteria** |
| Intake of methenamine hippurate within the last 12 months.<br>Allergy for methenamine hippurate.<br>Current antibiotic prophylaxis for UTI.<br>Urinary catheter (chronic indwelling catheters as well as intermittent urinary catheterisation).<br>Known severe chronic renal failure or estimated creatinine glomerular filtration rate ≤30 ml/min (known = registered in GP' clinical records).<br>A known condition or treatment associated with significant impaired immunity (e.g., long-term oral steroids, chemotherapy, or immune disorder).<br>Known severe hepatic impairment.<br>Severe dehydration.<br>Any previous episode of gout (uric acid)<br>Need for long term use of antacids such as magnesium hydroxide, magnesium carbonate, aluminum hydroxide.<br>Life expectancy estimated by a clinician to be less than six months.<br>Involvement in, including completion of, follow-up procedures, in another clinical trial of an investigational medicinal product in the last 90 days.<br>Incontinence too severe to be able to provide a voided urine specimen.<br>Participation in ImpresU Work Package 2*.<br>Significant known abnormal renal tract anatomy/physiology (i.e., single kidney, persistent urinary tract stone disease, severe vesicoureteral reflux) or neuropathic bladder disorders.<br>Lactose intolerance. |

* *An antibiotic stewardship intervention to improve antibiotic prescribing for urinary tract infections in frail elderly.*

### Subject enrolment and randomisation

Four sets of 100 random numbers, one set for each participating country, will be created by a member of the research team using Research Randomizer [42]. A block randomization will

be performed. Block size will be concealed to prevent functional un-blinding. The outcome will be transferred to a separate Excel spreadsheet for each country, and each country will follow their randomisation list strictly sequentially as subjects are eligible for randomisation. If a subject discontinues from the study, the subject number will not be re-used, and the subject will not be allowed to re-enter the study. The inclusion will stop when a total of 400 participants are included in the study.

**Discontinuation and withdrawal of subjects**

Subjects are free to discontinue their participation at any time without prejudice to further treatment. Participants developing SAEs possibly due to methenamine hippurate will discontinue study medication. Alkalizing antacids can potentially reduce the effect of methenamine hippurate and should be avoided. Study participants requiring long-term use of antacids during the first six months of study will discontinue study medication. If prophylactic urinary antibiotics are initiated after enrolment and randomisation in the study, the participants will discontinue study medication. Participants developing serious illness, making it impossible for them to continue taking the study tablets or comply with study requirements, will discontinue study medication and/or withdraw from study participation. Other reasons for discontinuing treatment or withdrawing a subject are incorrect enrolment and subjects lost to follow-up. Participants who prematurely discontinue treatment, except for patients' withdrawing their consent, will be followed up in the same framework as participants receiving study medication.

**Patient and Public Involvement**

The concept and patient information material was presented for a group of users prior to study start to ensure readability and comprehension. Input from participating patients and clinicians early in the study will be used to adapt and improve study implementation.

**STUDY TREATMENTS**

**Identity of investigational medicinal products (IMP)**

IMP will be purchased from the pharmaceutical company Mylan A/S. The IMP and corresponding placebo will be sent to Kragerø Tablet factory AS for packing and labelling according to the randomisation list. Kragerø Tablet factory AS will deliver the IMP to a designated pharmacy in each country, which in turn will distribute to participating sites. The IMP will be handed out consecutively to participants for six months' use. Boxes with active substance consist of tablets with methenamine hippurate 1 gram. Boxes with placebo will contain tablets with the equivalent dose of lactose. The placebo tablets will have identical shape, size and markings as the methanmine tablets. The boxes will have identical labelling with corresponding labels for each participating country in local language. Only the participants' study ID on the label will be linked to the randomisation list, revealing the content of the IMP.

**Storage and handling**

One pharmacy/medical distributor will be responsible for delivering the IMP to the relevant sites in each country. The medication will be stored at each site in a locked cupboard in a secure access room together with the sealed code envelopes. IMPs will be stored with a

controlled temperature not exceeding 30 °C. A member of the research team will collect and count any remaining IMP by the end of the treatment period to report treatment compliance. Any unused IMP will be sent to the designated pharmacy for drug count and destruction.

**Blinding**

Participants, GPs meeting patients, pharmacists dispensing drugs, the investigators and persons involved in statistical analysis will not be aware of group allocation until all statistical analyses are done (triple blind).

**Breaking the blinding in an emergency situation**

The study code should only be broken for valid medical or safety reasons. There will be one sealed opaque envelope for each medication ID available at the study sites, revealing the identity of the IMP. On patient/physician information cards, there will be a telephone number provided by the Sponsor to be used in emergency situations. The coordinating center (or the Sponsor) provides the treating physician with treatment allocation details, and the treating physician deals with the participant's medical emergency accordingly.

**Study Objectives and Variables**

The primary objective of this study is to investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTIs (table 4). The remaining objectives are considered secondary. Pyelonephritis, hospitalization and death will be registered as safety endpoints.

**Table 4.** Study objectives and variables in the ImpresU clinical trial.

| Objectives | | Outcome Measures / variables / endpoints | Time point(s) of evaluation of this outcome measure (if applicable) |
|---|---|---|---|
| **Primary Objective** | | | |
| **1** | To investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTIs (measured as number of antibiotic courses). | Number of UTI antibiotic treatments during the six months of treatment. If the participant receives >1 antibiotic course for UTI without symptom relief, it is regarded as one episode and counted as one antibiotic treatment. If there has been an asymptomatic period of at least 14 days in-between two UTI antibiotic courses, this is regarded as a new antibiotic treatment. | After six months of treatment. |

| Secondary Objectives | | | |
|---|---|---|---|
| **2a** | To investigate if methenamine hippurate will have a prolonged effect on antibiotic usage even after discontinuation. | Number of UTI antibiotic treatments during the six months following completion of treatment. If the participant receives >1 antibiotic course for UTI without symptom relief, it is regarded as one episode and counted as one antibiotic treatment. If there has been an asymptomatic period of at least 14 days in-between two UTI antibiotic courses, this is regarded as a new antibiotic treatment. | Six months after completing (12 months after commencing) treatment. |
| **2b** | To investigate if methenamine hippurate reduces the incidence of UTIs. | Number of UTIs (acute symptoms specific/related to the urinary tract) during the six months of treatment. If the participant has had >1 UTI episode without symptom relief, it is regarded as one episode. If there has been an asymptomatic period of at least 14 days in-between two UTI episodes, this is regarded as a new episode. | After six months of treatment. |
| **2c** | To investigate if methenamine hippurate can reduce severity of UTI symptoms. | Registration of symptom severity when initiating treatment for UTI. | After six months of treatment. |
| **2d** | To investigate if methenamine hippurate can reduce duration of UTI episodes. | Registration of number of days of symptoms during UTI episodes. | After six months of treatment. |
| **2e** | To investigate if number of complications such as pyelonephritis and hospital admission for UTIs differ between methenamine hippurate and placebo. | Registration of number of pyelonephritis and hospital admission for UTI. | Six and 12 months after commencing treatment. |
| **2f** | To investigate if strain characteristics/phylogenetic subgroups of *E. coli* found at inclusion is an effect modifier in all the above outcomes. | (See above) | (See above) |

**Handling, storage and destruction of biological samples**

At inclusion, a urine specimen will be collected for culture and dipstick urinalysis. After analysis, the urine specimen will be destroyed. However, we will freeze isolates of *E. coli* from the inclusion urine culture. Bacteria are not regarded human material and do not need biobank registration. The study team will order copies of medical records from acute UTI episodes including laboratory urinalysis results.

**SAFETY**

Methenamine hippurate is a well-tolerated drug, and the adverse effects are generally mild [24]. Anticipated adverse drug reactions in the study includes gastric irritation, irritation of the bladder, nausea and vomiting (all uncommon), diarrhoea and abdominal pain (incidence unknown). Skin and subcutaneous disorders like rash and pruritus are both registered as uncommon [15]. Participants developing clinically significant dehydration or receiving a course of sulphonamide antibiotics, will pause IMP due to theoretical increased risk of crystalluria. The participants will continue with study treatment when dehydration is clinically resolved and/or the sulphonamide antibiotic treatment is completed.

**Adverse Events (AE)**

As methenamine hippurate has been in clinical use for decades, non-serious adverse events will not be recorded for the purpose of this study - except in The Netherlands, where the Medical Ethical Committee required registration of all AEs. It will be left to the Investigator's clinical judgment to decide whether a symptom or side effect is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily discontinue treatment due to intolerable symptoms or side effects.

**Serious Adverse Event (SAE)**

All SAEs that are life threatening or results in death will be reported. SAEs requiring inpatient hospitalization or prolongation of existing hospitalization, and SAEs resulting in persistent or significant disability/incapacity will only be reported if relationship with IMP cannot be excluded or the SAE is a complication of a UTI. SAEs representing expected events in a frail older population will not be reported. If relationship with IMP cannot be excluded, these SAEs are possibly, probably or definitely related to the trial medication. These adverse events will be reported as SAR (Serious Adverse drug Reaction) if expected and included in SmPC or as SUSAR (Suspected Unexpected Serious Adverse Reaction) if unexpected and not included in SmPC (Figure 1). SAEs will be registered throughout the whole study period. In case of a SAE not resolved by the end of the study, this SAE will be followed until resolution.

**[Insert Figure 1: Safety reporting flowchart for the ImpresU clinical trial.]**

**Premature termination of the study**

A data safety monitoring committee (a statistician and two external researchers with experience from clinical trials and UTI infections in primary care) will meet every six months to ensure data safety. The difference between groups in SAEs deemed to be linked to methenamine hippurate, will be continuously monitored. The study will be terminated if there is a significant difference between the two trial arms regarding SAE, SAR and SUSAR

probably or definitely related to the trial medication or UTI. This will be evaluated by comparing the two groups without breaking the code. The code will be broken if the difference between groups is statistically significant ($p<0.05$). The study will be prematurely terminated if the statistical difference is to the disadvantage of active IMP. SAE, SAR and SUSAR possibly related to the trial medication or UTI will be registered but not used for decision-making.

## STATISTICS

### Sample size calculation

The sample size calculation is made for the primary objective described in table 1. We assume these selected older women will have an average of two courses of antibiotics for suspected UTIs every six months (4). We assume a 25% reduction of antibiotic prescriptions during the first six-month after introduction of methenamine hippurate based on a consensus in the research group that a smaller effect would be less clinically relevant. This means that the intervention group would have an average of 1.5 prescriptions while the control group is assumed to remain around 2.0. We assume the standard deviation in each group to be 1.5. This will result in an effect size of 0.33 (small effect). We assume the level of significance being 0.05, the power to be 0.80 and that a two-tailed test is explored. We use Student's t-test as the statistical analysis but also calculate for Mann-Whitney test (if the outcome variable is not normally distributed). The planned statistical method will be multivariable linear regression. Student's t-test and Mann-Whitney test are used as surrogate methods to estimate sample size. Under the assumptions given above, an effective sample size of 286 patients (143+143) is required if t-test can be used. However, if Mann-Whitney's test is required we need 298 (149+149) patients. To achieve an effective sample size of at least 298, after considering a 25% loss to follow-up, we aim to include 400 patients.

### Statistical analysis

We will adjust all analysis for confounding variables obtained at visit 1 (table 5).

**Table 5.** Confounding variables to be adjusted for in the analysis in the ImpresU clinical trial.

| **Confounding variables obtained at visit 1** |
|---|
| Patient's age.<br>Urine acidity (pH).<br>Number of antibiotic courses for UTIs in the 12 months preceding inclusion in the study.<br>Presence of urease/stone-producing bacteria in urine culture day 1 such as *Proteus spp*, *Klebsiella spp*, *Morganella morganii*, *Corynebacterium urealyticum* and *Providencia*.<br>Use of local oestrogen.<br>Patient has diabetes mellitus.<br>Obesity defined as BMI ≥30.<br>Presence of known mild abnormality of the urogenital tract. |

| |
|---|
| If the patient is sexually active.<br>If the patient previously has experienced urinary tract stone.<br>Strain characteristics and phylogenetic subtype of *E. coli* in the urine culture at inclusion will be analysed in a separate analysis. |

Planned statistical analysis for primary and secondary objectives are listed in table 6.

**Table 6**. Study objectives and statistical analysis in the ImpresU clinical trial.

| | Objectives | Statistical analysis | Time point(s) of evaluation of this outcome measure (if applicable) |
|---|---|---|---|
| **Primary Objective** | | | |
| **1** | The primary objective of this study is to investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTI (measured as number of antibiotic courses). | Standard linear regression will be used where the number of UTI antibiotic treatments will be the dependent variable. Group allocation together with the confounding variables above will be independent variables. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p-value will be delivered, but no useful effect size if a rank transformation is used. | After six months of treatment. |
| **Secondary objectives** | | | |
| **2a** | To investigate if methenamine hippurate will have a prolonged effect on antibiotic usage even after discontinuation. | Will be analysed using the same statistical approach as objective 1. | Six months after completing (12 months after commencing) treatment. |
| **2b** | To investigate if methenamine hippurate reduces the incidence of UTI. | Will be analysed using the same statistical approach as objective 1. UTIs will be the dependent variable. | After six months of treatment. |
| **2c** | To investigate if methenamine hippurate can reduce severity of UTI symptoms. | The outcome variable is measured at first day of UTI using a six-grade ordinal scale. The median value of all UTIs will be used if the patient has more than one episode of UTI. The dependent variable will be transformed using a rank transformation and analysed with linear regression using the same covariates as when analysing objective 1. | After six months of treatment. |

| | | | |
|---|---|---|---|
| **2d** | To investigate if methenamine hippurate can reduce duration of UTI episodes. | Will be analysed using the same statistical approach as objective 1. Number of days with symptoms will be the dependent variable. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p-value will be delivered, but no useful effect size if a rank transformation is used. | After six months of treatment. |
| **2e** | To investigate if the number of complications such as pyelonephritis and hospital admission for UTI differ between methenamine hippurate and placebo. | Will be analysed using the same statistical approach as objective 1. Number of severe events such as pyelonephritis or hospital admission will be the dependent variable. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p-value will be delivered, but no useful effect size if a rank transformation is used. | Six and 12 months after commencing treatment. |
| **2f** | To investigate if strain characteristics/phylogenetic subgroups of *E. coli* found at inclusion is an effect modifier in all the above outcomes. | Phylogenetic subtype of pure cultures of *E. coli* in the inclusion urine culture will be analysed in a separate statistical analysis if the number of cultures available for typing is at least 60. All statistics above will be repeated adding phylotype as an extra independent variable. Purely descriptive statistics will be presented if the number is less than 60. | (See above) |

**Primary and secondary statistical analysis and management of missing data**

The primary statistical analysis is intention to treat. Patients who have completed only a part of the first six months, will contribute data up until they leave the study. Their data will be recalculated as if they had participated all six months. Patients leaving during the second six-month period will also contribute with data as above. Patients leaving the study before the second six-month period commence will have their value for this period set to be the median value for both groups. A complete case analysis and a per-protocol analysis will also be made as secondary analysis and reported.

**DATA MANAGEMENT**

**Recording and management of data**

We will use the electronic data capture system Research Online (RO) for data collection. RO meets all requirements according to Good Clinical Practice for electronic data entry with respect to safeguarding data integrity and data security regulations. Web-based case report forms are implemented into the system to facilitate data collection. Participants will be identified by a unique trial specific number. All source data will be stored at the coordinating centers for a minimum period of fifteen years after termination of the trial. After the data of the last subject is entered, a clean file will be produced for further analysis and publication, and the database will close. Direct access to the data will be granted to authorised

representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections

**Study sponsor**

University of Oslo, Norway.

**Monitoring**

A study monitor will be appointed by the sponsor to monitor the study in all four countries. The quality control will have a risk-based approach. The monitor will have regular contacts with the coordinating centers and sites, and the extent of monitoring will be defined in a separate monitoring plan. Authorized representatives of the sponsor or regulatory authorities may perform audits or inspections, including source data verification.

## DISCUSSION

AMR in urinary pathogens is on the rise. With increasing life expectancy and current antibiotic use, this trend will continue unless appropriate prescribing and feasible and effective non-antibiotic preventive measures are implemented. If methenamine hippurate is safe and effective in reducing UTI episodes in older women with frequent UTIs, it could potentially change the management of recurrent UTIs outside Scandinavia. Less use of urinary antibiotics will reduce antibiotic pressure and potentially slow the progression of AMR. If methenamine hippurate is not effective, the result will still be beneficial as many women can avoid unnecessary medication.

This study also sets out to unravel whether methenamine hippurate, if proven effective, have a prolonged effect even after discontinuation of a six-month treatment period. If so, this will guide the preparation of more precise guidelines for prophylactic use of this drug.

Including only women ≥70 experiencing the highest number of UTIs in the twelve months preceding inclusion increases the chance of a spontaneous reduction in episodes in the following twelve months – regardless of any intervention [43]. As a result, we expect a decrease in the number of UTIs in both the placebo and intervention groups in the intervention period. However, the RCT design compensates for the possible effect of regression to the mean.

Management of acute UTIs are handled by regular health services in this study. With four European countries participating, the guidelines differ slightly. The individual interpretation of diagnosis and treatment guidelines will probably also differ on a physician level. In case of acute UTIs, patient symptoms will be reported directly from the patient, making the data prone to recall bias. In cases where the study team are notified of a UTI the same day, the patient symptoms are recorded in real time minimizing bias. However, missed UTIs discovered at monthly follow-up or when checking the patient records at end of study will be recorded retrospectively.

## Ethics and dissemination

All participants will receive standard medical care in case of a UTI. The participants will receive written information with contact details to the PI, the study team and a study telephone manned at all hours during the study period. A data monitor committee will ensure data safety. The risk of the study is considered very small, and our risk/benefit analysis concludes that the possible benefits of this study greatly outweigh the potential risk. The study protocol has been approved by the Norwegian Medicines Agency (NoMA, 18/16628-15), the Regional Committee for Medical and Health Research Ethics, NO (REK south-east, 2018/2502 A), the Swedish Medical Product Agency (5.1-2019-103684, 5.1-2021-35901, 5.1- 2021-64842 and 5.1-2021-92970), the Swedish Ethical Review Authority (2019-02749, 2020-00360 and 2021-03992), Committee of Bioethics of the Medical University of Lodz, PL (RNN/311/19/KE), Office for Registration of Medicinal Products, Medical Devices and Biocidal , PL (UR/DBL/D/417/2021), Centrale Commissie Mensgebonden Onderzoek, NL (NL71512.041.19.) and Medical Ethical Review Committee, METC Utrecht, NL (20/032).

Substantial amendments will be communicated to relevant competent authorities. Within one year after the end of the study, the sponsor will submit a study report with the results of the study to the accredited competent authority. In addition, the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## Insurances

The Norwegian study subjects are covered by “Legemiddelansvarsforsikringen”. The Swedish study subjects are covered by “The Swedish Pharmaceutical Insurance”, LFF Service AB. The Dutch study subjects are covered by CNA Insurance Company (Europe) S.A. The Polish study subjects are covered by Towarzystwo Ubezpieczeń i Reasekuracji “WARTA”.

## Trial status

Subject enrolment started in December 2019 and will be completed by end of June 2022. All follow-ups are expected to be completed by the end of June 2023.

## Author Contributions

ML, PS, CH, TV and MGC conceptualized the ImpresU project and obtained funding. ML, PS, RG, SHO and ESA drafted the protocol for the RCT, and SH, NG, CÅ, WG, HVK, TP, AK, MGC, CH and TV revised the protocol. SHO drafted the manuscript. All authors critically revised the article draft and approved the final manuscript.

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funders will have no role in study design, data collection, management, analysis and interpretation, nor in writing and submission of reports for publication.

**Competing interests statement**

None declared.

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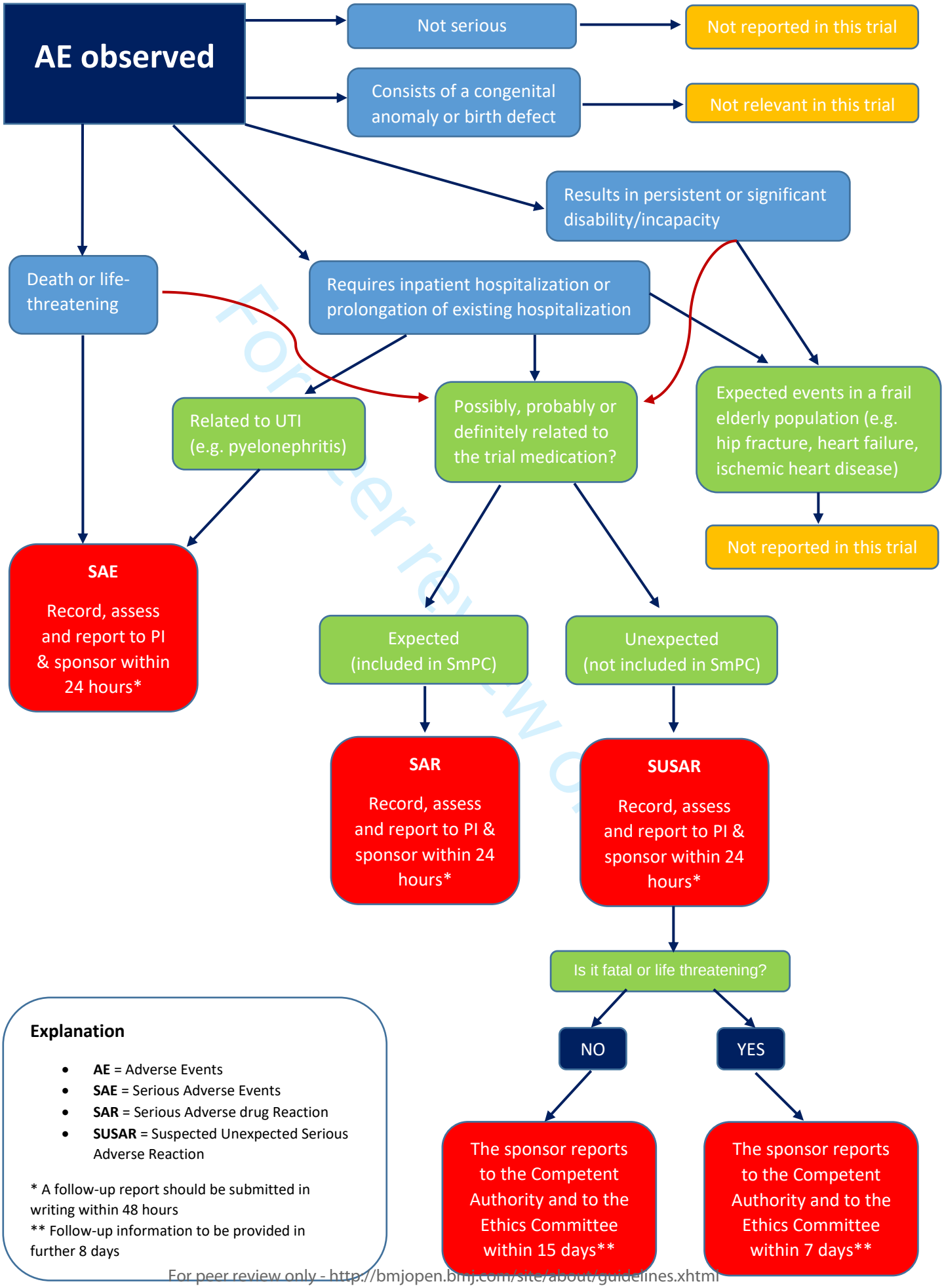
## Legends

**Figure 1.** Safety reporting flowchart for the ImpresU clinical trial.

**Supplementary file 1**: Model informed consent form in the ImpresU clinical trial

**Supplementary file 2**: Model patient information pocket card (front/back) in the ImpresU clinical trial



Request to participate in drug trial

# Version 3

# ImpresU - can Methenamine reduce episodes of urinary tract infections (UTI) in women over 70 with recurrent UTI?



This is a request for you to participate in a research project testing the drug methenamine hippurate. Methenamine disinfects the urinary tract and is not regarded as an antibiotic. Methenamine is the most commonly used drug for preventive treatment of urinary tract infections in Norway. The aim of the study is to determine whether methenamine has a preventive effect and leads to fewer infections in women over the age of 70 with frequent urinary tract infections. Your General practitioner (GP) has, through a computer program searching his/her medical records, found that you are a patient frequently suffering from urinary tract infections. Based on these finding, he/she has contacted you to require your participation in a study testing a preventive drug for urinary tract infections.

The study is conducted by the (Insert national research group/university), and the sponsor of the study, The University of Oslo.

## What does the project entail?

In this study, we wish to investigate whether methenamine has a preventive effect on urinary tract infections in women over the age of 70. In order to do so, we will be testing methenamine against placebo over a period of six months. In the Norwegian part of the study, 100 patients will be participating. One half of the patients will get methenamine, while the other half will get placebo tablets. The study is blinded, which means that neither your doctor nor the research team will know whether you get methenamine or a placebo. This information is sealed and only to be revealed if a situation where it is important to know whether you are getting the active drug or not occurs. The medicine is free of charge, and you will be given medication for six months of treatment. After the treatment period, we wish to continue the follow up for an additional six months in order to investigate whether methenamine has a prolonged preventive effect even after the treatment is completed.

At the first meeting, a representative from the research team will give you information on the study, and you will get the opportunity to ask any questions you might have. If you wish to participate, we will get your GP to help us determine whether you are an eligible

candidate for the study. By signing this declaration, you consent for the research team getting access to relevant information in your medical records through your GP. We will also be asking you for a urine sample during this meeting.

If you are getting symptoms of a urinary tract infection within the study period, we ask you to contact your GP in the normal manner for an evaluation of treatment. At this consultation, a urinary sample will be taken. We also ask you to contact the research team on the same day using the listed number. After this, our study nurse will contact you once a week until your infection has cleared. During these calls we will register symptoms and the degree of symptoms, what kind of treatment you receive and the duration of the treatment. Any side effects or complications due to the study medicine will also be recorded. Our study nurse will call you once a month throughout the treatment period the first six months of the study to check up on you and to see how you are doing.

If you get a urinary tract infection and your doctor is not available, we ask you to contact other health care institutions to get an evaluation of treatment and thereafter call the research team on the listed number. By signing this declaration, you give your consent for the research team to collect relevant data from your medical records at the health care institution you received your treatment if necessary.

## POSSIBLE ADVANTAGES AND DISADVANTAGES AND SERIOUS SIDE EFFECTS

Methenamine has been used for nearly 50 years without a documented effect. It is important to clarify whether methenamine actually can reduce the number of episodes in women with frequent urinary tract infections. If so, more patients can benefit from an effective preventive treatment. This will lead to a reduction in antibiotic prescriptions for urinary tract infections, and contribute to reduce the development of antibiotic resistance in the future, as well as saving patients from the unnecessary side effects of antibiotics.

If methenamine does not show a preventive effect on frequent urinary tract infections, this will cause many women not to be prescribed unnecessary medicine.

Since methenamine has been used on a large scale in this country, the drug has a well-documented safety profile with few and mild side effects. We do not know of any serious side effects linked to the use of methenamine. The most common side effects that can occur are all less common (more than 1 of 1000, less than 1 of 100) and include stomach disorders such as nausea/vomiting, stomach irritation, upset stomach and rash/itching and irritation of the bladder. A rare side effect (more than 1 of 10 000, less than 1 of 1000) is microscopic (not visible) blood in the urine.

The treatment of every episode of a urinary tract infection is determined by your doctor in the normal manner. Participation in the study will therefore not result in any other treatment for your urinary tract infection than you would otherwise have.

## VOLUNTARY PARTICIPATION AND POSSIBILITY TO WITHDRAW CONSENT

It is voluntary to participate in the project. If you wish to participate, you have to sign the consent form on the last page. You can, whenever you like and without stating a reason, withdraw your consent without any consequences for further treatment.

If you consent to participate in the study, you have the right to gain access to the information registered on you and have the information corrected should there be any mistakes in your information. You also have the right to gain insight into the security measures taken in the processing of your data. If you wish to withdraw from the study, there will not be registered any more information on you, but data already collected will not be deleted.

If you wish to withdraw your consent or have questions about the project, you can contact (Insert contact information for Principal Investigator).

## WHAT HAPPENDS TO THE COLLECTED DATA ON YOU?

The tests will be done in the same manner as any other tests taken in your GP's office, and are requisitioned by your doctor. We will not collect biological material, and are only interested in the results from the tests your doctor required.

The results we will require are from urinary dipsticks, ph and culture. If there is growth of bacteria in your urine culture, the bacteria will be investigated further, but your urine sample will be destroyed in the usual manner.

The tests taken, and the information registered on you, are only to be used as described in the purpose of the project.

All the data on you is processed without a name or a national identification number, or any other recognizable information. A code will link you to your information through a list of names.

It is only (insert all persons that have access to the national list) who have access to this list. The list will be securely stored at the research center.

This study is a cooperation project between Norway, Sweden, the Netherlands and Poland. The study will take place simultaneously in the four participating countries. After coding, the data on you will be gathered in a database in the Netherlands where final analyzes will take place. The data from all the participating countries will be analyzed collectively and are later to be published in international journals.

By participating in the project, you consent to the information being transferred to other countries as a part of a research and publishing collaboration. The project leader will make sure that your data is taken care of in a safely manner.

The code that links you to your personal identifiable information is not transferred.

Your collected data is to be deleted 15 years after the project has ended.

It will not be possible to identify you in the results of the published study.

## APPROVAL

(Insert name of Competent Authority) has evaluated the project and given their approval (Insert study reference number).

According to the new personal data act, the data controller institution, (Insert name of university and name of Principal Investigator), have a personal responsibility to ensure that the handling of your information has a legal basis. This project has the legal basis in the EUs General Data Protection Regulation, article 5, article 6 1a and article 9 2a, and your consent.

You have the right to complain about the processing of your information to the Data Protection Authority.

## CONTACT INFORMATION

If you have any questions about this project, please contact (Insert name and contact information for coordination researcher).

You can contact the Data Protection Official at the institution if you have questions about the processing of your personal data in the project. At the (insert university), questions about data protection are addressed to (insert contact information).

## WHAT INFORMATION ABOUT YOU WILL BE REGISTERED?

- Relevant past medical history to determine if you are eligible to participate in the study.
- Year of birth and residency
- Certain other health information important for the evaluation of the results of the study. We will be collecting this information from your GP, your medical records and from you directly.
- During the first meeting, we will take a urine sample and register the results of this test.
- With every episode of a urinary tract infection, we will register symptoms and the degree of the symptoms, what treatment you receive and the duration of the treatment. The results of the urine test taken by your doctor with every episode will also be registered. In every case of a urinary tract infection, we will follow up to register the course of the infection until the infection has cleared. Any side effects or complications due to the study medicine will also be recorded. Our study nurse will call you once a month throughout the study to check up on you and to see how you are doing.

- If you receive treatment for a urinary tract infection from other health professionals than your GP, it may be necessary to collect information from their medical records as well in order to obtain the information listed above.

- Representatives from The University of Oslo (the sponsor of the study), The Norwegian Medicines Agency and control authorities, both domestic and abroad, can gain access to study information from relevant parts of your medical record. The purpose of this is to ensure that the registered study information match the information in your medical record. Everyone with access to your medical record have a duty of confidentiality.

## FINANCE

The study is funded by (Insert source of funding); the sponsor of the study is The University of Oslo.

## INSURANCE

You are insured in accordance to the product liability law in (Insert national insurance company).

## INFORMATION ABOUT THE OUTCOME OF THE STUDY

The participants in the study have the right to get information about the outcome of the study if desirable.

I CONSENT TO PARTICIPATE IN THE STUDY AND THAT MY PERSONAL INFORMATION CAN BE USED AS DESCRIBED.

---

(Signature of participant, date)

CONFIRMATION OF GIVEN INFORMATION

I confirm to have given information about the project

---

(Signature, role in the project, date)

*Note: The model consent form will be adapted according to rules and regulations from the competent authorities in each participating country.

Date/start medication:_____

ImpresU

PatientstudyID:_____

**PATIENT INFORMATION**

- The study medication is taken 1 tablet twice daily for 6 months. The total study period is 12 months.
- In case of a urinary tract infection: contact your doctor.
- Bring a urine sample to the doctor's appointment.
- After the doctor's appointment, contact: (study phone)
- The study team will call you once a week until the infection has cleared.
- The study team will also call you once a month in the 6 months of medication to check how you are doing.

SHOW THIS CARD IF YOU ARE IN CONTACT WITH HEALTH CARE PERSONNEL OTHER THAN YOUR GP

ImpresU

**HEALTH CARE PERSONNEL**

- The study lasts for 12 months from start of medication.
- The first 6 months, the patient will receive:

**Methenamine hippurate 1g x 2 OR placebo 1 tbl x 2**

- In case of a UTI, we ask that symptoms are recorded and that a copy of the relevant EPJ note and results of dipstick/culture, if taken, are sent to the patients' GP.
- Methenamine hippurate has few and mild side-effects.
- In case of a serious adverse event, contact (study phone)
- If the patient is starting long-term treatment with antacids (Your generic names®) while receiving study medication, the patient has to be excluded from the study.
- The study medication has to be temporarily paused in the case of severe dehydration or treatment with sulphonamide antibiotics (your generic names®) until rehydrated/end of sulphonamide treatment.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 1, 2, NCT04077580 |
| Protocol version | 3 | Date and version identifier | 1 |
| Funding | 4 | Sources and types of financial, material, and other support | 17 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 17 |
| | 5b | Name and contact information for the trial sponsor | 1, 16 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 17 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 12-13, 15-16 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3-4 |
| | 6b | Explanation for choice of comparators | 4 |
| Objectives | 7 | Specific objectives or hypotheses | 4, 10-11 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5-7, NCT04077580 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 4-9 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6-10 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 6-9 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 10-11 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 5-6 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8-9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8-10 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6, 8-9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 10 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 10 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 5-7, 13,15 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 5-7, 9, 15 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 15 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13-15 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13, 15 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 15 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 12 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 12 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 6,7,12 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 16 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 16-17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 17 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N.A. |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 17 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 17 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 17 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 17 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Not included in this article |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | 6, supplementary files |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 11-12 |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

TIDieR
Template for Intervention Description and Replication

## The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

| Item number | Item : Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU). | Where located ** | |
|---|---|---|---|
| | | Primary paper (page or appendix number) | Other † (details) |
| | **BRIEF NAME** | | |
| **1.** | Provide the name or a phrase that describes the intervention. | 1 | Protocol version 11.1 (07.07.21) |
| | **WHY** | | |
| **2.** | Describe any rationale, theory, or goal of the elements essential to the intervention. | 2-4 | Protocol version 11.1 (07.07.21) |
| | **WHAT** | | |
| **3.** | Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL). | 6-7 | Supplementary files<br>Protocol version 11.1 (07.07.21) |
| **4.** | Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities. | 5-7 | Protocol version 11.1 (07.07.21) |

| | | | |
|---|---|---|---|
| | **WHO PROVIDED** | | |
| **5.** | For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given. | | Protocol version 11.1 (07.07.21) |
| | **HOW** | | |
| **6.** | Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group. | 6-7 | Protocol version 11.1 (07.07.21) |
| | **WHERE** | | |
| **7.** | Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features. | 6-7 | Protocol version 11.1 (07.07.21) |
| | **WHEN and HOW MUCH** | | |
| **8.** | Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose. | 5-7 | Protocol version 11.1 (07.07.21) |
| | **TAILORING** | | |
| **9.** | If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how. | 9 | Protocol version 11.1 (07.07.21) |
| | **MODIFICATIONS** | | |
| **10.‡** | If the intervention was modified during the course of the study, describe the changes (what, why, when, and how). | N/A | N/A |
| | **HOW WELL** | | |

| | | | |
|---|---|---|---|
| **11.** | Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them. | 7 | Protocol version 11.1 (07.07.21) |
| **12.‡** | Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned. | N/A | N/A |

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).