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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 1 g or placebo tablets two times per day for a treatment period of 6 months, followed by a drug-free follow-up period of 6 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 *Escherichia 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 registration number ClinicalTrials.gov Registry (NCT04077580); EudraCT: 2018-002235-15.

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections in humans.[1] Women are more prone to develop

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to examine the preventive effect of methenamine hippurate using a randomised, 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 urinary tract infections (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.

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 the 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 hydrolysed to formaldehyde and ammonia in acidic urine. Formaldehyde acts as a bacteriostatic agent, denaturising 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 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 carcinogenicity.[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 a 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 with 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 randomised to 12-month treatment with methenamine hippurate or low-dose antibiotics. The study was open-labelled, that is, the participants were aware of their treatment allocation. Although the ALTAR Study demonstrated non-inferiority, methodologically, the gold standard for demonstrating effect of a drug intervention is to compare the effect with 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 healthcare. 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 using a triple-blind, randomised, placebo-controlled trial design (RCT).

Escherichia coli

E. coli is a part of the human gastrointestinal microbiota.[31] Uropathogenic *E. coli* from faecal 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 extraintestinal infections.[35–37] The management of UTIs is complicated by increasing prevalence of antibiotic-resistant strains of *E. coli*.[38] Persistent or relapsing 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 12 months or ≥2 episodes during the last 6 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 g

methenamine hippurate ×2, standard recommended dose[15]) or control (one placebo tablet two times per day) for 6 months. To evaluate if there is a prolonged effect of treatment, another 6 months of follow-up will be performed. A total of 400 patients will be randomised, approximately 100 patients in each participating country. Study visits and procedures are listed in table 1.

Study assessments
Visit 1: screening, inclusion and randomisation
Eligible patients will be found through a screening procedure of the electronic patient record in the general practitioner (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 (online supplemental 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 (ie, urinary bladder dysfunction, diabetes mellitus, obesity (body mass index >30), local treatment with oestrogen, sexual activity or abnormality of the urogenital tract), as well as previous diagnosis of urinary tract stones, pyelonephritis and urosepsis. A voided urine specimen will be collected for dipstick analysis of pH, nitrite and leucocyte 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 online supplemental files 1 and 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 7 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 (ie, pyelonephritis, urosepsis or hospital admissions). Relevant serious adverse events (SAEs) will be registered.

Telephone contacts every 30 days during the first 6 months and at the end of study
The study participants will be contacted by telephone every 30 days in the 6-month 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 healthcare 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 (box 1).

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 randomisation will be performed. Block size will be concealed to prevent functional unblinding. 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 reused, 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. Alkalising antacids can potentially reduce the effect of methenamine hippurate and should be avoided. Study participants requiring long-term use of antacids during the first 6 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
Investigational medicinal products (IMPs) will be purchased from the pharmaceutical company Mylan. The IMP and corresponding placebo will be sent to Kragerø Tablet factory for packing and labelling according to the

Table 1 Study visits and procedures

Time point	Study period								
	Enrolment	Allocation	Treatment period				Follow-up period		
	Screening	Baseline	At time of UTI Days 2–180	Follow-up UTI* Days 2–180	Monthly follow-up Days 2–180	End of IMP Day 180	At time of UTI Days 180–360	Follow-up UTI* Days 180–360	End of study Day 360
Enrolment									
Eligibility screen	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
Assessments									
Midstream urine dipstick/culture		X	X§				X§	X§	
UTI record			X	X	X		X	X	
Patient-reported outcome			X	X	X	X	X	X	X
Adverse event assessment			X	X	X	X	X	X	X¶

Standard Protocol Items: Recommendations for Interventional Trials figure for the ImpresU clinical trial.
*Every episode of acute UTI both in intervention period and follow-up period will be followed with registrations every 7 days until the patient is restored.
†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.
CRF, case report form; GP, general practitioner; IMP, investigational medicinal product; UTI, urinary tract infection.

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? 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 □

*State the degree of the problem on a scale from 0-6 where: 0 = normal/no problem, 1 = little problem, 2 = some problem, 3 = moderate problem, 4 = large problem, 5 = bad, 6 = as bad as it can be
UTI, urinary tract infection.

randomisation list. Kragerø Tablet factory will deliver the IMPs to a designated pharmacy in each country, which in turn will distribute to participating sites. The IMPs will be handed out consecutively to participants for 6 months' use. Boxes with active substance consist of tablets with methenamine hippurate 1 g. Boxes with placebo will contain tablets with the equivalent dose of lactose. The placebo tablets will have identical shape, size and markings as the methenamine 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 IMPs.

Storage and handling
One pharmacy/medical distributor will be responsible for delivering the IMPs 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 IMPs by the end of the treatment period to report treatment compliance. Any unused IMPs 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).

Box 1 Inclusion/exclusion criteria in the ImpresU clinical trial

Inclusion criteria
⇒ Woman.
⇒ Age ≥70 years.
⇒ Recurrent urinary tract infections (UTIs) (≥3 episodes of antibiotic-treated acute cystitis the last 12 months or ≥2 episodes the last 6 months).
⇒ Able and willing to comply with all trial requirements.
⇒ Able and willing to give informed consent.

Exclusion criteria
⇒ Intake of methenamine hippurate within the last 12 months.
⇒ Allergy for methenamine hippurate.
⇒ Current antibiotic prophylaxis for UTI.
⇒ Urinary catheter (chronic indwelling catheters as well as intermittent urinary catheterisation).
⇒ Known severe chronic renal failure or estimated creatinine glomerular filtration rate ≤30 mL/min (known=registered in general practitioners' clinical records).
⇒ A known condition or treatment associated with significant impaired immunity (eg, long-term oral steroids, chemotherapy or immune disorder).
⇒ Known severe hepatic impairment.
⇒ Severe dehydration.
⇒ Any previous episode of gout (uric acid).
⇒ Need for long-term use of antacids such as magnesium hydroxide, magnesium carbonate, aluminium hydroxide.
⇒ Life expectancy estimated by a clinician to be less than 6 months.
⇒ Involvement in, including completion of, follow-up procedures, in another clinical trial of an investigational medicinal product in the last 90 days.
⇒ Incontinence too severe to be able to provide a voided urine specimen.
⇒ Participation in ImpresU Work Package 2.*
⇒ Significant known abnormal renal tract anatomy/physiology (ie, single kidney, persistent urinary tract stone disease, severe vesicoureteral reflux) or neuropathic bladder disorders.
⇒ Lactose intolerance.

*An antibiotic stewardship intervention to improve antibiotic prescribing for UTIs in frail older adults.

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 centre (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 3). The remaining objectives

Table 3 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 6 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 6 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 6 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 6 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 6 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 6 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 6 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 *Escherichia coli* found at inclusion are an effect modifier in all the above outcomes.	See above	See above

UTIs, urinary tract infections.

are considered secondary. Pyelonephritis, hospitalisation and death will be registered as safety endpoints.

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 include 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 sulfonamide 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 sulfonamide antibiotic treatment is completed.

Adverse events

As methenamine hippurate has been in clinical use for decades, non-SAEs will not be recorded for the purpose of this study—except in the Netherlands, where the Medical Ethical Committee required registration of all adverse events (AEs). It will be left to the investigator's clinical judgement 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

All SAEs that are life-threatening or result in death will be reported. SAEs requiring inpatient hospitalisation or prolongation of existing hospitalisation, 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 AEs will be reported as SAR (serious adverse drug reaction) if expected and included in Summary of Product Characteristics (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.

Premature termination of the study
A data safety monitoring committee (a statistician and two external researchers with experience in clinical trials and UTIs in primary care) will meet every 6 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 IMPs. 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 6 months . We assume a 25% reduction of antibiotic prescriptions during the first 6 months after the 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 SD 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 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 analyses for confounding variables obtained at visit 1 (box 2).

Planned statistical analyses for primary and secondary objectives are listed in table 4.

Primary and secondary statistical analyses and management of missing data
The primary statistical analysis is intention to treat. Patients who have completed only a part of the first 6 months will contribute data up until they leave the study. Their data will be recalculated as if they had participated in all 6 months. Patients leaving during the second 6-month period will also contribute with data as above. Patients leaving the study before the second 6-month period commences 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 centres for a minimum period of 15 years after termination of the trial. After the data of the last subject are 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 centres and sites, and the extent of monitoring will be defined in a separate monitoring plan. Authorised 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
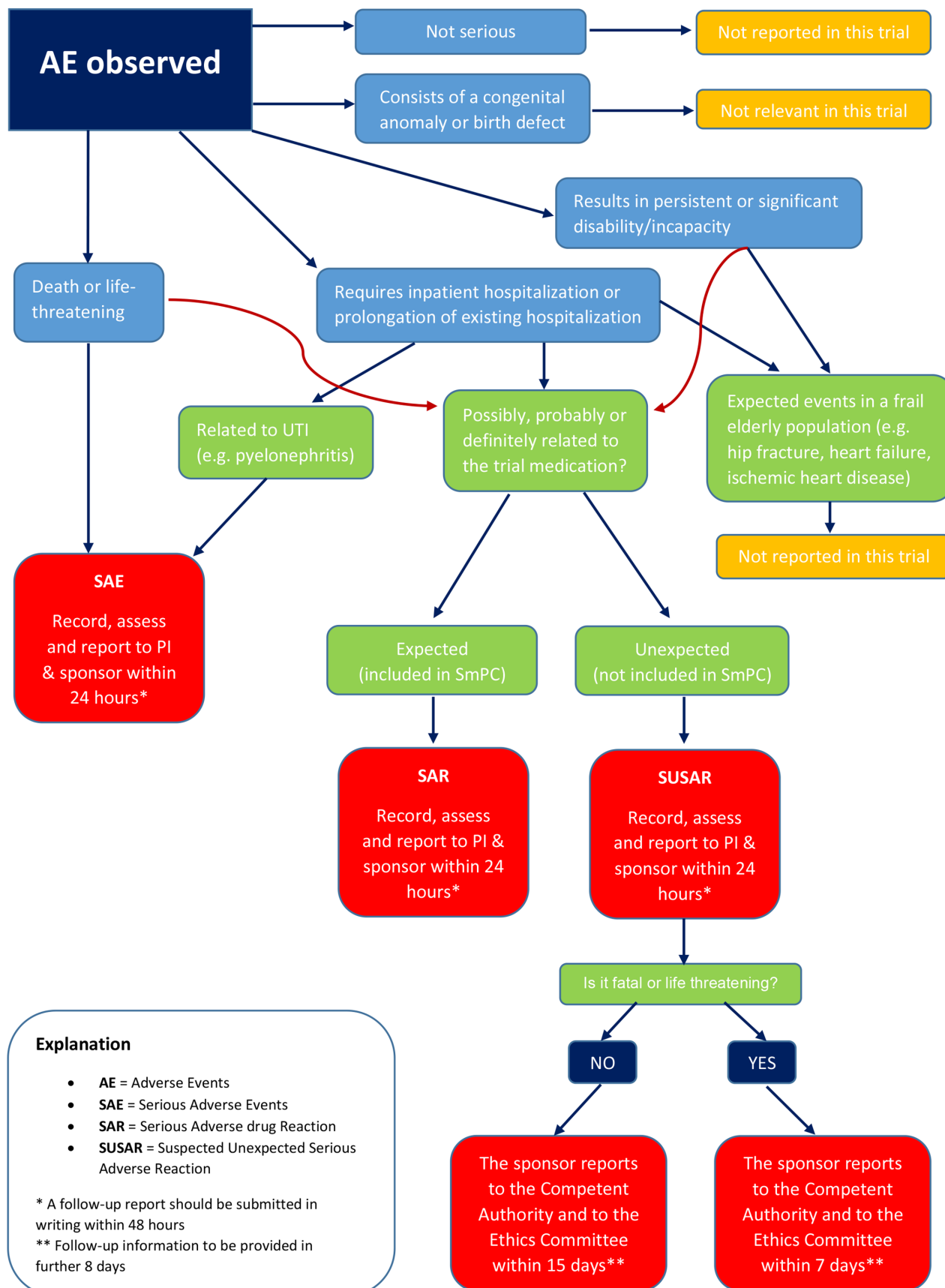
Figure 1 Safety reporting flow chart for the ImpresU clinical trial. *A follow-up report should be submitted in writing within 48 hours. **Follow-up information to be provided in further 8 days. AE, adverse event; PI, principal investigator; SAE, serious adverse event; SAR, serious adverse drug reaction; SUSAR, suspected unexpected serious adverse reaction; UTI, urinary tract infection.

> **Box 2 Confounding variables to be adjusted for in the analysis in the ImpresU clinical trial**
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> **Confounding variables obtained at visit 1**
> ⇒ Patient's age.
> ⇒ Urine acidity (pH).
> ⇒ Number of antibiotic courses for urinary tract infections in the 12 months preceding inclusion in the study.
> ⇒ Presence of urease/stone-producing bacteria in urine culture day 1 such as *Proteus* spp, *Klebsiella* spp, *Morganella morganii*, *Corynebacterium urealyticum* and *Providencia*.
> ⇒ Use of local oestrogen.
> ⇒ Patient has diabetes mellitus.
> ⇒ Obesity defined as body mass index ≥30.
> ⇒ Presence of known mild abnormality of the urogenital tract.
> ⇒ If the patient is sexually active.
> ⇒ If the patient previously has experienced urinary tract stone.
> ⇒ Strain characteristics and phylogenetic subtype of *Escherichia coli* in the urine culture at inclusion will be analysed in a separate analysis.

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, has a prolonged effect even after discontinuation of a 6-month treatment period. If so, this will guide the preparation of more precise guidelines for prophylactic use of this drug.

Including only women ≥70 years experiencing the highest number of UTIs in the 12 months preceding inclusion increases the chance of a spontaneous reduction in episodes in the following 12 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 is 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

Table 4 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 6 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 6 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 6-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 6 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 6 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 *Escherichia coli* found at inclusion are 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

UTI, urinary tract infection.

reported directly from the patient, making the data prone to recall bias. In cases where the study team is notified of a UTI the same day, the patient symptoms are recorded in real time minimising 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 principal investigator, 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, Norway (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, Poland (RNN/311/19/KE), Office for Registration of Medicinal Products, Medical Devices and Biocidal, Poland (UR/DBL/D/417/2021), Centrale Commissie Mensgebonden Onderzoek, the Netherlands (NL71512.041.19.) and Medical Ethical Review Committee, METC Utrecht, the Netherlands (20/032).

Substantial amendments will be communicated to relevant competent authorities. Within 1 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.

Insurance

The Norwegian study subjects are covered by 'Legemiddelansvarsforsikringen'. The Swedish study subjects are covered by the 'Swedish Pharmaceutical Insurance', LFF Service. The Dutch study subjects are covered by CNA Insurance Company (Europe). 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.

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