[To be printed on to Trust headed paper]

ALternatives **T**o prophylactic **A**ntibiotics for the treatment of **R**ecurrent urinary tract infection in women

Patient Information Sheet

You have been invited to take part in a research study

Before you decide, it is important that you understand why the research is being done and what it will involve

Please take time to read the following information carefully and discuss it with others if you wish

The ALTAR Trial is funded by the National Institute for Health Research's HTA Programme.

Project Summary

- When antibiotics are used too often they can become less effective at treating infections and the bugs causing the infection can eventually become resistant to antibiotics. This means that the treatment may no longer work.

- Doctors would like to use fewer antibiotics where possible to prevent bugs from becoming resistant, but they need to be able to use another treatment that they know will work at least as well if not better than the antibiotics.

- The ALTAR trial is about finding out whether taking a non-antibiotic drug known as Methenamine Hippurate or Hiprex® twice a day is as good at preventing repeated urinary infections in women as taking a once daily dose of antibiotic (antibiotic prophylaxis).

- We have invited you to take part because you have had repeated urinary infections that you and your doctor agree require treatment.

- When doctors don't know which way of treating patients is best we compare different treatments directly to find out. We put patients into groups and give each group one of the different treatments. To try to make sure the groups are the same to start with each patient is put into a group by chance using a computer program. This is called **randomisation.**

- If you agree to take part, we will ask you to sign a consent form and then you will be put into one of the two groups (randomised). One group will be given a once daily antibiotic for a year (prophylaxis), whilst the other group will take Hiprex® twice daily (Morning and Evening) for a year. We will monitor you for a further 6 months after you have finished your treatment to see which treatment is best at preventing the infections from coming back.

- During the course of the study (twelve months of treatment and for six months after you finish treatment) we will ask you to keep a simple diary of any symptoms of urinary infection. We will also ask you to complete a short health questionnaire every 3 months and at any time you have symptoms of a urinary infection. When you finish treatment after 12 months and again after 15 and 18 months we will ask you to fill out a questionnaire about how satisfied you are with the treatment you received.

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- We also intend to collect some samples from you during the study. This will consist of a total of:
    - 7 urine samples – one at the start of the study and one each time you attend for a follow-up visit (every 3 months).
    - 7 blood samples one before treatment begins and then after 3, 6, 9 and 12 months of treatment. There will also be a requirement for 2 additional blood samples in the 6 months after you finish your treatment, one at 15 months and one at 18 months after randomisation.
    - 4 **optional** rectal or perianal swabs – one at the start of the study and one at the 6, 12 and 18 month visits.

- It is possible you may experience some side effects as a result of taking the antibiotics or the Hiprex® in this study. Most people don't have any, but there is more detail on possible side effects in Part 1 of this leaflet.

- You don't have to take part unless you want to do so; your decision will not affect the care you receive from your doctors and nurses. If you agree to take part and change your mind later, you can withdraw from the study at any time. We cannot guarantee that the study will benefit you personally.

- With your permission, we'd like to collect information from your healthcare records that relates to the research. Only individuals connected to the study would have access to these records and all information would remain strictly confidential.

If you are interested in taking part, please continue to read the rest of this leaflet.

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PART 1

What is the purpose of this study?

The ALTAR trial is about finding out whether taking a drug known as Methenamine Hippurate (Hiprex®) twice a day is as good at preventing repeated urinary infections in women as taking a once daily dose of antibiotic (antibiotic prophylaxis). When antibiotics are used too often they become less effective at treating infections and the bugs causing the infection can eventually become resistant to the antibiotic. This means that the treatment may no longer work. Doctors would like to use fewer antibiotics where possible to stop the bugs from becoming resistant, but they need to be able to use another treatment that they know will work at least as well if not better than the antibiotics.

Hiprex® is a non-antibiotic treatment for urinary infection but doctors are not sure if this works as well as antibiotic prophylaxis which is the usual treatment for repeated urine infections.

Why have I been invited?

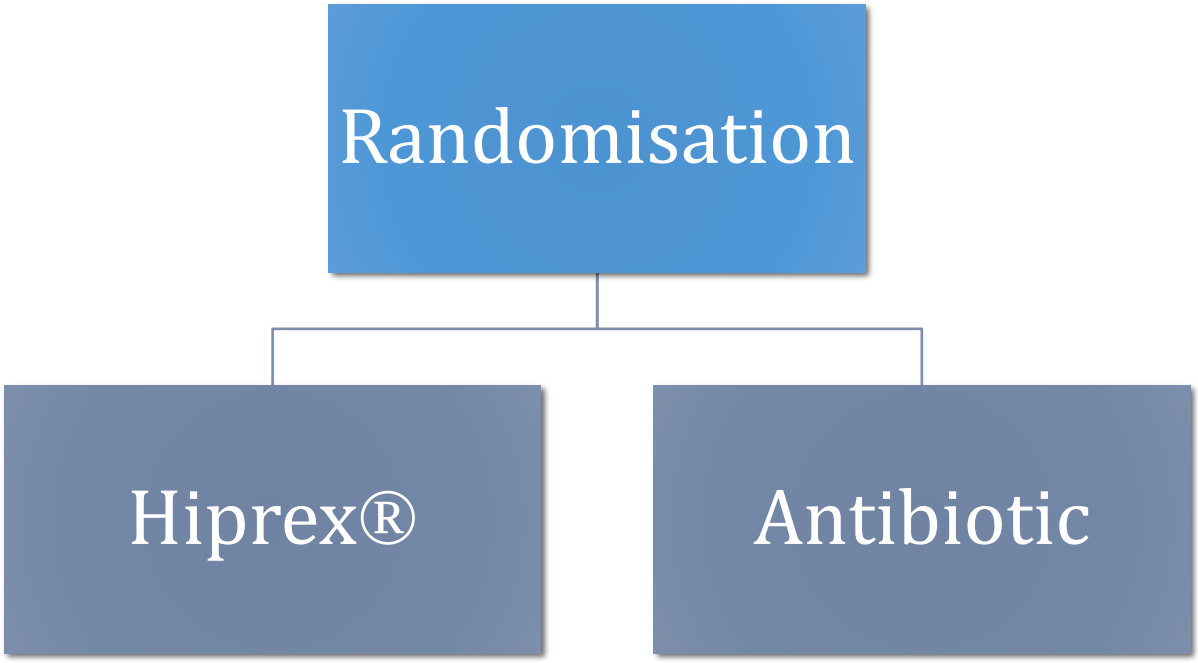
We have invited you to take part because you have had repeated urinary infections that you and your doctor agree requires treatment.

Do I have to take part?

No. It's up to you to decide and your decision won't affect the standard of care you receive. We will describe the study and go through this information sheet with you. If you agree to take part we will ask you to sign a consent form. You can withdraw from this study at any time without giving a reason. Withdrawal from the study would not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part in the study you will go through a process known as randomisation. In the ALTAR study randomisation is performed by a computer programme to ensure the two treatment groups are the same. The randomisation programme decides by chance which treatment option you will receive whilst you are taking part in the study, a bit like flipping a coin. The only thing the randomisation process can do is to select which of the two treatment options you will take for the next year. You will either receive the drug we are testing which is called Hiprex® or you will receive an antibiotic prophylactic which is usually what clinicians choose to treat recurrent urinary infections.



It is important to understand that to take part in the ALTAR trial neither you nor your doctors can decide which of the two options you will have. The computer will select the treatment option at random and you will need to continue with the allocated treatment for a year. To take part you must be prepared to accept whichever treatment is allocated; either Hiprex® or antibiotic.

What will I have to do?

Apart from randomisation we have designed this trial so that your health care is much the same as that which you would usually receive. The extra things that we ask you to do will consist of providing samples for our labs to test and fill out questionnaires relating to your symptoms and your experiences during your time on the study. The samples we will ask you to provide are:

Urine samples: We will ask you to provide a urine sample at the start of your time on the study and then at 3 monthly intervals until the end of your participation in the study (18 months later). A total of 7 urine samples will be collected. If you suffer from a UTI during the study we will also ask you to provide an additional urine sample at this time for our labs to determine the type of bug causing the infection.

Blood samples: : We will ask you to provide a blood sample at the start of your time on the study and then at 3 monthly intervals until the end of your participation in the study (18 months later). A total of 7 blood samples will be collected.

Rectal or Perineal swab: We will ask you to provide a skin swab from the area near to your anus at the start of the study and then at 6 month intervals until the end of your participation in the study at 18 months. You will be asked to provide a total of 4 skin swabs. These swabs are optional but are not invasive and taken from the skin surface near to the anus.

The urine specimens and skin swabs will allow us to keep track of any changes to the 'healthy' bugs on your skin and any harmless bugs in your urine that may be detected when you are on treatment. We will give you the urine specimen pots and swabs together with appropriate packaging to post them back to our laboratory.

The questionnaires tell us how often you have had an infection and what effect this has had on your general health. They will also tell us the impact the infection and treatment is having on your life in terms of cost and benefit. You will be asked to fill them out once before you start the study and at 3, 6, 9, 12, 15 and 18 months during the study. You will

be given a diary to use to keep a record of any urinary infections as they happen – this will make filling in the three-monthly questionnaire easier. When you do get an active infection we will ask you to send us a urine specimen in the post using the secure packaging that we will give you. This will allow us to keep a track of which bugs are causing the infection. We will require you to fill out additional questionnaires at 12 months and 18 months for you to record your satisfaction with the treatment you have received whilst taking part in the trial.

You won't need to worry about remembering to fill the questionnaires in on time – a member of the study team will contact you when they need to be completed. You'll have the option of completing the questionnaires on paper and posting them back to us, or online using our secure website.

Is there anything else I might be asked to do?

With your permission, we'd like to collect information from your healthcare records that relates to the research. Only individuals connected to the study would have access to these records and all information would remain strictly confidential.

We are also conducting an interview study for women who are invited to participate in the ALTAR trial. We are keen to talk to both women who agreed and those who did not agree to take part in the main trial. Exploring the views and experiences of both will help us to improve how we run the main trial and any future trails in this field.

The main aim of the interviews is to find out how women who were invited to take part in the ALTAR trial felt about that and, if they did take part, their experiences of the trial itself. If you are interested in the interview study please let us know and we can provide you with more information. There is a box on the attached consent form for you to initial if you are willing to take part. Your views and opinions will help us to improve the content of the information we give to women, the way in which we recruit women into the study, and how we collect data from the women that take part in the study.

As part of the assessment for the main study we will take a blood sample to check your kidney and liver function. We would like to keep the rest of the blood sample that would otherwise have been thrown away, and store it for future research. This future research may include testing your DNA to find out if differences in any genes make it more likely that a person will get recurrent urinary infections. Researchers will not know your identity and your samples will only be identified by an anonymised code. Your DNA will not be used for any other purposes other than approved medical research. The consent

form attached has a box to initial to indicate that you give permission for us to keep this blood sample for this purpose. Consent is optional and if you do not wish for your sample to be used in this way, simply leave the box blank and your sample will be destroyed after the kidney and liver function tests are completed.

Expenses and payments

You will be seen for review every three months whilst on the study which is slightly more frequent than usual. We will reimburse any extra expenses you incur as a result of taking part so you will not be left out-of-pocket; for example, the cost of travel to the hospital when you wouldn't normally have needed to attend and any prescription charges for study drugs. We will provide pre-paid envelopes for returning questionnaires, swabs and urine samples, so that you don't have to pay for postage.

What are the benefits of taking part?

During the trial you will be under closer follow-up than normal and will learn more about your problem from the information we will give you. It is uncertain as to which treatment will work best and this is why we are doing the study. Whichever group you are allocated to you will be helping to improve the treatment of urinary infections and enabling us to get essential information which will benefit future patients with repeated urinary infections.

What are the disadvantages or risks of taking part?

The disadvantage of randomisation is that you will not be able to choose between the two methods of preventative treatment (Hiprex® or antibiotic) for your recurrent urinary infections; some people may see this as a disadvantage, although you must remember that we do not really know which is better. You should be prepared to have either option for the year of the treatment period of the study. In addition it is usual practice to stop preventative treatment (Hiprex® or antibiotic) after 12 months and we have built this into the study design. You will be monitored for 6 months following completion of treatment. This will allow us to find out if the effects are prolonged when the treatment

stops. We also advise people with health insurance to check if taking part in this study affects them in anyway.

What are the side effects of Hiprex and antibiotic prophylaxis for recurrent urinary infections?

Hiprex is an antiseptic form of prophylaxis (preventative treatment) used as an alternative to antibiotics in the treatment of urine infections. It has no common side effects and very few less common side effects. These are described in the table below. It is possible that women who have experienced side effects in the past when using antibiotic prophylaxis may experience less side effects when using Hiprex®.

Hiprex®

Common (less than 1 in every 10 people)	Less Common (less than 1 in every 100 people)	Rare (less than 1 in every 1000 people)
	• Rashes • Severe itching of the skin without a rash (pruritis) • Gastric irritation • Irritation of the bladder	

The types of antibiotics used for prophylaxis, nitrofurantoin, trimethoprim and cefalexin do not have any common serious side effects. You will likely have already used one or more of them to treat a urinary infection in the past and have some idea which one suits you best in terms of any side effects. If you are randomised to the antibiotic group you and your doctor will be able to discuss which one of the three antibiotics will be best for you to start off with. You can also swap to a different one during the trial if the first one causes problems.

Some people who take the daily antibiotics report minor gut problems like feeling sick (nauseated) and having frequent bowel movements (diarrhoea) but these are usually mild and settle if you swap to a different drug. Women sometimes get thrush (vaginal candidiasis) with trimethoprim or cefalexin but can then use nitrofurantoin instead. The use of any drug should be avoided if possible during pregnancy which is why we will not ask women who are pregnant, or who want to become pregnant, to take part. The great majority of people taking antibiotic prophylaxis for urinary infections don't get any side effects but the more common ones and some of the rare ones for each antibiotic that can

be used are detailed below. In general if a side effect occurs you should stop taking the antibiotic and tell us what has happened but maybe able to start a different one after a period of time.

If you do become pregnant while on the ALTAR study, we will ask that you consent to us following up on your pregnancy and birth.

Nitrofurantoin

Common (less than 1 in every 10 people)	Less Common (less than 1 in every 100 people)	Rare (less than 1 in every 1000 people)
• Feeling as if you are going to be sick (nauseated) • Skin rash (mild allergic reaction)	• Runny or frequent bowel movements (diarrhoea)	• Cough and shortness of breath • Jaundice (yellow skin) and liver inflammation (hepatitis) • Tingling and numbness of the hands and feet • Anaemia (becoming pale and having low blood counts) • Severe allergic reaction (anaphylaxis)

Trimethoprim

Common (less than 1 in every 10 people)	Less Common (less than 1 in every 100 people)	Rare (less than 1 in every 1000 people)
• Feeling as if you are going to be sick (nauseated) • Runny or frequent bowel movements (diarrhoea) • Vaginal thrush in women • Headache • Skin rash (mild allergic reaction)	• High levels of the mineral potassium in the blood	• Anaemia (going pale and having low blood counts) • Cough and shortness of breath • Jaundice (yellow skin) and liver inflammation (hepatitis) • Severe allergic reaction (anaphylaxis) • Joint pains

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Cefalexin

Common (less than 1 in every 10 people)	Less Common (less than 1 in every 100 people)	Rare (less than 1 in every 1000 people)
• Tummy upset (crampy abdominal pain) • Runny or frequent bowel movements (diarrhoea) • Vaginal thrush in women • Skin rash (mild allergic reaction)	• Feeling as if you are going to be sick (nauseated).	• Severe bowel inflammation • Kidney inflammation • Anaemia (going pale and having low blood counts) • Jaundice (yellow skin) and liver inflammation (hepatitis) • Joint pains • Severe allergic reaction (anaphylaxis)

The aim of this study is to find out if the chance of having a urinary infection is no greater when taking methenamine hippurate then it would be if you took a daily antibiotic preventative treatment. Despite taking preventative treatments (methenamine hippurate or antibiotics) you may still suffer from a urinary infection ("break-through infection") and need to take a treatment course of a different antibiotic. If this does occur and you have been allocated the daily antibiotic you should NOT take the daily antibiotic during the time you are taking a treatment course of antibiotics. Once the treatment course has been completed the daily dose of preventative antibiotic can be resumed. If you experience a breakthrough infection whilst taking Methenamine hippurate (Hiprex®) then it is advised you CONTINUE to take you twice daily tablets in conjunction with the course of antibiotics you will receive for the breakthrough infection.

What happens when the research study stops?

Your active participation in the ALTAR study will end 18 months after you begin treatment. If you require further treatment for urine infections after this time then you and your doctor can discuss which treatment might be best for you.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given below.

This completes Part 1 of the information sheet. If the information in Part 1 has interested you and you are thinking about taking part, please read the additional information in **Part 2** before making a decision.

PART 2

What will happen if I don't want to carry on with the study?

If you have problems during the study we will try as far as possible to help you complete the study. However you can withdraw from this study at any time without giving a reason. If you did we would if possible like to continue to collect information from your healthcare records if you were happy for us to. We would also like to use the information you have already given us for our research. We would need your permission to do this if you decide to withdraw.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers first who will do their best to answer your questions (their contact number is 0191 208 7258). If you remain unhappy and wish to complain formally, you can do this through the National Health Service complaints procedure. Details can be obtained from

the Patient Advice and Liaison Service (PALS http://www.pals.nhs.uk/) at your local hospital. Their contact number is [LOCAL PALS CONTACT].

If something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation against the NHS Trust that treated you or the trial's sponsor organisation Newcastle upon Tyne Hospitals NHS Foundation Trust, but you may have to pay your legal costs. The normal NHS complaints mechanisms will always be available to you.

Will my taking part in the study be kept confidential?

Yes. If you agree to take part in this study, the records obtained while you are in the study as well as related health records will remain strictly confidential. Your information will be held securely on paper and electronically at your treating hospital and at the secure trial centre office in the Newcastle Clinical Trials Unit at Newcastle University from where the research is being managed. Your name will not be passed to anyone who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on trial forms. Information about you which leaves the trial offices will have your name and address removed. Your contact details will be kept securely so we can stay in touch regarding your progress and send you the trial questionnaires for you to complete. Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by Newcastle upon Tyne Hospitals NHS Foundation Trust, which is the Sponsor organisation responsible for ensuring that the study is carried out correctly. By signing the study consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study. A requirement of the study's funder is to share the data we collect, with the rest of the research community so that the data can be used to help inform other research and policy development. No recognisable information that can identify you will be shared and your confidentiality will be maintained. We will use secure electronic systems for transferring data.

In line with the regulations, at the end of the study your data will be securely stored for 15 years. Arrangements for confidential destruction will then be made.

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Will my GP be informed of my involvement?

With your permission your GP and other doctors who are treating you will be informed that you are taking part in the ALTAR trial.

What will happen to the results of the research study?

The results will be presented at research meetings, and published on the National Institute for Health Research Health Technology Assessment programme website and in scientific journals. We will also make the results widely available to the public. You will not be identified in any report or publication.

Who is organising and funding the research?

This study is being organised by the Newcastle University's Clinical Trials Unit. It is sponsored within the NHS by the Newcastle upon Tyne Hospitals NHS Foundation Trust and funded by the National Institute for Health Research Health Technology Assessment programme.

Who has approved the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your interests. This study has been reviewed and given favourable opinion by the North East – Tyne & Wear South Research Ethics Committee.

What do I do now?

You will be contacted by a member of the research team. Please let them know whether you would like to take part.