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D-mannose to prevent recurrent urinary tract infections

Submission date	Recruitment status	[X] Prospectively registered
12/11/2018	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[X] Statistical analysis plan
22/01/2019	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
09/10/2024	Urological and Genital Diseases	

Plain English summary of protocol

Background and study aims
Recurrent urinary tract infections (UTIs) have a significant negative impact on quality of life and have a high impact on healthcare costs. To date, antibiotics are the only treatment which has been shown to be beneficial for recurrent UTIs, although a recent large study suggests some benefit from cranberry juice. Reduction in antibiotic use could improve quality of life, save money, and help preserve the usefulness of existing antibiotics. D-mannose is a type of sugar which binds bacteria so that they do not bind to the bladder; it is present in foods such as coffee, baker's yeast, egg white, fruits and legumes. D-mannose has shown benefits in animal models. It is currently available as a food supplement which is used by women who have recurrent UTIs, but there is little evidence to support its use. D-mannose has the potential to offer a valuable alternative to antibiotics in women who experience recurrent UTIs. This study will evaluate whether D-mannose helps women suffering with recurrent UTI presenting to UK primary care and its cost effectiveness.

Who can participate?
Women aged 18 and over with recurrent UTIs

What does the study involve?
Participants are randomly allocated to take either D-mannose or a placebo (dummy) supplement once a day for six months. They are contacted by text/email weekly and a phone call monthly to see if they have had symptoms of a UTI. They are asked to complete a symptom diary every day they experience symptoms of a UTI. Furthermore, they are asked to send in a urine sample when they present to their GP with a suspected UTI, two days after the UTI has resolved and when they are symptom free after two months of using the study product.

What are the possible benefits and risks of participating?
Participants may not experience any direct benefits by taking part. However, it is hoped that this study will benefit future patients who have recurrent UTIs if it is shown that D-mannose helps to reduce UTI episodes or symptoms. There is a slight chance that participants might experience diarrhoea as a previous study showed that 8 in 100 women experienced this, but still felt they were able to continue taking D-mannose.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
January 2019 to September 2021

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
245539

Central Portfolio Management System (CPMS)
40192

Study information

Scientific Title
D-mannose to prevent recurrent urinary tract infections: a double-blind randomised placebo-controlled study

Acronym

MERIT

Study objectives
The hypothesis is that daily use of D-mannose compared with placebo will be effective in preventing symptomatic urinary tract infections (UTIs) in women who experience recurrent UTIs.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 06/12/2018, South West – Central Bristol Research Ethics Committee (Whitefriars Level 3, Block B, Lewin's Mead, Bristol, BS1 2NT, United Kingdom; None available; nrescommittee.southwest-bristol@nhs.net), ref: 18/SW/0245

Study design
Randomised; Interventional; Design type: Prevention, Dietary

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Urinary tract infection

Interventions
This is a two-arm, individually randomised, double-blind placebo-controlled trial. Women will be randomised 1:1 into either placebo or intervention:
Placebo: women will take 2 grams (due to differences in density this can vary between 1.5 and 2.5 grams) of fructose daily for six months
Intervention: women will take 2 grams (due to differences in density this can vary between 1.5 and 2.5 grams) D-mannose daily for six months

Recruitment
Recruitment will be performed by GP surgeries who have agreed to participate in the trial. Patients identified by GP database searches will be invited to take part. Furthermore, posters will be displayed in and near participating GP surgeries and potential participants can contact the research team directly.

Sample size
The aim is to recruit 203 participants in each arm assuming a 20% loss to follow up adding up to 508 participants in total. This sample size is adequate to detect a 50% reduction in the change of a further UTI during the period of prophylaxis.
Qualitative Interviews: 20-25 participants will be recruited across both study arms for the nested qualitative study.

Randomisation
Randomisation will be stratified by practice ensuring a balance of the two arms within each practice. Participants will be randomised to receive 6 months of D-mannose or matched placebo using an allocation ratio of 1:1.

Follow up
All participants will be in the study for six months and during that time they will receive monthly phone calls, weekly texts and the study product by post every other month. They will also be asked to complete a daily symptom diary whenever they experience symptoms of a UTI.

Methods for qualitative interviews
The qualitative researcher will be unblinded to support appropriate participant selection. The topic guide will include participants' experiences and perceptions of recruitment to, and participation in a study requiring a daily treatment (whether D-mannose or placebo), exploring the level of benefit required to continue this type of regime and facilitators and barriers to prophylactic treatment. For participants' convenience, interviews will be conducted by telephone.

Sample handling
After two months of prophylaxis, at a time when participants are asymptomatic (or have the same mild symptoms as usual), they will be asked to send a urine sample to the study laboratory using the packaging supplied at or after their baseline appointment. If the participant presents to ambulatory care with UTI symptoms during the six months following recruitment, they will also be requested to send an additional urine sample to the study laboratory at that time and two days after resolution of symptoms. These samples will be:
1. Cultured using standard NHS laboratory procedures, with bacterial presence recorded to 103 cfu/ml
2. Examined with microscopy to identify epithelial cells, red cells and white cells
3. If further funding is successfully obtained: analysed using visual qualitative techniques, using microbiological assays to evaluate adhesion and invasion of the urothelium, phylotyping techniques and next generation DNA sequencing techniques

Although urine samples are generally assumed to be sterile, there is a small possibility that trace amounts (<0.1%) of human DNA may be found in these samples using sequencing techniques. When the DNA samples are sequenced and electronic DNA sequences generated, the trialists will immediately use an automated computer programme that looks for human DNA and removes it, without performing any analysis, so that stored electronic DNA sequences on University servers, which are subsequently analysed, have these trace amounts removed.

Consent will be sought to store the frozen samples and to perform a range of additional anonymous biochemical and microbiological analyses relevant to UTI, including in vitro mechanistic studies and work by commercial parties within the EU and outside. The samples will be labelled according to laboratory procedures, including participant ID and date of collection.

Intervention Type
Supplement

Primary outcome(s)
The proportion of women experiencing at least one further episode of clinically suspected UTI for which they contact ambulatory care (Out of hour (OOH) primary care, in hours primary care, ambulance or A and E). Assessed by medical notes review within 6 months of study entry.

Key secondary outcome(s))
Secondary outcome measures:
1. Number of days of moderately bad (or worse) symptoms of UTI, assessed using a participant diary throughout the study

2. Time to next consultation with a clinically suspected UTI, assessed during a notes review 6 months after study entry
3. Number of clinically suspected UTIs, assessed during a notes review 6 months after study entry
4. Number of microbiologically proven UTIs, assessed during a notes review 6 months after study entry
5. Number of antibiotic courses for UTI; DDD and total mg by antibiotic type, assessed during a notes review 6 months after study entry
6. Report of consumption of antibiotics using diary during periods of infection, recorded in the participant diary throughout the study
7. Proportion of women with a resistant uropathogen cultured during an episode of acute infection, assessed during a notes review 6 months after study entry
8. Hospital admissions related to UTI, assessed during a notes review 6 months after study entry
9. Quality of life recorded in the participant diary at baseline, 6 months and during UTI episodes on day 1, 3 and 5
10. Healthcare utilisation recorded in the participant diary and during a notes review 6 months after study entry
11. Acceptability and process evaluation conducted via telephone interviews with up to 25 women throughout the study

Tertiary outcome measures:
1. Antibiotic usage and urine culture results in the five years prior to study entry, assessed during a notes review 6 months after study entry
2. Urine culture results for samples sent during the study period, recorded in the lab results
3. (Dependent on further funding): Patterns of microbial presence as demonstrated by Next Generation DNA Sequencing in RUTI, exploring association between frequency of infection and microbial presence and evaluating the impact of D-mannose on microbial presence, assessed throughout study

Completion date
30/09/2021

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the study
2. Participant is able to comply with study procedures
3. Female, aged 18 years or above
4. Presented to ambulatory care with symptoms consistent with UTI three or more times in the last year or two or more times in the last six months

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Total final enrolment
598

Key exclusion criteria
1. Female participant who is pregnant, lactating or planning pregnancy during the course of the study
2. Formal diagnosis of interstitial cystitis or overactive bladder syndrome
3. Prophylactic antibiotics started in the last 3 months and unwilling to discontinue, or intention to start during the next 6 months
4. Currently using D-mannose and unwilling to discontinue for the duration of the study
5. Nursing home resident. Residential home residents will not be excluded
6. Catheterised, including intermittent self-catheterisation
7. Use of Uromune (an 'immunostimulant')
8. Participants who have participated in a research study involving an investigational product in the past twelve weeks
9. Previous participation in this study

Date of first enrolment
18/03/2019

Date of final enrolment
01/02/2020

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
Primary Care Clinical Trials Unit
Nuffield Department of Primary Care Health Sciences, University of Oxford
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research (NIHR); Grant Codes: 385

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
IPD sharing plan as of 29/04/2024:
The datasets generated during and/or analysed during the current study are/will be available upon request via PrimDISC (primdisc@phc.ox.ac.uk) at https://www.phc.ox.ac.uk/intranet/better-workplace-groups-committees-open-meetings/primdisc-committee.

Previous IPD sharing plan:
Once publications are complete, study data will be available to share with qualifying researchers who submit a proposal with a valuable research question as assessed by a committee formed from the trial management group, including senior statistical and clinical representation. Interested researchers should contact Gail Hayward (gail.hayward@phc.ox.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		08/04/2024	09/04/2024	Yes	No
Protocol article	protocol	13/01/2021	15/01/2021	Yes	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan	version 1.0	15/02/2021	18/04/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes