Study Protocol

Background:

Urinary tract infection (UTI) is a common infection of the urethra, bladder and/or kidneys, commonly associated with symptoms including needing to urinate more frequently and urgently than normal, a painful or burning sensation during or after urination, among others.

Recurrent UTI (rUTI) is defined as experiencing either two or more UTI episodes in six months or three or more in one year. This chronic condition is debilitating, with existing research indicating a significant impact to quality of life and considerable socioeconomic burden. However, the majority of existing research in this area focuses on the causes behind the condition and treatment options while considering antimicrobial resistance, for example. This means that the patient-reported experience of what it means to live with rUTI is often neglected.

Clinical diagnosis of a UTI often requires positive urine dipstick or urine culture results. However, it is understood that these tests may not be consistently reliable. This can lead to missed diagnosis, and potentially missed treatment, of UTI episodes, in turn leading to prolonged symptoms and feelings of patient dissatisfaction.

A patient-reported outcome measure (PROM) is a measurement tool which can be used to gain insight into a patient's own perspective on certain aspects of their health. For example, a PROM may seek to understand a patient's views on how severe they feel their symptoms are, or how much their condition has interfered with their lifestyle. PROMs are typically designed to be used alongside clinical outcome measures, e.g. urinalysis results, in order to build a more holistic picture of the patient's health and health-related quality of life.

While there are several generic PROMs which effectively measure areas relevant to rUTI, e.g., health-related quality of life (e.g. 36-Item Short Form Survey), there are no existing validated rUTI-specific PROMs. Condition-specific PROMs can be especially useful in gathering information about aspects of health which may be unique to or present differently in the relevant patient population, and it is recommended that they are used as well as generic PROMs. In this study, we aim to develop and validate two new rUTI-specific PROMs: one measuring rUTI symptoms and symptom intensity, and one measuring rUTI impact. Our intention is that these measures could be used to assess effectiveness of treatments and interventions for people living with rUTI.

A crucial element of PROM development is the involvement of patients. This study will ground its development in existing qualitative research of rUTI patient experiences as well as conducting cognitive interviews with rUTI patients to obtain their perspective on whether the PROM questions are appropriate and valid for the population and their experiences of rUTI. Following this, pilot data collection of the PROMs alongside existing standardised measures of contextually relevant health aspects (e.g. pain) will be conducted to perform further statistical validity checks. The cognitive interviewing and piloting of the PROMs may include a mild risk of anxiety or discomfort due to the sensitive nature of some questions and need to reflect on potentially challenging experiences. Participants will maintain the right to withdraw at any point and will be encouraged to seek support from their GP/healthcare professional if needed.

Research Questions:

Primary aims:

1. To develop a patient-reported outcome measure of rUTI symptoms.
2. To develop a patient-reported outcome measure of rUTI impact.

Secondary aims:

1. To validate the rUTI symptom PROM by conducting statistical tests of its internal consistency, test-retest reliability, construct validity and criterion validity.

2. To validate the rUTI impact PROM by conducting statistical tests of its internal consistency, test-retest reliability, construct validity and criterion validity.

Design and Procedure:
An initial rUTI symptom scale and rUTI impact questionnaire have been developed based on existing qualitative research and literature review. The rUTI Symptom Scale includes a UTI-related symptom intensity subscale, and a UTI-pain intensity sub-scale. This PROM is designed to assess symptom intensity over the past 24 hours. The rUTI Impact Questionnaire includes a personal wellbeing subscale (covering psychological wellbeing and sleep/exercise disruption), a social subscale (covering social impact, isolation and anxiety), a work impact subscale, a sexual subscale (covering sexual impact and pain), and a patient satisfaction subscale. This PROM is designed to assess rUTI impact over the past two weeks.

A three-stage methodology will be employed:

(1) **Expert screening for content validity**

Following ethical approval, these PROMs will be initially screened for content validity by a 6–10 experts in the domain of rUTI and general medicine. Between 6–10 experts in medical fields relevant to rUTI will be required to participate in one-to-one interviews, an appropriate sample size for calculating content validity (Yusoff, 2019). A modified two-stage Delphi methodology will be implemented, obtaining experts' views over two "rounds" in order to reach consensus on item validity via a survey built in REDCap. The second round will take place 28 days after the first.

In the first round, participants will be asked to read the Information Sheet and sign the Consent Form before completing the demographics questionnaire. Then, they will be asked to rate each questionnaire item for relevance within the field of recurrent UTI on a scale of 1 (not relevant at all) to 9 (highly relevant), and for clarity, on a similar scale (1 (not clear at all) to 9 (very clear). This scaling system is the most commonly used in Delphi studies (McMillan et al., 2016). Participants will also be invited to provide free-text qualitative feedback to justify their ratings. They will also be asked if they have any general comments about each PROM. Participants will be provided with a debrief form at the end, reminding them to look out for their reminder email in 28 days' time with the link to access the second and final part of the study.

In the second round, participants will be asked to do this again, except now being provided with their previous relevance and clarity ratings, the median rating across all expert-scores, and a diverse selection of the free-text comments received in the first round. Participants will be able to retain their original scores or make changes, giving additional free-text responses if desired. In this survey, there will be an updated information sheet, consent form and debrief form. This step will provide us with both content validity and clarity scores as well as qualitative feedback on the measures. This feedback will allow for further refinement of the PROMs before the main participant studies are conducted, as detailed below in steps 2 and 3.

(2) **Cognitive interviewing and at-home completion of the rUTI Symptom PROM:**

A diverse sample of adults with recurrent UTI will be recruited to participate. To obtain diversity of perspectives, approximately 10 participants from the UK, 10 from the USA, and 10 from Canada will be sought. The link to the REDCap page which contains the Participant Information Sheet, Consent Form and Demographics Questionnaire will be advertised. Participants who wish to take part should complete the consent form and demographics questionnaire, agreeing for the researchers to screen them for potential participation in the study. Participants will be selected based on the later-described sampling criteria. This Information Sheet details the aims and background of the study, what potential participation will involve and for how long, the possible risks, information on the storage of participant data, and the right to

withdraw at any point. Participants will need to read and sign the online Consent Form to confirm that they have read and understood the information provided to them.

Selected participants will be contacted to arrange a suitable time for an online one-to-one semi-structured interview via Microsoft Teams. It is expected that the interview will take approximately 45-60 minutes, and it will both be audio- and video-recorded with the permission of the participant. The interviewer will use the "screensharing" function to display the PROMs during each interview, having emailed PDF copies to the participant in case of any connectivity issues.

During the interview, the interviewer (AN) will flexibly use the topic guide to appropriately focus the discussion. Firstly, the interviewer will go through the information sheet with the participant again and describe the procedure in full, providing the opportunity for questions or clarification. The interviewer will check that the participant can view the PDF copies of the PROMs during the interview, in case the screen-sharing feature does not work effectively due to connectivity issues. Then, starting with the rUTI symptom PROM, the interviewer will ask each questionnaire item to the participant, inviting them to "think aloud" (i.e. share their thought processes out loud) while thinking of their responses. The interviewer will use a mixture of the prescribed "verbal probes" in the topic guide and spontaneous open-ended verbal probes thought of at the time to help participants to elaborate.

The same procedure will apply for the rUTI impact PROM. After completing both questionnaires, the interviewer will thank the participant for their time, provide them with the opportunity to ask any questions, and describe what will happen next in the wider research project and how their feedback will be used. The participant will be provided with the Debrief Form which provides them with recommended links to access support should they need it. This form will also invite participants to contact the researchers should they wish to receive a copy of the final PROMs and/or report.

Due to the personal nature of some questions in both rUTI PROMs and the need for participants to reflect on their experiences of living with their chronic illness, there is a mild risk that participants may experience negative feelings such as anxiety. This is explained in the Information Sheet and will also be explained verbally at the start of the interview, and the participants reminded of their right to withdraw from the study/interview at any point.

After one "round" of cognitive interviews, both the rUTI symptom and impact PROMs will be refined based on findings. A second "round" will then take place with a new set of participants with rUTI, before further refinement ahead of the pilot study.

It is planned that approximately 30 participants will be recruited to participate in cognitive interviews across rounds 1 and 2, as described in the procedure section. A sample size of approximately 30 participants is recommended to sufficiently perform pre-tests of new psychometric questionnaires (Perneger et al., 2015). It is suggested that smaller samples of between 5-15 participants "may fail to uncover even common problems" of misunderstandings and ambiguities in instrument items. In a similar PROM development study to this rUTI study, which developed two new symptom and impact PROMs for endometriosis, recruited a sample of 31 participants for their cognitive interviews, also split across two interview rounds (Gater et al., 2020).

(3) **Online pilot of rUTI PROMs and other comparable measures:**

To obtain data to perform statistical validity checks of these two new PROMs among comparable other measures, a two-part online survey of adult rUTI patients will then be conducted. Parts 1 and 2, which will be separated by 24 hours which to allow for test-retest reliability assessment, will follow identical procedures (with the exception of Part 1 additionally including a demographics questionnaire). It is planned that a minimum of 132 participants will be recruited to take part in the online PROM data collection stage. A minimum of 100 participants will be

required to complete both parts, based on the COSMIN guidelines (Mokkink et al., 2018) and common practice for conducting exploratory factor analysis (Fabrigar et al., 1999). With an anticipated attrition rate of 25%, based on that found in a study examining retention rates in health outcome measure surveys (Hall et al., 2018), a minimum of 132 participants should be recruited to retain adequate statistical power.

The Part 1 online survey, built in REDCap, will start with a Participant Information Sheet and then Consent Form. Participants who wish to take part will be able to complete this survey virtually, e.g. from home. The Information Sheet is similar to the one used in the cognitive interviewing stage, except the procedure description is updated accordingly. In order to access the main study, the participant will be required to confirm their consent by ticking each item on the Consent Form page and providing an electronic signature. They will then access and complete a Demographics Questionnaire.

The rest of the survey will present a series of questionnaires to the participant. Two will be the new rUTI PROMs which we have developed and refined, and there will also be a number of existing standardised measures which measure similar concepts of symptom intensity and health impact: the symptom severity subscale of the UTI Symptom Assessment (Clayson et al., 2005), Numerical Pain Rating Scale (Jensen & Karoly, 2011), UCLA Loneliness Scale Version 3 (Russell, 1996), Work Productivity and Activity Impairment questionnaire (Reilly et al., 1993), Female Sexual Distress Scale – Revised (Derogatis et al., 2008), Patient Satisfaction Questionnaire Short-Form (Marshall & Hays, 1994), Generalised Anxiety Disorder – 7 (Spitzer et al., 2006), and Patient Health Questionnaire – 9 (Kroenke et al., 2001). It is explained in the Information Sheet that the participant may be asked questions which seem to measure the same thing; this is due to the inherent similarity in some of the measures and the participant should continue to answer all questions in the survey. It is expected that the total survey will take the participants approximately 30 minutes to complete, which is noted in the Information Sheet.

At the end of the survey, the participant will be shown a Debrief Form which provides them with the aforementioned recommended links to access rUTI or mental health support should they need/want it, and reminds them that in 24 hours' time they will receive an email with a link to access and complete the Part 2 survey. The link in this email will be unique for each participant, linking their Part 1 and Part 2 responses in REDCap.

The Part 2 survey, to be completed approximately 24 hours' after Part 1, follows the exact same procedure as in Part 1, with the wording updated in the Participant Information Sheet, Consent Form and Debrief Form to reflect that this is the final part of their participation and no more communication will be required following this step. As in the cognitive interview debrief form, participants will be invited to contact the researchers should they wish to receive a copy of the final PROMs and/or report. The same mild risk of feelings of anxiety in the cognitive interview stage applies here. Similarly, participants will be fully informed of this possible risk and the reasons for the personal nature of the questions asked, as well as their right to stop their participation at any point.

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