

Cranberry extract for symptoms of acute, uncomplicated Urinary Tract Infection

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I dedicate this thesis to my Mum and Dad. Thank you for your unwavering love and support.

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List of Abbreviations

ACF – Academic Clinical Fellowship

AE – Adverse Event

CFU – Colony Forming Units

CI – Chief Investigator or Confidence Interval

COVID-19 – Coronavirus disease 2019

CRF – Case Report Form

CRN – Clinical Research Network

CUTI - Cranberry for Urinary Tract Infection

DMC – Data Monitoring Committee

E.coli – Escherichia coli

EMIS – Egton Medical Information Systems

GP – General Practitioner

HR – Hazard ratio

ICER – Incremental Cost-Effectiveness Ratio

ICF – Informed Consent Form

ICTRP – International Clinical Trials Registry Platform

ID – Identification

IQR – Interquartile range

IRR – Incidence Rate Ratio

ITT – Intention to treat

MD – Mean Difference

MSU – Midstream Urine

NAPCRG - North Atlantic Primary Care Research Group

NDPCHS – Nuffield Department for Primary Care Health Sciences

NHS – National Health Service

NICE - National Institute for Health and Care Excellence

NIHR – National Institute for Health Research

NSAID – Non-Steroidal Anti-Inflammatory Drugs

O&G – Obstetrics and Gynaecology

OR – Odds ratio

OTC - Over-the-counter

PAC – Proanthocyanidins

PAC-A – Proanthocyanidins with A-type linkages

PAC-B - Proanthocyanidins with B-type linkages

PHE – Public Health England

PI – Principle Investigator

PIL - Participant Information Leaflet

PPI – Patient and Public Involvement

QALY – Quality Adjusted Life Year

RCT – Randomised Clinical Trial

REDCap – Research Electronic Data Capture

RISP – Research Information Sheet for Practices

RTI – Respiratory Tract Infection

SAE - Serious Adverse Event

SAP – Statistical Analysis Plan

SD – Standard Deviation

SIGN - Scottish Intercollegiate Guidelines Network

SIVs - Site initiation visits

SOP- Standard operating Procedure

TMG – Trial Management Group

TSC – Trial Steering Committee

UK – United Kingdom

UTI – Urinary Tract Infection

WHO – World Health Organisation

Abstract

Background

There is growing interest in using non-antibiotic treatments for common bacterial infections, such as Urinary Tract Infections (UTI). One potential non-antibiotic treatment for acute uncomplicated UTI is cranberry extract.

Methods

The existing evidence for using cranberry extract to treat acute, uncomplicated UTIs was systematically reviewed. An open-label, randomised feasibility trial was conducted to determine the feasibility of trialling cranberry extract as a treatment for symptoms of acute, uncomplicated UTI in primary care. Adult women with acute UTI symptoms were randomly assigned to one of three groups: 1) Immediate antibiotic prescription (controls) 2) Immediate antibiotic prescription and immediate cranberry capsules 3) Immediate cranberry capsules and a delayed antibiotic prescription. Two qualitative studies were embedded within the feasibility trial: The first was conducted with UTI patients (both participants and non-participants of the feasibility trial); and the second was conducted with feasibility trial recruiters.

Results

The systematic review found that the evidence base for or against using cranberry extract for treating acute UTIs was limited. Four General Practices (100% of target) recruited to the feasibility trial, with nine participants recruited per month on average. Forty-six participants were recruited (one beyond target). 89.1% (41/46) of electronic symptom diaries contained some participant entered data, and 69.6% (32/46) were fully completed.

Interviewed UTI patients (n=26) and recruiters (n=8) felt that the feasibility trial addressed an important question, and generally found trial processes straightforward. Many UTI patients indicated that they would be happy to delay antibiotic treatment and try initial symptomatic treatment, such as cranberry extract, for acute UTI symptoms in certain circumstances (e.g. with milder symptoms).

Conclusions

The safety and effectiveness of using cranberry extract as a treatment for acute, uncomplicated UTIs represents an evidence gap. The present research programme demonstrates that it is feasible and acceptable to UTI patients to trial cranberry extract for managing symptoms of acute, uncomplicated UTIs. Having established the feasibility of this approach, an adequately powered efficacy trial of cranberry extract for acute UTI is indicated.

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Statement of Contribution

Chapter 2

Dr Nia Roberts (NR – specialist librarian) provided assistance with search terms for the systematic review.

Dr Elizabeth Spencer (ES) and Dr Joseph Lee (JL) – departmental researchers - conducted dual: Title and abstract screening; full text screening; data extraction from included studies; and risk of bias assessment of included studies.

Chapter 3

Ms Christine Symon (CS) in the Clinical Research Network presented the Research Information Sheet for Practices (RISP) to research active General Practices.

Mrs Nicola Williams (NW – senior statistician) generated the randomisation sequence for the feasibility trial.

Ms Rui Zhao (RZ), Mr Luis Castello (LC) and Mr David Judge (DJ) – data programmers - built the REDCap and Sentry electronic databases that were used to store participant data.

Ms Maria Coates (MC – trial administrator) manned the trial telephone when I was out of office, and forwarded telephone messages to me.

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Dr Christine A'Court (CA – General Practitioner Research Champion) built the Egton Medical Information Systems (EMIS) Web search strategy that was used at the interview study General Practice.

Dr Chloe Evans (General Practitioner) ran the EMIS Web search at the interview study General Practice.

Mr Dan Richards-Doran (DRD – head of communications) created two posters to advertise the trial and interview studies, respectively.

Chapter 6

The lay explainer video of the CUTI feasibility trial was created by a freelance video animator.

Dr David Gillespie (DG – statistician) ran the efficacy trial sample size calculation based on data that I provided.

1. Chapter 1: Introduction

1.1. The problem of antimicrobial resistance

Alexander Fleming discovered the world's first antibiotic, Penicillin, in 1928 (1). This discovery, and the subsequent development of other antibiotic classes, has saved many millions of lives (2). However, an unintended consequence has been antibiotic resistance. Antibiotic resistance is the ability of bacteria to escape being killed by antibiotics (3). The use of antibiotics places selection pressures on bacteria (4). Random mutations in bacterial genetic material leads to some bacteria having a survival advantage over others (5). For example, these mutations may prevent antibiotics from binding to the bacterial cell surface, or allow bacteria to neutralise the effects of antibiotics (5). These gain of function mutations confer a survival advantage over other bacteria, leading to a predominance of resistant bacteria through 'survival of the fittest'. Furthermore, bacteria are able to share their genetic material (plasmids) with other bacteria through horizontal gene transfer, allowing resistant bacteria to propagate (4). The more that antibiotics are used, the greater the selection pressure placed on bacteria, and the more likely they are to develop antibiotic resistance.

If antibiotic consumption is not reduced, we may reach a stage at which simple infections are no longer susceptible to available antibiotics (6). This is exacerbated by the fact that there have been no new classes of antibiotic discovered in the past four decades (7). Whilst the Coronavirus disease 2019 (COVID-19) pandemic has been raging, Dame Sally Davies, United Kingdom special envoy on antimicrobial resistance and erstwhile Chief Medical Officer for England, has described antimicrobial resistance as the "silent global pandemic" that must not be ignored (8). In 2019, the National Institute for Health Research (NIHR)

launched a new campaign to tackle antimicrobial resistance (7), and has highlighted the importance of research in abating the impending antibiotic resistance crisis as a consequence of "excessive and inappropriate" antibiotic use. The World Health Organisation (WHO) describes antibiotic resistance as "one of the biggest threats to global health." (9) The WHO launched a global action plan to tackle antimicrobial resistance in 2015, which included strengthening research and optimising antimicrobial use (9).

1.2. Antibiotic consumption for Urinary Tract Infection

In the UK, 71.4% of all antibiotics are prescribed by primary care clinicians (10). Acute Urinary Tract Infection (UTI) represents an attractive target for reducing antibiotic consumption in primary care. Firstly, acute UTIs are common, accounting for up to 3% of all primary care consultations (11, 12), costing the National Health Service (NHS) approximately £270,000,000 per annum (13, 14), and are responsible for nearly 14% of all antibiotic prescriptions in primary care (12). Secondly, acute UTIs are almost always managed with an immediate antibiotic prescription (15), yet, most acute UTIs are uncomplicated and typically have a self-limiting course (15). Uncomplicated UTIs are UTIs occurring in women with no underlying urinary tract abnormalities, and with no signs of an upper UTI (e.g. fever or loin pain) (16). Up to 90% of uncomplicated UTIs are caused by infection with uropathogenic *Escherichia. coli (E.coli)* (17). Uropathogenic *E.coli* attach to the uroepithelial surface to form a biofilm using Type 1 (mannose-sensitive) fimbriae and P-fimbriae (18, 19).

E.coli urinary isolates are resistant to many commonly used antibiotics; 52% are resistant to amoxicillin, 36% are resistant to Trimethoprim, 12% are resistant to Ciprofloxacin and

11% are resistant to cephalexin (20). Antibiotic resistant *E.coli* UTIs are associated with significantly increased odds of feeling unwell for over five days [odds ratio 1.41 (95% CI: 1.07 to 1.87)] and of re-consulting a General Practitioner (GP) within 30 days [odds ratio 1.47 (95% CI: 1.10 to 1.95)] compared with antibiotic sensitive *E.coli* UTIs (21). One of the leading risk factors for developing an antibiotic resistant UTI is recent antibiotic use for a UTI (22). In a meta-analysis of five studies, the odds of culturing resistant bacteria from the urinary tract were over four times higher in those who had received antibiotics in the past month, compared with those who had not [pooled odds ratio 4.40 (95% CI: 3.78 to 5.12)] (23). This association waned with time, but persisted for up to 12 months [pooled odds ratio 1.33 (95% CI: 1.15 to 1.53)] (23).

E.coli infection is the commonest cause of bacteraemia; it is the causative organism in 23% of cases (24). The rise in *E.coli* resistant UTIs is contributing to the increasing incidence of *E.coli* bacteraemia, which has had an upward trajectory since Public Health England (PHE) annual laboratory surveillance reports of *E.coli* bacteraemia in 2009 (25). The prevalence of *E.coli* bacteraemia increased from 55.2 per 100,000 in 2014, to 60.2 per 100,000 in 2015, to 65.3 per 100,000 in 2016, to 69.2 per 100,000 in 2017, and was 70.7 per 100,000 in 2018 (25). Approximately half of *E.coli* bacteraemias are due to UTI (26), the majority of which (up to 57%) are caused by community acquired UTI (rather than nosocomial) (27). There were approximately 40,000 *E.coli* bacteraemias in England from February 2020 to February 2021 (28), with mortality approaching 20% (26). E.coli bacteraemia is associated with an excess length of hospital stay of four days, and an annual cost to the NHS of £14.3 million (29). E.coli bacteraemia therefore has a substantial impact on morbidity and mortality, and causes an economic burden.

An observational study of antibiotic use in 26 European countries demonstrated that increased outpatient prescription of antibiotics is associated with increased antibiotic resistance (30). Conversely, reduced outpatient antibiotic prescription is associated with reduced antibiotic resistance (31). An observational study investigating the association between changes in antibiotic dispensing and changes in antibiotic resistance in bacterial isolates from urine samples in General Practices in Wales found that reduced antibiotic dispensing was associated with a statistically significant decrease in ampicillin and trimethoprim resistance (31). Over a seven year period, the quartile of General Practices that reduced their ampicillin and trimethoprim prescribing the most resulted in significant reductions in ampicillin resistant [5.2% reduction (95% CI: 2.9% to 7.4%)] and trimethoprim resistant [3.4% reduction (95% CI: 1.3% to 5.4%)] urinary isolates, respectively (31). There is therefore good reason to try to reduce antibiotic prescribing and consumption for acute UTI.

1.3. Non-antibiotic management of acute Urinary Tract Infection

A meta-analysis of five trials comparing treatment of acute UTIs with antibiotics versus placebo found that treatment with antibiotics led to better symptom and microbiological outcomes, but safety outcomes were comparable (32). The meta-analysis found that clinical cure was significantly more likely in those women receiving antibiotic treatment [four randomised clinical trials (RCTs); odds ratio 4.81, 95% CI: 2.51 to 9.21] (32). This was also the case for microbiological success, defined by the authors as a negative urine culture at the end of treatment [three RCTs; odds ratio 10.67, 95% CI: 2.96 to 38.43] (32). There was a non-significant increase in the odds of pyelonephritis in women receiving placebo [two RCTs; odds ratio 0.33, 95% CI: 0.04 to 2.70], but significantly higher odds

of experiencing adverse events in women receiving antibiotics [four RCTs; odds ratio 1.64, 95% CI: 1.10 to 2.44] (32).

The delayed antibiotic approach has also been trialled. A trial by Little *et al* assessed the effectiveness of five different approaches to managing acute UTI, namely: Immediate empirical antibiotics; antibiotics dependent on having two or more cardinal UTI symptoms; antibiotics dependent on a positive urine dipstick; antibiotics dependent on a positive urine culture result; or empirical delayed antibiotics (waiting 48 hours) (33). Compared with taking immediate empirical antibiotics (97% consumed antibiotics), the other four management strategies all led to a reduction in the proportion of women consuming antibiotics. This reduction was most significant in the empirical delayed antibiotics group [77% consumed antibiotics; odds ratio 0.12 (95% CI: 0.03 to 0.59)] (33). There were no significant differences between groups in terms of symptom control, although those women delaying their antibiotics for 48 hours or more experienced symptoms rated moderately bad or worse for longer [incidence rate ratio 1.37 (95% CI: 1.11 to 1.68); $p<0.001$] (33). No serious adverse events occurred.

Trials of non-steroidal anti-inflammatory drugs (NSAIDs) as a symptomatic treatment for UTI have been conducted. The first of these was a double-blind, randomised controlled pilot trial of 80 women presenting to primary care in Germany with symptoms of acute, uncomplicated UTI (34). Women were randomly assigned to receive a three day course of either ibuprofen or ciprofloxacin. There was no significant difference between groups in symptom resolution by day four ($p=0.744$) or day seven ($p=0.306$), nor in the mean symptom score between day zero and day seven ($p=0.816$) (34). Two thirds of women in the ibuprofen group recovered without antibiotics (34). Adverse events occurred fairly

evenly between groups, with none believed to be related to the trial treatments, and no reported episodes of pyelonephritis (34).

The same group of authors subsequently conducted an adequately powered double-blind randomised trial of similar design comparing ibuprofen with fosfomycin in 494 women presenting to primary care with acute UTI (35). Significantly fewer women consumed antibiotics up to 28 days in the ibuprofen group compared with the fosfomycin group [mean difference -64.7% (95% CI: -70.7% to -58.7%)], however, the symptom burden was significantly higher in the ibuprofen group [mean difference 5.3% (95% CI: 3.5% to 7%)] (35). There was no significant difference in serious adverse events between groups (2% in the ibuprofen group versus 0% in the fosfomycin group, p=0.06), nor in episodes of pyelonephritis (2% in ibuprofen group, 0.4% in fosfomycin group, p=0.12) (35).

Comparable results have been found in two further trials of NSAIDs. In a randomised, double-blind trial of 253 women presenting to Swiss primary care with acute, uncomplicated UTI, significantly more women achieved the primary outcome of symptom resolution by day 3 of the trial in the norfloxacin group compared with the diclofenac group [risk difference 27% (95% CI: 15% to 38%), p<0.001] (36). However, significantly fewer women consumed antibiotics up to day 30 of the trial in the diclofenac group [risk difference 40% (95% CI: 29% to 51%), p<0.001] (36). There were significantly more episodes of pyelonephritis in the diclofenac group [risk difference 5% (95% CI:1% to 8%), p =0.031], and also significantly more adverse events related to UTI (such as recurrent UTI and persistent symptoms) in the diclofenac group [risk difference 11% (95% CI: 3% to 20%), p=0.012] (36). In a further randomised, double-blind trial of 383 women with acute UTI, the primary outcome of feeling cured by day 4 was achieved in significantly

more women receiving pivmecillinam compared with ibuprofen [74% versus 39%, adjusted risk difference 35% (95% CI: 27% to 43%)] (37). All seven cases of pyelonephritis occurred in the ibuprofen group [adjusted risk difference -4% (95% CI: -8% to -1%)]; five of these patients were hospitalised (37). The seemingly worse adverse event profile and higher risk of progression to pyelonephritis in trials of women taking NSAIDs, compared with women taking placebo in trials of acute UTI, has led to the suggestion that NSAIDs may in some cases have a detrimental effect on the host response to UTI (38).

Herbal treatments have also been tested as a possible means of managing acute UTIs. The herbal medicine *uva ursi* was trialled alongside ibuprofen in women presenting to primary care in the United Kingdom (UK) with an acute UTI. A two-by-two, factorial, randomised, double-blind design was employed. Women were randomly assigned to either *uva ursi* or placebo; half of the women in each of the two groups were additionally advised to take ibuprofen (39). All women received a delayed antibiotic prescription. There was no significant difference in the primary outcome of mean urinary frequency severity (which included patient ratings of frequency, urgency and dysuria) from days two to four inclusive between women receiving *uva ursi* and women receiving placebo [least squares mean difference -0.06 (95% CI: -0.33 to 0.21), p=0.661] (39). This was also the case when the result was adjusted for antibiotic use [least squares mean difference -0.05 (95% CI: -0.32 to 0.21), p=0.704] (39). No episodes of pyelonephritis occurred in this trial; the authors suggest that this may have been a result of all participants receiving a delayed antibiotic prescription, or because women with more severe symptoms were less likely to take part due to the lack of an immediate antibiotic arm (39).

The herbal extract Canephron (containing centaury powder, lovage root powder and rosemary leaf powder) was trialled against fosfomycin in a randomised, double-blind trial of 659 presenting to primary care centres in Europe with acute UTI symptoms (40). The authors found that Canephron was non-inferior to fosfomycin with respect to the primary outcome of requiring additional antibiotic between days 1 and 38 [16.49% versus 10.23% required antibiotics in Canephron versus fosmfomycin groups, respectively; difference -6.26% (95% CI: -11.99 to -0.53%, p=0.0014); non-inferiority margin pre-specified at -15%] (40). Mean symptom scores were significantly lower in the fosfomycin group at day 4 (p=0.0166), but not by day 8 or at the end of follow-up (p>0.05) (40). More cases of pyelonephritis occurred in women taking Canephron (n=5) compared with women taking fosfomycin (n=1) (40).

1.4. Cranberry extract as a candidate non-antibiotic acute UTI treatment

Cranberry fruit (*Vaccinium macrocarpon*) is native to North America (41), and is classed as a functional food due to the naturally high content of compounds such as polyphenols, which are believed to have antioxidant and health-promoting properties (42). Wide-ranging health benefits from cranberry consumption have been reported, from cardio-protective effects due to improved cholesterol profiles (43) to aiding digestive health (44). Cranberry exists in various forms, such as the raw fruit (fresh and dried), cranberry juice and cranberry extract in capsule/tablet formulations (45).

Many *ex vivo* and *in vitro* studies have been conducted to determine whether there is an effect of cranberry extract on uropathogens, specifically *E.coli*. Initial theories suggested that it was the acidity of cranberry juice that exerted an antibacterial effect (19, 46). One of the first studies to suggest that cranberry juice contains compounds exhibiting unique

activity against uropathogenic *E.coli*, over and above other fruit juices, was conducted by Zafriri and colleagues (47). In this study, yeast agglutination caused by *E.coli* was used as a proxy for the ability of type 1 fimbriae to adhere to epithelial cells, as the two processes are correlated (47). The addition of cranberry juice and other fruit juices to the yeast/uropathogenic *E.coli* combination *in vitro* led to inhibition of aggregation; this inhibitory effect was mediated by fructose (47). In a further assay, haemagglutination was used as a surrogate measure of the ability of P-type fimbriae to adhere to epithelial cells (47). Cranberry juice, but not the other fruit juices tested, led to inhibition of bacterial aggregation. This suggested that there was a bioactive compound in cranberry juice, not present in the other fruit juices, which was mediating an anti-adhesion effect against uropathogenic *E.coli* (47).

Through *in vitro* experimentation, Howell and colleagues found that proanthocyanidins (PAC) isolated from cranberry inhibit the adhesion of P-fimbriated uropathogenic *E.coli* to uroepithelial cells (48). PACs are a diverse group of polymers (substances consisting of repeated subunits) that are present in many fruits, seeds and plants (49). The basic building blocks of most PACs are flavan-3-ol (flavanol) compounds, such as catechin and epicatechin (49). The most commonly occurring PACs found in nature have 'B-type' linkages between the building block flavanol compounds (19). However, the PACs found in cranberry uniquely contain 'A-type' linkages between the flavanol building blocks (19).

The anti-adhesion effect of PAC with A-Type linkages (PAC-A), rather than PAC with B-Type linkages (PAC-B), has been demonstrated through *ex vivo* experimentation (50). The anti-adhesion activity of the urine of healthy volunteers following consumption of cranberry juice containing PAC-A was compared with urine following consumption of

substances containing PAC-B, such as grape juice, apple juice and dark chocolate (50). When uropathogenic *E.coli* cultures were incubated with urine collected following cranberry juice consumption, a haemagglutination assay showed that a significant anti-adhesion effect was exhibited, peaking at 4-6 hours and lasting for at least eight hours (50). No such effect was exhibited with urine collected after consumption of substances containing PAC-B, nor with urine collected from volunteers prior to cranberry juice consumption (50).

Further *ex vivo* experimentation showed that the anti-adhesion effect of PAC-A was dose-dependent (51). In an *ex vivo*, placebo-controlled randomised study, healthy volunteers consumed cranberry capsules containing different amounts of PAC (placebo, 18 mg, 36 mg or 72 mg) (51). The urine of volunteers consuming PAC exhibited significant anti-adhesion activity against uropathogenic *E.coli* cultures, compared with the urine of volunteers consuming placebo ($p<0.0001$) (51). Peak anti-adhesion activity was detected in urine samples collected between one and six hours after cranberry capsule consumption, and the activity was significantly greater in volunteers consuming either 36 mg or 72 mg PAC compared with 18 mg PAC ($p=0.002$) (51), with the anti-adhesion effect waning by 24 hours. The authors therefore suggest that the optimal dosage of PAC to cause an *E.coli* anti-adhesion effect in the urine is 36 mg twice daily (morning and evening) (51).

Ex vivo and *in vitro* studies suggest that whilst the bioavailability of intact PAC-A may be low, metabolic breakdown products of PAC-A can cross colorectal cells (52), are found in the urine after cranberry consumption (53), and mediate anti-adhesion effects against uropathogenic *E.coli* (54). PAC-A may therefore be metabolised and de-polymerized by

the gut microbiome into constituent compounds (e.g. epicathechin), which in turn may be broken down into a range of compounds such as valerolactone derivatives (54). These breakdown products may be mediating the anti-adhesion effects observed following cranberry consumption.

A number of studies have tested cranberry extract as a means of preventing recurrent UTI, with systematic reviews and meta-analyses of these studies largely suggestive of a benefit with cranberry consumption in this context (55-60). A 2017 meta-analysis synthesised the results of 25 studies, and found that there was a significant reduction in recurrent UTIs with cranberry consumption compared with placebo (weighted risk ratio 0.68, 95% CI 0.55-0.80, $p<0.0001$) (58). A further meta-analysis in 2017, focusing on women at risk of UTI, similarly found that cranberry consumption reduced the risk of UTI by 26% compared with placebo/other control [pooled risk ratio: 0.74;95% CI: 0.55 to 0.98; I^2 = 54%] (57). However, a Cochrane meta-analysis last updated in 2012 produced a conflicting result. In this review of 24 RCTs (n = 4473 participants overall), the authors found that cranberry consumption did not significantly prevent repeat symptomatic UTI in all populations (including men, women, children and those with complicated UTI) compared to placebo or no treatment (13 RCTs meta-analysed; RR 0.86, 95% CI 0.71 to 1.04), nor specifically in women with recurrent UTI (4 studies meta-analysed; RR 0.74, 95% CI 0.42 to 1.31) (56). The conflicting findings of various meta-analyses may be due to differences in review eligibility criteria, different weighting of subgroups and differences in review authors' handling of heterogeneity (61). Furthermore, many of the included trials of recurrent UTI suffer methodological problems, such as a lack of reporting of the amount of PAC (believed to be the active ingredient) in interventions, as

well as high participant drop-out of up to 55%, attributed to the unpalatability of drinking large volumes of cranberry juice over long periods of time (56).

Whilst multiple trials have assessed the use of cranberry in the prevention of urinary tract infection, fewer studies have been conducted to assess the use of cranberry extract as a means of treating acute UTIs (62). During an acute UTI, the uroepithelium is a dynamic environment. The shearing forces of urine, coupled with host defences such as the exfoliation of superficial uroepithelial cells, lead to a process of *E.coli* flux into the bladder lumen and subsequent re-attachment to the uroepithelium (63). Given that PAC-A in cranberry extract reduces *E.coli* adhesion to the uroepithelium, this could help to prevent biofilm formation in an acute UTI, reducing the organism's pathogenicity. It could additionally render antibiotics more effective, enhancing their ability to attach to and kill pathogenic microorganisms. The robust body of mechanistic work evaluating the uropathogenic anti-adhesion effects of cranberry extract, combined with the generally promising findings of trials of cranberry extract for recurrent UTI, in addition to the fact that 27% of women report using cranberry extract as a means of managing an acute UTI (64), all provide justification for conducting research to determine whether cranberry extract can safely and effectively treat an acute UTI.

1.5. Hypothesis

There is scope to safely and meaningfully reduce antibiotic consumption for acute, uncomplicated UTIs in primary care through the consumption of cranberry extract.

1.6. Thesis aims and outline of thesis structure

1) To identify and appraise the existing evidence base for using cranberry extract as a treatment for symptoms of acute, uncomplicated UTI.

2) To establish the feasibility of conducting a trial of cranberry extract for symptoms of acute, uncomplicated UTI in primary care.

3) To establish the views of UTI patients on using cranberry extract for symptoms of acute UTI, and barriers and facilitators to women taking part in trials of such an intervention.

4) To understand barriers and facilitators to recruitment to a primary care trial of cranberry extract for acute UTI.

1.6.1. Chapter 1

Through an introductory narrative review, the background and rationale for this research programme have been outlined. The scale of the antibiotic resistance crisis has been highlighted, and the rationale for focusing on cranberry extract as a possible treatment for acute, uncomplicated UTIs explained. I describe the aims of this thesis, and how I plan to achieve them in subsequent chapters.

1.6.2. Chapter 2

In this chapter, I present the findings of a systematic review that I conducted to identify and appraise the existing evidence for and against the use of cranberry extract as an acute UTI treatment. This systematic review confirms that limited studies have addressed this question, and there is therefore an important evidence gap that this research programme goes some way towards filling. This systematic review has been published in the peer-reviewed journal ‘Antibiotics,’ and was selected by the journal to feature as the cover story of Volume 10, Issue 1 (65).

1.6.3. Chapter 3

In this chapter, I present the findings of the Cranberry for Urinary Tract Infection (CUTI) feasibility trial. This was a randomised, parallel-group, interventional feasibility trial of cranberry extract for symptoms of acute, uncomplicated UTI in primary care. The protocol paper and feasibility trial results have been published in the peer-reviewed journals 'Trials' and 'BMJ Open,' respectively (66, 67).

1.6.4. Chapter 4

In this chapter, I present the findings of 26 interviews I conducted with women who had recent experience of an acute UTI, some of whom were participants of the CUTI feasibility trial. In these interviews, women were invited to tell their story from the beginning of their illness episode, up until its conclusion. Their views were sought on non-antibiotic treatments for UTI (including cranberry extract and other over-the-counter formulations), as well as their experiences of, and perspectives on, taking part in the CUTI feasibility trial. A manuscript based on this chapter is under preparation for submission to a peer-reviewed journal, and will include some insights from interviews from recruiters (recruiter interviews discussed in detail in chapter 5).

1.6.5. Chapter 5

In this chapter, I present the findings of eight interviews conducted with clinicians who recruited to the CUTI feasibility trial. I explore recruiters' initial thoughts on the trial, their experiences of recruitment, and perceived barriers and facilitators to effective opportunistic recruitment. In addition, recruiters' and UTI patients' thoughts on, and experiences of, CUTI trial practical procedures (e.g. use of the electronic symptom diary)

are explored. A manuscript based on this chapter is under preparation for submission to a peer-reviewed journal.

1.6.6. Chapter 6

In this discussion chapter, I summarise and draw together the key findings of all of the chapters, explaining how they complement, contrast with, and add to the existing evidence. Implications of the findings for clinicians and researchers are discussed, with emphasis on how the research has influenced my plans for conducting a rigorous, adequately powered, placebo-controlled, randomised trial of cranberry extract at a post-doctoral level.

2. Chapter 2 - Systematic review of cranberry extract for symptoms of acute, uncomplicated UTI

2.1. Summary

In Chapter 1, I highlighted the pressing need to reduce antibiotic consumption for acute UTI. I hypothesised that offering cranberry extract to women with symptoms of acute, uncomplicated UTI has the potential to meaningfully reduce antibiotic consumption. However, before testing the feasibility of such a trial in primary care, it is important to first identify and critically appraise the existing evidence for or against this approach. In this chapter, I present the results of a systematic review that I conducted. Excerpts of this chapter have been published in a peer-reviewed journal. The article was selected to appear as the journal's cover story for the issue:

Gbinigie, O.A., Spencer, E.A., Heneghan, C.J., Lee, J.J. and Butler, C.C., 2021. Cranberry Extract for Symptoms of acute, Uncomplicated Urinary Tract Infection: A Systematic Review. *Antibiotics*, *10*(1), p.12.

2.2. Introduction

Prior to embarking on this DPhil programme of research, I conducted an informal, scoping literature review of the use of cranberry extract for managing acute UTI and found that limited research had been conducted in this area. However, I considered that it was important to formalise this process and conduct a rigorous systematic review. Well-conducted systematic reviews are regarded as the highest level of research evidence (68) and employ reproducible methods (69, 70). Through the synthesis, or meta-analysis, of multiple studies, systematic reviews and meta-analyses have the potential to provide

definitive answers to research questions, thereby informing clinical practice (71). Conversely, systematic reviews can highlight areas in which more evidence is needed, helping to direct future research efforts.

Cranberry extract could be a potential, non-antibiotic treatment for acute, uncomplicated UTIs. Up to 27% of women already report using cranberry extract in this way (64). Proanthocyanidin with A-type linkages (PAC-A), or their metabolites, are believed to be the active ingredient in cranberry, preventing *Escherichia coli* (*E. coli*) from binding to the bladder uroepithelium (50), thus reducing the ability of *E. coli* to cause and sustain a UTI. Systematic reviews assessing the use of cranberry in the management of *recurrent* UTIs provide mixed evidence of benefit (55, 56, 58).

Whilst many studies have evaluated the use of cranberry extract as a means of managing recurrent UTI, fewer have assessed its ability to treat the symptoms of an acute UTI. The aim of the present systematic review was to synthesise and critically appraise the evidence for or against the use of cranberry extract as a way of managing clinically apparent acute UTI.

2.3. Methods

I registered the systematic review protocol on the PROSPERO database on 13th March 2020, accessible via the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020166785

2.3.1. Search strategy

I devised the search strategies for electronic databases (see Appendix 2. 1), having sought some assistance from a specialist outreach librarian (NR). The electronic searches were run in Medline, Embase, The Cochrane Library, Amed, Web of Science and Cinahl from inception up to 3rd February 2020. No language restrictions were imposed. In addition to electronic database searches, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) and Google Scholar were searched for relevant studies. Searching these additional sources increased the chance of discovering relevant grey literature, such as unpublished studies, thereby reducing the chance of publication bias (72). Experts in the area (experienced acute UTI and cranberry researchers) were consulted, as well as manufacturers of cranberry products (Ocean Spray and Trophikos, LLC) to identify any further, relevant studies. Identified citations were imported into Endnote, before being uploaded into Covidence. Covidence is a web-based software that facilitates dual screening of studies (73). Each citation was independently assessed for eligibility by myself and another reviewer, with disagreements resolved by discussion. Had it not been possible to achieve consensus through discussion, the opinion of a third reviewer would have been sought. Dual abstract screening has been shown to reduce the chance of missing relevant studies (74).

2.3.2. Eligibility criteria and study selection

Blinded and open-label randomised clinical trials (RCTs) comparing the effectiveness of cranberry extract with any other treatment (or placebo/no treatment) for acute uncomplicated UTIs in patients aged 18 years and above, with a symptom duration of less than seven days were suitable for inclusion. Non-randomised studies (including cohort studies, case-control studies and quasi-randomised studies) assessing the use of cranberry

in treating acute UTIs were also eligible. For inclusion, cranberry extract needed to be orally administered as juice, fruit or as capsules/tablets/pills. In studies in which a cranberry product was combined with another intervention/exposure, data allowing the effect of cranberry on the outcome(s) of interest to be isolated were required. Included studies needed to report at least one primary or secondary outcome. Primary outcomes were: Assessment of participants' symptoms/clinical status/wellbeing assessment (e.g. symptom burden or time to resolution of symptoms); antibiotic use (immediate and/or delayed); and clinical cure. Secondary outcomes were: Microbiological cure/assessment; biochemical assessment; assessment of mechanisms of action; and assessment of harms/adverse events. Whilst I was interested in discovering potential mechanisms of action of cranberry extract, I wanted this to be in the context of clinically apparent acute UTI; that is, research studies conducted in (biological specimens of) women with an acute, uncomplicated UTI.

Studies of exclusively complicated UTI (e.g. catheterised, self-catheterising, spinal cord injury, renal tract abnormalities, male UTIs and pyelonephritis) were excluded. In such cases, it would not usually be appropriate to consider a non-antibiotic treatment or a delayed antibiotic strategy. Studies assessing recurrent UTI, animal studies, case reports, and systematic reviews were also excluded. Systematic reviews were, however, used as potential sources for references.

2.3.3. Risk of Bias

The risk of bias of included RCTs was assessed using the Cochrane risk of bias tool (75). The Cochrane risk of bias tool examines the following domains: Method of sequence generation; concealment of allocation; blinding of care providers and participants; blinding

of outcome assessors; incomplete outcome data (attrition and intention to treat analyses); selective outcome reporting; and other bias, such as funding disclosure (75). Had any non-randomised studies been identified, the reporting quality of these studies would have been assessed using the ROBINS-I tool (76). The hierarchy of evidence of included studies was rated according to The Oxford Levels of Evidence 2 criteria (68).

The quality of each included study was independently assessed by myself and another reviewer, with disagreements resolved through discussion. Had consensus not been achieved, a third reviewer would have arbitrated.

2.3.4. Data extraction

I created a data extraction sheet in Microsoft Excel. For included RCTs, when possible, the following data were extracted: Authors; study location/setting; types and numbers of participants; demographics (age, ethnicity); study duration; intervention; comparator; primary and secondary outcome measures; and study results. Had any non-randomised studies been identified, the following data would have been extracted: Authors; study location/setting; study type; characteristics of cases and controls (if applicable); demographics (age, ethnicity); study duration; intervention/exposure; comparator (if applicable); primary and secondary outcome measures; and study results. Myself and another reviewer independently extracted data with disagreements resolved through discussion. Had consensus not been achieved, the opinion of a third reviewer would have been sought.

Given sufficient data with adequate homogeneity, Review Manager software (77) would have been used to perform meta-analysis (78). Meta-analysis involves the combination of

results from two or more studies (78). Meta-analysis allows more precision in effect estimates, but if used inappropriately (e.g. in studies with insufficient homogeneity), it can produce misleading results (78).

In light of varied doses and formulations of cranberry extract, and wide variation in outcomes assessed in cranberry studies, I anticipated that there would be heterogeneity in identified studies. Given this, a random effects meta-analysis would have been used (78). The random effects model's underlying assumptions account for the effects of both random chance and true variation in effect size differences between studies (78). Heterogeneity between studies would have been identified visually (assessing the degree of overlap between confidence intervals of included studies), and statistically using the I^2 statistic (78). I^2 statistic values of 25%, 50% and 75% would indicate low, medium and high heterogeneity, respectively (79). Heterogeneity would have been investigated using subgroup analysis (for example, based on participant age), with a subgroup interaction test performed to test for statistically significant differences between subgroups (80). Sensitivity analyses (based on study quality) would have been used to test the overall robustness of the data. If ten or more studies were statistically pooled for any outcome, I would have used a funnel plot to test for publication bias (81).

2.4. Results

2.4.1. Study screening

Electronic database searches identified 3,337 results (see Figure 2. 1). Searches of ClinicalTrials.gov, Google Scholar and WHO ICTRP did not identify additional studies

suitable for inclusion. After the removal of duplicates, 1976 citations were screened at the title and abstract stage. At the end of title and abstract screening, 79 eligible articles were identified. Of these, thirty seven studies were excluded because the study design did not fit with the pre-specified systematic review criteria (48, 50, 66, 82-115). A number of these studies assessed the anti-adhesion effects of urine obtained from healthy volunteers following cranberry consumption, when combined with uropathogen cultures *ex vivo*. Eleven studies were excluded as they did not assess UTI (51, 54, 116-124). Seven studies were excluded as they assessed recurrent, rather than acute, UTI (125-131). Four studies assessed an intervention that did not fit our criteria, such as cranberry extract combined with additional compounds (132-135). Two studies were excluded as updated publications were available for eligibility screening (136, 137), and a further two studies were excluded as they assessed the wrong patient population (46, 138). One animal study was also excluded (139). Eight studies were excluded as they were duplicates of five eligible studies (48, 51, 97, 104, 126). After initially including seven studies, a further four were excluded; one was a duplicate (140), the author of a second study confirmed that they included patients with complicated UTI (141), one was a trial registration of an ongoing RCT (140), and one was the registration of the Cranberry for UTI (CUTI) feasibility trial (142), the results of which were not available at the time of the review, but are presented in detail in chapter 3 of this thesis. Three studies were therefore included in this systematic review (143-145).

As there were insufficient data or homogeneity to perform data synthesis, I present the results below in narrative.

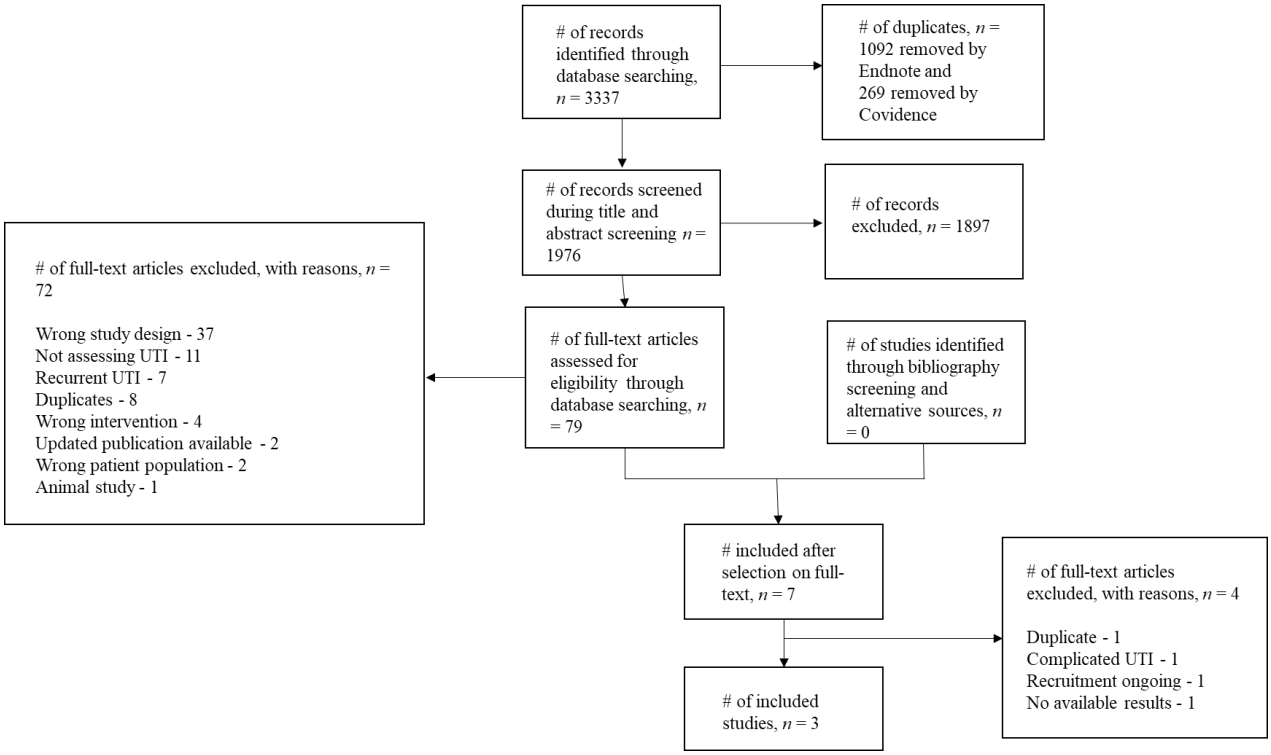


Figure 2. 1 Flow chart showing the process for identification of studies eligible for inclusion

2.4.2. Study characteristics

All three RCTs were conducted in outpatient settings, and included between 60 (145) and 319 (143) participants (see Table 2. 1). One study each was conducted in the USA (143), India (145) and the UK (144). The intervention used in two of the RCTs was cranberry juice (143, 144), whilst the other trial used encapsulated cranberry powder (145). The PAC content of the interventions varied greatly; participants in one study received between 7.5 mg (low dose) and 15 mg (high dose) of PAC daily (145), whilst participants in another study received on average 224 mg of PAC daily (143). One study did not report the PAC content in the intervention (144).

Table 2. 1 Characteristics of included studies and key results

Study ID and Country	Design	Participants and setting	Number of participants	Age (years)	Study Duration	Intervention	Control	Results
Barbosa-Cesnik *et al* (2011), USA	Randomised placebo-controlled trial	Women with an acute UTI (three or more urinary symptoms) presenting for urinalysis at the University of Michigan Health Service laboratory with symptoms of UTI	319 (155 received cranberry, 164 received placebo)	18-40	6 months	8 ounces of 27% low-calorie cranberry juice twice daily	8 ounces of Placebo juice twice daily	The presence of urinary and vaginal symptoms was similar between groups at 3 days and at 1-2 weeks
Little *et al* (2009), UK	Randomised controlled trial	Non-pregnant women presenting to General Practices in south-west England with a suspected uncomplicated UTI	309 (241 women in the juice comparisons: 75 advised to take cranberry juice, 78 advised to take orange juice, 88 advised to drink water)	17-70	Average follow-up time of 575 days (range 35-968 days)	Advice to drink cranberry juice	Advice to drink water	No significant impact of advice to consume cranberry juice on the duration of symptoms rated moderately bad or worse [IRR 1.18 (95% CI: 1.95 to 1.47), p=0.13], frequency symptom severity [mean difference -0.01 (95% CI: -0.37 to 0.34), p=0.94], severity of unwell symptoms [mean difference 0.02 (95% CI: -0.36 to 0.39), p=0.93], use of antibiotics [odds ratio 1.27 (95% CI: 0.47 to 3.43) p=0.64] or time to re-consultation [hazard ratio 0.74 (95% CI: 0.49 to 1.13), p=0.17].
Sengupta *et al* (2011), India	Randomised controlled trial	Women with mild symptoms of a UTI, urine culture positive and with a negative pregnancy test	60 (16 untreated controls, 21 received low dose cranberry, 23 received high dose cranberry)	18-40	90 days	Encapsulated PAC Standardized Whole Cranberry Powder (PS-WCP) - 500 mg (low dose – containing 7.5 mg PAC) and 1000 mg (high dose – containing 15 mg PAC)	No treatment	Significant *within-group* improvement of symptoms at day 10 compared to the baseline in both treatment groups, but not in the untreated controls. Significant *within-group* reduction in E. coli load in both treatment groups after 10 days of treatment (low dose, $p<0.01$; high dose $p<0.0001$), but not in the untreated controls. No significant between group differences in E.coli load at day 10 or day 30 (Chi^2 test; p=0.372 and p=0.981, respectively)

Abbreviations: IRR: Incidence rate ratio; PAC: proanthocyanidins; UTI: Urinary Tract Infection

Whilst the included RCTs provided information on outcomes relevant to this systematic review, the primary objective of these studies was not assessment of cranberry extract for acute UTI. Two studies focused on cranberry for preventing recurrent UTI (143, 145). Barbosa-Cesnik *et al* recruited women with an acute UTI, treating the index UTI with immediate antibiotics and concurrently randomly assigning the participants to receive either 8 ounces of 27% low-calorie cranberry juice twice daily or 8 ounces of placebo juice twice daily for 6 months (143). Women were followed up for 6 months or until they experienced a UTI, whichever came sooner. Sengupta and colleagues randomly assigned 60 women to receive either low dose encapsulated cranberry powder (500 mg daily – containing 7.5 mg PAC), high dose encapsulated cranberry powder (1000 mg daily – containing 15 mg PAC), or no treatment (145). The primary outcome was the ability of the different treatment regimens to prevent recurrent UTI over a 90 day period.

The primary objective of the trial by Little *et al* was to determine the effectiveness of five treatment strategies in the management of suspected acute, uncomplicated UTI, with participants randomly assigned to: (1) Immediate antibiotic prescription; (2) Delayed antibiotic prescription; (3) Antibiotics dependent on the participant's symptom score; (4) Antibiotics offered if the dipstick was positive; and (5) Antibiotics targeted to according to midstream urine results (146). Four forms of self-help advice were randomised across the five groups in a factorial design and included: (1) Information leaflet with tips on self-help; (2) Advice to use over-the-counter herbal remedies; (3) Advice to use bicarbonate; and (4) Advice to increase fluid intake with either cranberry juice or orange juice.

2.4.3. Risk of Bias

The risk of bias of included studies was judged as moderate (see Figure 2. **2** and Figure 2. 3), and they provided level 2 (randomised clinical trial) evidence according to The Oxford Levels of Evidence 2 criteria (68). All three studies were judged to have a low risk of selection bias and reporting bias. The RCT by Sengupta *et al* is described by the study authors as double-blind, however, women in the control group did not receive placebo (145). It was therefore judged by the review authors to have a high risk of bias with respect to participant blinding. The open-label RCT by Little *et al* was similarly judged to have a high risk of bias for this domain (144). Two of the three RCTs were judged to have a high risk of bias with respect to incomplete outcome data; Sengupta *et al* (145) did not conduct intention to treat (ITT) analyses, whilst Barbosa-Cesnik *et al* (143) conducted ITT analysis but had high attrition (26%).

Additional biases included cranberry industry involvement (143), and insufficient power to detect between-group differences for cranberry comparisons (144, 145). According to the power calculation by Barbosa-Cesnik and colleagues (143), recruiting 120 participants in both arms would have provided the study with 80% power to detect between-group differences, assuming that 30% of participants experienced a UTI during the follow-up period. In order to take into account greater loss to follow-up that might occur in the cranberry group compared with the placebo group, the authors planned to recruit 200 participants per group (400 in total). Although 419 women were randomised, 100 women had negative urine cultures and were therefore not eligible for the study and did not receive cranberry or placebo juice. 319 women were therefore included in the ITT analysis; less than the authors had planned. Loss to follow-up was not higher in the cranberry group compared

with the placebo group, however, recurrence of UTI occurred in 16.9% of participants - lower than anticipated by the authors - which may have adversely impacted the power of the study.

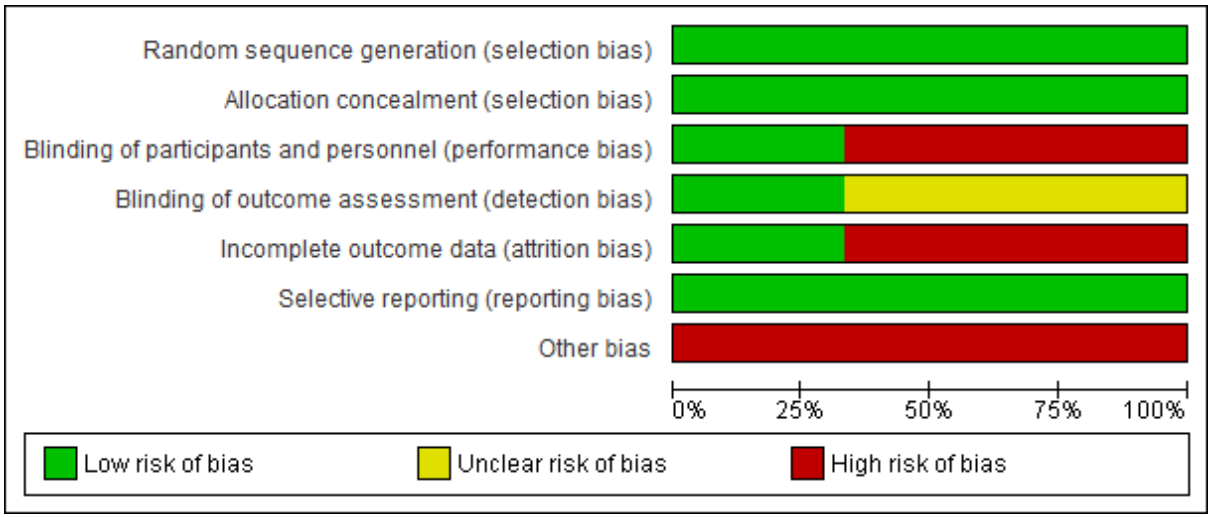


Figure 2. 2 Risk of Bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

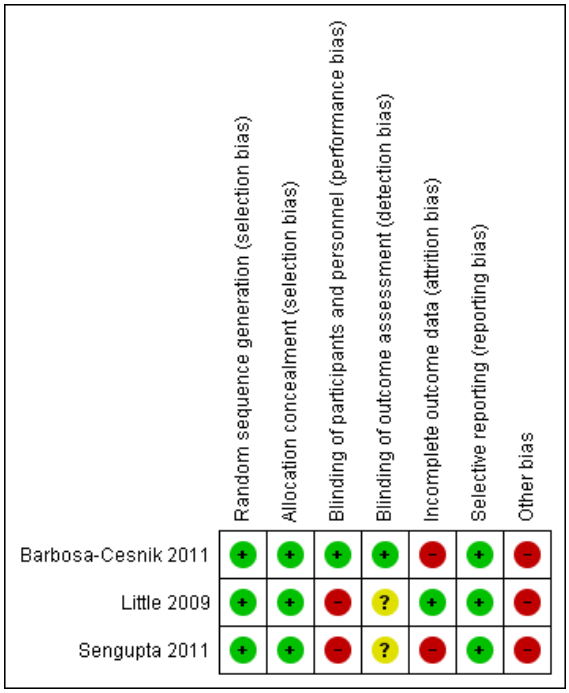


Figure 2. 3 Risk of Bias summary: Review authors' judgements about each risk of bias item for each included study.

2.4.4. Principal findings

2.4.4.1. Symptoms

Little *et al* (144) analysed the impact of the different treatment strategies on 'frequency symptoms' (day-time and night-time urinary frequency, dysuria and urgency) and 'unwell symptoms' (restriction of usual activities, abdominal pain and feeling unwell). There was no significant effect of advice to drink cranberry juice on the severity of frequency symptoms [mean difference (MD) -0.01 (95% CI: -0.37 to 0.34), p=0.94)], nor the severity of unwell symptoms [MD 0.02 (95% CI: -0.36 to 0.39), p= 0.93)], compared with advice to drink water. Advice to drink cranberry juice compared with water did not affect the duration of symptoms rated moderately bad or worse, that is, rated three or more on a scale of zero to six [incidence rate ratio (IRR) 1.18 (95% CI: 0.95 to 1.47), p= 0.13].

Sengupta and colleagues reported a significant within-group improvement in symptoms at ten days compared with baseline in both the high and low dose cranberry intervention groups, but not in the untreated controls (145). No empirical data were presented to support this finding, nor were between group comparisons reported.

Barbosa-Cesnik *et al* (143) reported that at three days and at 1-2 weeks after enrolment in the trial, the presence of urinary symptoms and vaginal symptoms was similar between the cranberry and placebo juice groups. No empirical data were presented to support this finding. In this study, all women received immediate antibiotics to treat their index UTI, thus, the findings described represent the effect of cranberry juice in addition to immediate antibiotics.

2.4.4.2. Antibiotic Use

One study found that advice to consume cranberry juice had no significant impact on the use of antibiotics, compared with advice to drink water [odds ratio (OR) 1.27 (95% CI: 0.47 to 3.43), p=0.64] (144).

2.4.4.3. Microbiological assessment

Sengupta *et al* (145) reported a significant within group reduction in the proportion of patients with *E.coli* growth in the urine after 10 days of treatment with both low dose cranberry ($p<0.01$) and high dose cranberry ($p<0.0001$), but not in the untreated controls. Although no between-group differences were reported by the authors, I used data available in the publication to compare the proportion of participants in each trial group who were *E.coli* positive at day 10 and day 30 of the trial. I found that there were no significant between group differences in the proportion of patients with *E.coli* positive urine (chi-squared test: $p = 0.372$ at day 10; $p= 0.981$ at day 30). There were insufficient data to perform an analysis adjusting for baseline urine *E.coli* status. Of note, there were considerable differences in baseline urine *E.coli* status between groups; 4/13 (30.8%) of the untreated controls were *E.coli* positive at baseline, whilst 14/21 (66.7%) of the low dose cranberry group and 17/23 (73.9%) of the high dose cranberry group were *E.coli* positive at baseline.

2.4.4.4. Time to reconsultation

One study found no significant impact of cranberry juice consumption compared with advice to drink water on time to re-consultation [hazard ratio (HR) 0.74 (95% CI: 0.49 to 1.13), p=0.17] (144).

2.4.4.5. Serious Adverse Events

There were no major adverse events (defined by the study authors as major illness, admission to hospital, death) reported for any group in the trial by Little *et al* (144). Sengupta *et al* (145) similarly reported no serious adverse events occurred during the course of the study. Barbosa-Cesnik and colleagues found that serious adverse events occurred equally between groups, and none were deemed to be related to treatment received in the trial; no further details of the serious adverse events were reported in their publication (143).

2.5. Discussion

The current evidence base for or against the use of cranberry extract in the management of acute, uncomplicated UTIs is inadequate. The existing, limited RCT evidence identified suggests that advice to consume cranberry juice does not improve urinary frequency symptoms, feeling unwell, nor the duration of symptoms rated moderately bad or worse in women with acute UTIs, compared with encouraging consumption of water. Advice to consume cranberry juice did not reduce use of antibiotics compared with promoting consumption of water, nor time to re-consultation. In women receiving immediate antibiotics and cranberry juice, urinary symptoms were not reduced compared with immediate antibiotics and placebo juice. Consuming encapsulated cranberry powder may reduce *E.coli* load and improve symptoms after 10 days of consumption compared with baseline. The studies did not report evidence of serious harm associated with cranberry consumption. These results must be interpreted with caution as they come from a limited number of studies with a moderate risk of bias for the outcomes of interest in this systematic review, which were not the primary objectives of the included trials.

2.5.1. Comparison with existing literature

Two trial registrations were identified, which were pertinent to this review. One of these was the trial registration for the CUTI feasibility trial, the findings of which are presented in detail in Chapter 3. The other was an open-label RCT in Spain (140). This trial aims to recruit 128 women aged 18 to 64 years from emergency departments and outpatient clinics with acute UTI to assess the non-inferiority of acute treatment with a single dose of a Cysticlean cranberry capsule (containing 240 mg PAC) compared with a one-off, 3 gram dose of fosfomycin. The trial status is 'ongoing' on the EU Clinical Trials Register (140). I contacted the author of the trial registration. Unfortunately, the trial was reported to have suffered some recruitment delays, and they were unable to share any data.

A Cochrane review assessing the use of cranberry products for symptoms of acute UTIs, with searches last updated in August 2020, did not identify any eligible studies (97). The review authors identified one trial registration, with unknown status, which fit their review criteria (133); of note, this study was excluded from the present review because the intervention tablets combined cranberry extract with three other active ingredients (147). The Cochrane review study eligibility criteria included RCTs or quasi-RCTs of cranberry products given for at least five days to men, women or children with a symptomatic upper/lower UTI, or an asymptomatic UTI. The primary outcome of the Cochrane review was the number of UTIs (symptomatic and asymptomatic) in each group at the end of the treatment period. Secondary outcomes included reduction in symptom severity, adherence to treatment and side effects. The Cochrane review did not include any of the studies identified in the present systematic review. It is possible that the Cochrane review authors excluded the studies in the present review because none of them focused on the use of cranberry extract for acute UTI

management. Nonetheless, all of the studies included in the present review provided relevant information. Furthermore, the Cochrane review did not identify either of the trial registrations identified in the present review, despite the Cochrane review authors conducting searches of clinical trial registries. Whilst the ongoing open-label RCT in Spain (140) does not fit the Cochrane review criteria (cranberry extract was not given for at least 5 days), the CUTI feasibility trial registration (142) does fit their criteria. The present systematic review therefore provides additional pertinent information.

Howell *et al* conducted a randomised double blind study to determine the optimal amount of PAC to consume to provide *E.coli* anti-adhesion activity in urine (51). Urine samples were collected from study participants before and after consuming cranberry capsules containing varying amounts of PAC or placebo capsules. Anti-adhesion activity of the participants' urine was tested *ex vivo* against a uropathogenic *E.coli* strain. There was a significant increase in the anti-adhesion activity of PAC compared with placebo ($p< 0.001$), and the effect increased in a dose-dependent fashion. They determined that the optimal amount of PAC to consume was 72 mg per day (51). In the study by Little *et al*, the amount of PAC consumed by participants in the cranberry juice arm was not specified, and in the trial by Sengupta *et al*, participants in the high dose cranberry group received 15 mg of PAC daily. It is therefore possible that participants in the cranberry arms of these studies were consuming sub-therapeutic doses of what is believed to be the active ingredient in the intervention.

The included studies did not identify any compelling evidence of harm associated with cranberry consumption. In addition, cranberry extract is purported to have health benefits within and outwith the urinary tract (46), which may make it an appealing, potential treatment candidate for future research in the context of acute, uncomplicated UTI management.

However, possible harms associated with cranberry consumption must be considered. There is mixed evidence of an interaction between cranberry and Warfarin (148), and of an association with urolithiasis (149).

2.5.2. Strengths and Limitations

A broad search strategy was employed to maximise the chance of capturing relevant studies, including grey literature. In addition to electronic database searches and trial registries, I contacted companies that sell cranberry products and experts in the field. When needed, I also contacted authors of eligible studies to check whether they were suitable for inclusion. These actions help to reduce the chance of missing studies relevant to the systematic review question.

However, I recognise that there are limitations to this review. It is possible that some studies that were suitable for inclusion were missed, particularly unpublished studies. Whilst no language restrictions were imposed, the searches were conducted in English, and it is possible that some studies published in languages other than English were not captured. Few studies were identified as being suitable for inclusion. The included studies were judged by the review authors as having moderate risk of bias, and empirical data were not provided for all of the outcomes assessed in this review. This is probably in part because the use of cranberry extract as an acute UTI treatment was not the primary focus of the included RCTs. There was heterogeneity in the outcomes reported by the studies, in the cranberry formulations used (juice versus capsules), and also in the amount of PAC (believed to be the active ingredient in cranberry) in the interventions used. This heterogeneity makes it difficult to make any direct comparisons between studies. Furthermore, there were insufficient data and insufficient homogeneity to perform meta-analysis.

The studies by Little *et al* and Sengupta *et al* were under-powered to determine the effects of cranberry on outcomes (144, 145), which can lead to exaggerated effect sizes (150). In addition, Sengupta and colleagues did not conduct intention to treat analyses (145). The study by Barbosa-Cesnik and colleagues had high attrition of 26% (143). Although not discussed by the authors in their publication, high loss to follow-up has been observed in other studies that have similarly required participants to consume large amount of cranberry juice over prolonged periods (56).

Sengupta *et al* reported within-group comparisons rather than between-group comparison (145); this can lead to high Type I error (rejection of a true null hypothesis) and misleading results (151). Whilst Little *et al* (144) did not find that cranberry improved UTI symptoms or antibiotic usage, the study authors noted that nearly half of the participants who were advised to drink water alone reported drinking cranberry juice (49%). It is possible that 'contamination' of the comparator group may have introduced Type II error (non-rejection of a false null hypothesis), making cranberry juice appear less effective than it is.

2.5.3. Implications for Future Research

Three studies were identified that have assessed the utility of cranberry extract in treating symptoms of acute UTIs. Given that up to 27% of women report using cranberry in this way (64), further adequately powered, well-conducted randomised clinical trials are required. These studies should use standardized interventions with a specified amount of PAC. Studies should be reported in line with CONSORT guidelines (152), including comprehensive reporting of any potential harms associated with cranberry consumption. Meaningful meta-analysis of studies is facilitated by harmonised outcomes. A core outcome set for trials of

uncomplicated UTI is currently being developed by researchers through a process of systematic review, Delphi process and consensus meeting (153).

Given the novel trial concept, conducting an initial feasibility trial (see chapter 3) would increase the chance of a future, adequately powered trial recruiting to target. Embedded qualitative interviews would provide useful information on acceptability of the intervention and trial procedures to patients (see chapters 4 and 5).

Once available, the results of the ongoing trial of Cysticlean cranberry extract versus fosfomycin should serve as an important addition to the current, limited evidence base (140). Disseminating the results of well-conducted studies evaluating cranberry extract as a treatment for acute UTI to both clinicians and the public will be important. Once more trials have been conducted in this area, it would be appropriate to update the present systematic review in light of the new and emerging evidence. If meta-analysis is possible and appropriate, this should also be performed.

2.5.4. Implications for Clinical Practice

There is a drive towards increasing the use of delayed antibiotic prescription for self-limiting bacterial infections in primary care (154). In primary care, this strategy has been shown to reduce antibiotic prescription for acute respiratory infections by 40% (155) and for UTI by 20% (33). National Institute for Health and Care Excellence (NICE) guidance advises that a delayed antibiotic prescribing strategy should be considered for acute UTI management (156). If cranberry extract was found to be effective through robust clinical trials in managing acute uncomplicated UTIs, it could be incorporated into a delayed antibiotic prescribing strategy; women could be advised to take cranberry products initially, taking antibiotics only

if symptoms fail to improve or worsen. However, in light of the limited evidence, no clinical recommendations can be made at present.

2.6. Conclusions

There is a paucity of studies evaluating cranberry in the management of acute UTIs; none of the identified trials was primarily focused on cranberry as an acute UTI treatment. The existing studies are at moderate risk of bias. Evidence of the effectiveness and safety of cranberry extract as a treatment for symptoms of acute, uncomplicated UTI is inconclusive; rigorous trials addressing these outcomes are required to address the identified evidence gap. Initial feasibility work would help to establish the acceptability of such a trial to participants, as well as participant recruitment and retention rates, with the goal of informing the design and conduct of an adequately powered trial. To this end, in chapter 3, I outline the design and findings of a randomised feasibility trial of cranberry extract for acute, uncomplicated UTI in primary care that I conducted.

3. Chapter 3 – Is a trial of cranberry extract for symptoms of acute, uncomplicated Urinary Tract Infection (CUTI) feasible? A randomised, parallel-group, interventional feasibility trial in Primary Care.

3.1. Summary

As discussed in chapter 1, there is an urgent need to safely reduce antibiotic consumption. My systematic review (chapter 2) highlighted that there is limited evidence for or against the effectiveness of cranberry extract as a treatment for symptoms of acute, uncomplicated UTI. I therefore conducted an interventional, randomised feasibility trial in General Practice to ascertain the feasibility of conducting a trial of cranberry extract for symptoms of acute, uncomplicated UTI.

Parts of this chapter feature in the following, peer-reviewed journal publications:

Gbinigie, O., Allen, J., Boylan, A.M., Hay, A., Heneghan, C., Moore, M., Williams, N. and Butler, C., 2019. Does cranberry extract reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections (CUTI)? Protocol for a feasibility study. *Trials*, *20*(1), pp.1-9.

Gbinigie, O., Allen, J., Williams, N., Moore, M., Hay, A.D., Heneghan, C., Boylan, A.M. and Butler, C.C., 2021. Does cranberry extract reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections (CUTI)? A feasibility randomised trial. *BMJ Open*, *11*(2), p.e046791.

3.2. Introduction

Acute UTIs are often self-limiting, and are almost always treated with immediate antibiotics (15). Identifying an effective non-antibiotic treatment option for acute, uncomplicated UTIs presents an opportunity to safely reduce antibiotic consumption.

Cranberry extract is often used by women as a treatment adjunct for acute UTI (64), but there is limited evidence for or against this approach (65). Trials have examined regular consumption of cranberry extract as a means of reducing *recurrent* UTI, with mixed results (56). These studies have been characterised by a high proportion of loss to follow-up of up to 55%, thought to be due to the unpalatability of consuming large volumes of cranberry juice for prolonged periods (56). Furthermore, the amount of proanthocyanidin with Type A linkages (PAC-A) in the interventions used in these studies has been poorly reported (56). PAC-A, or their metabolites following gut digestion, are believed to be the active ingredient in cranberry extract (54). Ex vivo studies have demonstrated that following consumption of cranberry extract containing standardised amounts of PAC, urine has anti-adhesion activity against *Escherichia coli (E.coli)* in a dose-dependent fashion (51).

Conducting a trial of cranberry extract in the context of acute UTI provides a novel and important addition to the current evidence base. Running an initial feasibility trial is likely to improve the chances of a future, adequately powered trial recruiting to target and therefore providing meaningful answers (157). A feasibility trial helps to determine whether it is possible to recruit to a trial of similar design, anticipated recruitment rates for an adequately powered trial, the ability to capture/completeness of outcome data, and helps to inform sample size calculations (157). The aim of this feasibility trial was to determine the feasibility

of conducting a trial of cranberry extract for symptoms of acute, uncomplicated UTI in General Practice.

3.3. Methods

3.3.1. Ethical Approval

In accordance with the Declaration of Helsinki, I sought ethical approval for the trial. The CUTI feasibility trial was approved by the South Central Oxford B Ethics Committee (REC reference: 18/SC/0673), the Health Research Authority (IRAS Project ID: 249672) and received confirmation of capability and capacity through the local Clinical Research Network (CRN) for each participating site prior to entering patients into the trial.

3.3.2. Study Design and setting

I designed an open-label, parallel-group, randomised feasibility trial in primary care. Women presenting to primary care with symptoms of an acute, uncomplicated UTI were randomly assigned to one of three groups:

- Group 1 (Control) – Immediate antibiotic prescription
- Group 2 (Intervention Group 1) – Immediate antibiotic prescription and immediate cranberry capsules
- Group 3 (Intervention Group 2) – Immediate cranberry capsules and a delayed prescription for antibiotics to be used if symptoms did not improve, or worsened.

Women were asked to complete a daily, electronic (online) diary for 14 days, rating their symptoms and recording any UTI treatments that they were taking.

3.3.3. Control

Women in group 1 received a prescription for immediate antibiotics. Recruiters were advised to prescribe first-line recommended antibiotics, which would usually be a three-day course of Nitrofurantoin (156). In keeping with pragmatic trial design, I did not stipulate the antibiotic that recruiters should prescribe.

3.3.4. Intervention

I obtained cranberry capsules from Indena S.p.A, an Italian manufacturer of Redicran capsules. Other than supplying the capsules free of charge, Indena S.p.A had no other involvement with the feasibility trial.

In an *ex-vivo* study, the urine of healthy volunteers consuming cranberry extract containing 36 mg of PAC had a significant anti-adhesion effect against *Escherichia coli* (*E.coli*) compared with placebo ($p<0.001$) for up to 24 hours, but peaking between one and six hours (51). The authors therefore suggest an optimal dosing of 72 mg of PAC per day, given in split doses at 12 hourly intervals (51). As each Redicran capsule contained 18 mg PAC, women receiving cranberry capsules were advised to take two capsules twice a day at 12 hourly intervals. As there was no previous research available to inform the optimal duration of treatment, I took a pragmatic decision and advised women to take cranberry capsules for up to seven days.

Women in group 2 (immediate antibiotics and immediate cranberry) were asked to take cranberry capsules until they felt better, but up to a maximum of seven days, alongside immediate antibiotics (first-line recommended antibiotics). The purpose of this group was to

determine whether there might be additive benefit through combining cranberry extract with antibiotics.

Women in group 3 (immediate cranberry with a delayed prescription for antibiotics) were asked to take immediate cranberry capsules until they felt better, but up to a maximum of seven days. Women in this group received a delayed prescription for first-line recommended antibiotics and were advised to start taking them if their symptoms were not better within 3-5 days, or if their symptoms worsened. The purpose of this group was to determine whether there is potential for women with an acute UTI to avoid consuming antibiotics altogether.

The study product was stored centrally at the Nuffield Department for Primary Care Health Sciences (NDPCHS), Oxford, and also at recruiting sites. Study product was kept at room temperature, out of direct sunlight, and behind two locked doors (e.g. in a locked cupboard within a locked room).

3.3.5. Recruitment of General Practices

Four General Practices were recruited to the feasibility trial. I created a Research Information Sheet for Practices (RISP), detailing the study background, eligibility criteria, details of recruiting site responsibilities and site reimbursement. The trial RISP was initially shared with four General Practices by the Clinical Research Network (CRN) on my behalf (the feasibility trial was adopted by the local CRN). All four General Practices expressed an interest in recruiting to the feasibility trial. After conducting Site Initiation Visits (SIVs – see section 3.3.6), but prior to opening sites to recruitment, one of the General Practices withdrew - the research lead at the practice was due to retire, and they no longer had capacity to recruit

patients. The CRN therefore approached another General Practice at my behest and on my behalf, and they expressed an interest in recruiting to the feasibility trial.

3.3.6. GP Site Set-up

I arranged site initiation visits (SIVs) with each of the practices, as well as an SIV with the CRN nurses. The CRN nurses work peripatetically and planned to assist with recruitment at participating General Practices. At the SIVs, I presented a PowerPoint to the General Practitioner (GP) research lead (Principle Investigator - PI) and practice research nurses. The presentation explained the feasibility trial background, rationale, aims, study procedures and the remit of recruiting practices. I gave demonstrations of the electronic systems involved in recruitment (see section 3.3.10). I answered the queries of prospective recruiters and all relevant documentation were signed (e.g. training log).

I created and supplied sites with a comprehensive site file containing all relevant trial documentation, including the most recent version of the protocol, public-facing documents, recruitment instructions (see Appendix 3. 1 and Appendix 3. 2), study product accountability logs and Serious Adverse Event (SAE) logs. I also supplied all sites with a study box containing participant information leaflets (PILs, see Appendix 3. 3), participant instructions (see Appendix 3. 4), informed consent forms (ICFs, see Appendix 3. 5), and the study product.

3.3.7. Participants

Women aged 18 years and above, presenting for the first time in this illness episode to a participating General Practice with symptoms suggestive of an acute, uncomplicated UTI, to

whom the clinician would normally prescribe immediate antibiotics, were eligible for recruitment to the trial.

3.3.8. Eligibility Criteria

For inclusion, women had to be willing and able to give informed consent for participation. Women were eligible if they consulted a participating General Practice with urinary symptoms suggestive of acute, uncomplicated lower urinary tract infection (namely dysuria, urgency, frequency, polyuria/nocturia, haematuria and/or suprapubic pain), which the GP or healthcare practitioner would normally treat with an immediate prescription of antibiotics. The symptom duration at the time of consultation needed to be six days or less, and the potential participant had to be willing to receive either an immediate or delayed antibiotic prescription.

Exclusion criteria were: Cranberry allergy; having taken an antibiotic in the past seven days; current regular cranberry product consumption (five or more days a week); known or suspected pregnancy; breastfeeding; taking anti-coagulants (e.g. Warfarin) or anti-platelet agents; inability to obtain a clean-catch/midstream urine sample (e.g. because of incontinence); in-dwelling catheter; receiving end of life care/palliative care; known underlying structural urological abnormalities; previous urological surgery; immunosuppression [e.g. active cancer (excluding localised skin cancer); receiving chemotherapy; taking regular high dose oral steroids (> 5mg/day); HIV infection]; diabetes mellitus treated with insulin; signs of clinically suspected upper UTI/pyelonephritis; inability to complete a diary accurately (e.g. due to dementia or psychosis); already involved in an interventional research study on UTI; inability to access the internet/email over the next two

weeks; and inability to decide on the same day that they contacted a primary care provider whether they would like to participate.

3.3.9. Recruitment of Participants and Randomisation

Recruitment of participants was opportunistic and performed by recruiters at participating General Practices (a combination of research nurses and GPs). Recruiters described the study to prospective participants (women presenting with symptoms of acute, uncomplicated UTI) to gauge interest. Women meeting all inclusion criteria and none of the exclusion criteria were randomly assigned to one of the three groups in a 1:1:1 ratio. The randomisation sequence was generated by a statistician (NW) based at NDPCHS, Oxford, using computer-generated block randomisation with variable block size, using Stata version 15.1. The randomisation code was accessible only by this statistician (NW). Neither the recruiter nor the participant knew to which group the participant had been randomly allocated in advance of this step.

3.3.10. Electronic Systems

Research Electronic Data Capture (REDCap) - a secure, password-protected web-based system - was used to randomise participants, store participant registration data, and to store participant symptom diary data. REDCap stored participant identification (ID) numbers, but no participant identifiable information. I designed the registration page and symptom diary (see Appendix 3. 6), but the electronic database was built by data programmers (RZ, LC and DJ) based at NDPCHS. Data entry and validation rules were incorporated to reduce data entry errors. I tested the diary multiple times during development to screen for errors, and it was updated iteratively. I based the diary closely on paper diaries that have been used in

analogous trials, and included the same set of eleven symptoms to be rated by participants (158).

Sentry is a secure, password-protected and encrypted database that was used to complete the registration process. Participant identifiable information, including the participants' names and email addresses were stored in Sentry. Sentry was also used to generate an electronic link to the diary, which was emailed to participants daily for fourteen days. The Sentry database was built by a data programmer (DJ), based at NDPCHS.

3.3.11. Participant Baseline Assessment (Day 1)

Women who were interested in taking part in the feasibility trial were given a PIL (Appendix 3. 3) to read and the opportunity to ask questions, before signing an ICF (Appendix 3. 5). Participant registration and eligibility confirmation took place electronically using REDCap (see section 3.3.10). At the baseline consultation, recruiters used REDCap to register participants, assign them an ID number, confirm eligibility, randomise participants, and document the antibiotic that had been prescribed (whether immediate or delayed).

During the baseline consultation, women were given a copy of the ICF, and both verbal and written instructions (Appendix 3. 4) about how to take the study product (if assigned to groups 2 or 3), electronic diary completion, and the need to seek medical attention if any symptoms suggestive of an upper UTI developed. Women were advised that they could take additional UTI treatments (e.g. analgesia), but women in the control group (immediate antibiotics alone) were advised not to take any cranberry products for the next 14 days.

Participants were asked to complete an electronic symptom diary over a period of two weeks. On the day of recruitment, participants were asked to enter baseline information (section 1 of the diary). This included documenting whether they had a history of UTIs and whether they had tried over-the-counter treatments before contacting a primary healthcare professional for their current UTI symptoms (e.g. cystitis sachets).

3.3.12. Participant Follow-up (Days 1 -14)

Participants were emailed a link to the electronic diary daily (Appendix 3. 6), and were asked to rate the severity of their symptoms each day for up to two weeks, depending on the duration of their symptoms, on a scale of 0-50. This was an adaptation of the seven point Likert scale used in previous studies of acute UTI (33, 39, 158), and validated by Watson *et al* (2001) (159).

0 = Normal/not affected

1-9 = Very little problem

10-19 = Slight problem

20-29 = Moderately bad

30-39 = Bad

40-49 = Very bad

50 = As bad as it could be

Participants were additionally asked to enter any treatments/medications that they were taking for their UTI each day (whether provided through the trial, or otherwise). Each day, participants were also asked whether they felt fully recovered from their illness. This

comprised section 2 of the electronic diary. Women rating all of their symptoms as 'zero' for two consecutive days did not need to continue rating symptoms, but they were still asked to record any treatments that they were taking, and to record whether or not they felt fully recovered. Part-way through the trial, I submitted a substantial amendment to the ethics committee to allow me to contact participants on day 3 of the trial if the diary was only partially complete, to check whether they were having difficulty using the electronic diary.

In the last section of the symptom diary (section 3 – completed on day 14), participants were asked to complete a final set of questions, including questions on adverse effects suffered as a result of participation in the trial, ease of use of the electronic diary, and how acceptable they found the study. Participants were also telephoned on day 14 to obtain a minimal data set and encourage completion of the electronic symptom diary if it was incomplete. Women who had provided prior written consent to be contacted about the interview study were asked whether they would like to take part in this additional study (see chapter 4). Willing trial participants were posted an interview study PIL and reply slip to return to me if they wished to proceed with the interview. Women who completed the electronic diary in full received a £10 voucher.

3.3.13. General Practice medical records review

Participants' medical records were reviewed by site-based trial recruiters to record any attendances to General Practice, hospital, or out-of-hours facilities within 28 days of the baseline assessment that were believed to be related to the original UTI episode. The result of the original urine culture was also recorded; a positive growth was defined as a growth of an organism greater than 10^5 CFU/ml (Colony Forming Units per millilitre). All data were documented by recruiters using REDCap.

3.3.14. Safety Reporting

3.3.14.1. Adverse events

As per the Primary Care Trials Unit adverse event reporting standard operating procedure definition, an adverse event (AE) was defined as any untoward medical occurrence that does not necessarily have a causal relationship with the medicinal product administered (160). As participants in group three of the feasibility trial did not receive immediate antibiotics, I anticipated that they may have been at higher risk of developing pyelonephritis. Participants were advised by the consenting clinician, and through information in the participant instructions (Appendix 3. 4), to urgently contact a medical professional if they developed upper urinary tract symptoms. I emphasised in study materials and when training recruiting clinicians that a seven-day course (rather than a three-day course) of antibiotics would be required, and that the first line recommended antibiotic for suspected pyelonephritis may be different to the antibiotic that the participant had been prescribed.

Discontinuation of cranberry capsules was advised if a participant had an adverse reaction to the capsules, became pregnant, or developed a concurrent illness that I, or the PI at that practice, felt precluded ongoing trial involvement.

It was possible to report AEs in four ways: (1) Participants could contact the trial team using the contact details within the study pack - of note, 24 hour cover was not provided as this was an open-label, low-risk study; (2) Participants could record details of AEs within the electronic symptom diary; (3) AEs could be reported to participating General Practices; (4) AEs could be picked up during participants' medical records reviews at one month.

3.3.14.2. Serious adverse events

In keeping with the Primary Care Trials Unit adverse event reporting standard operating procedure definition, a serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability/incapacity (160). Other 'important medical events' may also have been considered serious if they endangered the participant or required an intervention to prevent one of the above consequences (160). I would have reported any SAEs to the South Central Oxford B Ethics Committee if I judged that the event was 'related' (that is, resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures (160).

3.3.15. Outcomes

3.3.15.1. Primary

The primary outcomes were feasibility measures, namely: The proportion of diaries partially and fully completed by the end of participant follow-up; the rate of recruitment of participants; the number of participants lost to follow-up and withdrawing from the study; the proportion of eligible potential participants agreeing to participate in the trial; the proportion of invited GPs agreeing to participate in the trial; acceptability of the study to participants through descriptive presentation of participants' electronic diary responses and qualitative insights from interviews with trial and non-trial participants (see chapter 4); and, the acceptability of the study to recruiters through interviews with recruiters to the trial (see chapter 5).

3.3.15.2. Secondary

Secondary outcomes were exploratory, and included: The proportion of participants consuming a course (or part thereof) of antibiotics in intervention and control groups; the number of antibiotic courses (or part thereof) consumed by participants in each group; the duration of symptoms rated moderately bad or worse in treatment and control groups; the symptom burden in treatment and control groups; the proportion of participants experiencing one or more adverse events, serious adverse events, requiring additional input from a healthcare practitioner, or taking time off usual/paid activities in each arm of the trial; the proportion of participants randomised to receive antibiotics only that consumed cranberry products; the proportion of participants using additional treatments for their symptoms in each group; a comparison of time to feeling fully recovered between groups; and a comparison of the proportion experiencing 'double sickening' between treatment and control groups. Of note, I decided to conduct an exploratory analysis of the proportion of participants experiencing 'double sickening' (feeling fully recovered and then subsequently feeling unwell within 2 weeks of trial enrolment) after I had completed the statistical analysis plan, but before I had reviewed the trial data or commenced analyses. I defined double sickening as a participant who selected the fully recovered checkbox in the electronic diary, but subsequently selected the not fully recovered checkbox and did not rate all of their symptoms as zero.

3.3.16. Sample Size

As this was a preliminary study to inform the design and delivery plans for an adequately powered multi-centre randomised trial, I determined that a sample size of around 45 was sufficient to determine feasibility. Given that UTI consultations account for up to 3% of all

GP consultations (11, 12), I anticipated being able to recruit at least two participants per month per General Practice. This would equate to 18 participants from one General Practice over 9 months. I hoped to recruit from a minimum of three General Practices. With a sample size of 45, I would be able to estimate a drop-out rate of 20% with a confidence interval (CI) of 9.6%-34.6%. Sample sizes of between 24 (161) and 50 (162) have been suggested for pilot studies.

3.3.17. Statistical Analyses

3.3.17.1. Primary Analyses

Quantitative measures were expressed as counts and percentages, unless otherwise specified, with no formal statistical testing to assess between group differences.

3.3.17.1.1. Handling missing data

As this was a feasibility trial, I planned to report the absolute number and proportion of participants withdrawing from the study and lost to follow-up, as well as the number and proportion of diaries that were fully and partially completed by participants. Data elicited from minimal datasets obtained at 2 week follow-up calls were used to supplement incomplete diary entries.

3.3.17.1.2. Handling outliers

I did not anticipate outlier data due to the automated checks that were built into REDCap and fired upon data entry (e.g. range checks for numerical values).

Although not anticipated, I planned to transcribe any paper, participant-completed diaries received (due to failure of the electronic system) to an electronic database. I would have

performed a pre-entry review to rule out any obvious errors (e.g. missing pages from the multi-page diary). Had I discovered any irregularities, I may have needed to contact the participant for clarification.

3.3.17.2. Secondary Analyses

A preliminary assessment was made of a range of effectiveness measures, with intention to treat analyses conducted for all outcomes. I decided not to report p values; as the analyses were under-powered, p values may have been misleading. I presented 95% confidence intervals as a measure of precision for point estimates instead. The General Practice site was adjusted for by including a term for site in the model.

3.3.17.2.1. Binary outcomes

The number of participants in each group consuming a course (or part thereof) of antibiotics at two and four weeks, and the number of participants consuming cranberry in the antibiotics alone group were presented as frequencies and proportions. I originally planned to use Log binomial regression to compare the number of participants in each group consuming a course (or part thereof) of antibiotics between groups, with the treatment effects presented as relative risks with 95% Confidence Interval (CI). However, it was not possible to run this regression using the data that I had; an error message was generated by Stata (StataIC 16). This was probably because two of the three groups did not have some people who did and who did not take antibiotics, thus the model was unable to distinguish between them and had insufficient information to work with (see section 3.4.3). I therefore used the 'csi' command in Stata to estimate the difference in proportions with 95% confidence intervals.

3.3.17.2.2. Continuous outcomes

The mean symptom burden for each participant was calculated by summing the total symptom burden for the participant between day two and day four (inclusive) and dividing this by the number of symptom ratings made by the participant between day two and day four (inclusive).

Hierarchical manual imputation (see section 3.3.17.2.5) was used for missing values. To be included in the analysis, after manual imputation, no more than five of the 33 total symptom ratings (11 symptoms rated over three days) could be missing. A linear regression model was fitted with mean symptom burden as the dependent variable and treatment group and mean symptom burden at baseline (i.e. day one) as independent variables. The difference in means with 95% CI was presented. The mean symptom burden at baseline for each participant was calculated by summing the total symptom burden at baseline (on day one) and dividing this by the number of symptom ratings made by the participant on day one. To be included in the analysis, after manual imputation, no more than two of the 11 baseline (day one) symptom ratings could be missing.

3.3.17.2.3. Time to event outcomes

The time to feeling fully recovered was presented using the median, inter-quartile range and range for each group. A Kaplan-Meier plot of the curves for each group along with hazard ratios estimated using the Cox proportional-hazards model was presented. I tested the proportional hazards assumption; all tests of model assumptions conducted can be found in Appendix 3. 10.

3.3.17.2.4. Count outcomes

The number of antibiotic courses (or part thereof) consumed by participants was presented as the mean of each group at two weeks and at four weeks.

I originally planned to use the Chi squared test, or Fisher's exact test if numbers were small, to compare the proportion of AEs/SAEs in each arm of the trial. However, I instead used the 'csi' command to compare the proportion of AEs between groups at two weeks and four weeks, as Fisher's exact test would have generated a p value rather than an effect size estimate with a 95% confidence interval.

The duration of symptoms rated moderately bad or worse was analysed as a count outcome (that is, the number of days of symptoms rated moderately bad or worse), presented using the median and inter-quartile range for each group, and was compared between groups using a negative binomial regression model with duration of moderately bad symptoms as the dependent variable and treatment group as the independent variable. The incidence rate ratio with 95% CI was presented.

The duration of symptoms rated moderately bad or worse was calculated in the following way: Participants with at least one symptom rated at least moderately bad or worse on day 1 of the study were included. Resolution of symptoms was defined as the time at which all symptoms were rated as slightly bad or better. *All symptoms* had to be rated as a slight problem or better for two consecutive days (that is, rated less than 20), in line with methods that have been used in an analogous trial (39). To be included in the analysis, after manual imputation (see section 3.3.17.2.5), no more than two symptom ratings per day could be missing during these two consecutive days.

For example:

Symptom	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Pain	45	40	35	10	5	0
Frequency	15	10	6	_	_	0
Nocturia	30	30	15	9	8	5

In the example above, the duration of symptoms rated moderately bad or worse would be 3 days.

3.3.17.2.5. Handling missing data

As this was a feasibility trial that was not powered for effectiveness outcomes, I did not perform multiple imputation of missing data. A process of hierarchical manual imputation was used, when possible, to complete missing symptom ratings, and is outlined below.

3.3.17.2.5.1. Symptoms resolved tick box

If the 'Do you feel completely recovered today' tick box was selected, zeros were entered from this point onwards for any missing symptom severity ratings.

If the tick box had not been selected at all, resolution of symptoms was taken as the first day at which all symptoms were rated <10.

3.3.17.2.5.2. Interpolation of symptom ratings

Any missing symptom rating that was preceded with a value and followed by the same value, was entered with the same value.

3.3.17.2.5.3. Mean symptom burden

As described in section 3.3.17.2.2, participants were included in this analysis if, after manual imputation, no more than five of the 33 symptom ratings between days two and four (inclusive) were missing, and no more than two of the 11 baseline symptom ratings (Day one) were missing.

3.3.17.2.5.4. Duration of symptoms rated moderately bad of worse

As described in section 3.3.17.2.4, participants were included in this analysis if, after manual imputation, no more than two of the 11 symptom ratings were missing per day during the two consecutive days of symptoms being rated a slight problem or better.

3.3.17.2.5.5. Hierarchy of data

Participant electronic diary information was used as the primary data source, with the following exceptions:

Upon finding a discrepancy between electronic diary data and information obtained at the two week follow-up call, electronic diary data was taken as the primary data source, unless the participant specifically mentioned at the two week phone call that they filled in the electronic diary erroneously.

If there was a discrepancy between the participant record and the data in the medical records review, I queried it with the recruiter that completed the medical records review. Once the query was resolved, the data in the medical records review took precedence.

If data had not been captured within the electronic diary, it was obtained from the minimum data set collected at the two week follow-up call and/or information obtained from the medical records review.

When I could not obtain data from any of these sources, and calculation of a given secondary outcome using the participant's data was not be possible, the participant's data was counted as missing for the secondary outcome in question.

All data were analysed using intention to treat (ITT) analysis. Participants were therefore analysed according to the group that they were randomised to, irrespective of the treatment they actually received. I wrote a Statistical Analysis Plan (SAP), which was signed off by NW (statistician).

3.3.18. Qualitative Analyses

Upon completing the final day of the electronic diary (day 14), free-text boxes allowed participants to provide narrative feedback on their trial experience. Participants were able to provide general comments about the trial, as well as comments specifically about any difficulties using the electronic diary, difficulties using the rating scale of 0 to 50, and any problems related to consuming cranberry capsules (if applicable). I summarised the quotes and present the findings below (section 3.4.5). Of note, the results of formal qualitative interviews with trial participants are presented in chapters 4 and 5.

3.3.19. Trial Management and Oversight

In addition to being the Chief Investigator (CI), I assumed the role of Trial Manager. I was in regular contact with the recruiting sites and responded to their queries. I sent weekly newsletters providing recruitment updates and helpful tips based on queries that had been raised or issues that I had noticed. I manned the trial telephone; when I was not available, this was diverted to a trial administrator (MC), who would take a message and forward it to me.

Throughout the feasibility trial, I ensured that all sites were well stocked with study supplies and that site files were up to date; posting or hand-delivering updated trial documents (e.g. informed consent forms) and study product as needed.

The Trial Steering Committee (TSC) provided overall supervision for the trial. The composition of the TSC is detailed in Appendix 3. 7. As I anticipated this to be a low risk study, there was no separate Data Monitoring Committee (DMC). The TSC assumed the role of the DMC in safeguarding the interests of trial participants and monitoring the overall conduct of the trial. I set the agenda and created reports for TSC meetings. I also chaired the meetings (three in total), and typed and circulated the minutes to committee members.

Recruitment to the trial was slow initially. I convened a TSC meeting, and from the data in the report that I prepared, it was evident that some women declined to take part as they were not keen on the idea of delaying antibiotics. The TSC suggested that I could create a script to both explain and positively frame the delayed antibiotic group (as an opportunity to potentially avoid antibiotics), and also to create desk prompts for sites. In addition to these initiatives, I met in person and/or spoke on the telephone with each of the sites to discuss recruitment, to find out what was/was not working well, and to share successful strategies with sites. Recruitment subsequently improved substantially.

I led regular meetings with the smaller Trial Management Group (TMG) at roughly monthly intervals during active recruitment (see Appendix 3. 8 for the TMG composition). I provided updates on the day-to-day running of the trial. I created the agenda, chaired the meetings (eleven in total), and circulated meeting minutes to members.

3.3.20. Patient and Public Involvement (PPI)

Through advertisement in local and national PPI fora, I recruited four members of the public to form a PPI group. These PPI contributors have been closely involved with the trial from the outset, and two of the PPI members sat on the TSC (see Appendix 3. 7). During trial conception and development, they confirmed that the topic chosen was important. They critiqued all public facing trial documentation to ensure that it was free of jargon, and their feedback was incorporated. They were also involved in the design of the electronic diary, helping to ensure that it was user-friendly. PPI contributors unanimously felt that the diary would not be onerous for participants and suggested it might make the experience of participating in the trial more meaningful, stating "…completing the symptom diary hooks people in. It makes them feel that they are contributing." The results of the feasibility trial were shared with PPI contributors, allowing them to give their views on ways to explain the findings, which have been incorporated into the discussion. PPI contributors have also helped to inform the dissemination of the study findings, and have provided feedback on an explainer video of the findings that is aimed at the lay public (see section 6.4.1).

3.4. Results

3.4.1. Baseline Tables

Baseline information was completed electronically by participants upon accessing the electronic diary on day one of enrolment, prior to inputting their day one symptom ratings. The mean age of participants was 48.3 years (range: 18 to 81 years). The mean age of women in the immediate cranberry and delayed antibiotics group was lower than the other two groups. There was no evidence of failure of randomisation, thus, this was most likely to be a spurious finding, which would likely not have occurred had the trial been adequately powered for the secondary outcomes. Most women had experienced a previous UTI (85.4%, 35/41). 75.6% (31/41) of respondents were expecting antibiotics. 61% (25/41) believed that cranberry could help their symptoms, whilst 24.4% (10/41) believed that their symptoms could improve without antibiotics (Table 3. 1).

Table 3. 1 Baseline characteristics of participants

Proportion (%), unless otherwise specified	Immediate antibiotics alone (n=15)	Immediate antibiotics and immediate cranberry (n=15)	Immediate cranberry and delayed antibiotics (n=16)	Total (n=46)
Age in years, Mean (SD) [range]	52.4 (21.4) [18-81]	52.4 (22.4) [19-81]	40.8 (14.0) [20-63]	48.3 (19.9) [18-81]
Previous UTI				
Yes	12/15 (80%)	12/13 (92.3%)	11/13 (84.6%)	35/41 (85.4%)
No	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6)
Missing	0/15	2/15	3/16	5/46
Previous UTI in the past year				
Yes	7/15 (46.7%)	6/13 (46.2%)	6/13 (46.2%)	19/41 (46.3%)
No	5/15 (33.3%)	6/13 (46.2%)	5/13 (38.5%)	16/41 (39.0%)
N/A *(Have never had a previous UTI)*	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6%)

Missing	0/15	2/15	3/16	5/46
If had a UTI in the past year, number of months since last UTI – mean (SD), median [range]	5.4 (4.5), 4 [0-12] n=7	5 (4.2), 5 [0-11] n=5	7 (3.6), 7 [3-12] n=5	5.8 (4.2), 5 [0-12] n=17
Can't remember	0/15 (0%)	1/13 (7.7%)	1/12 (8.3%)	2/40 (5%)
Not applicable	8/15 (53.3%)	7/13 (53.9%)	6/12 (50%)	21/40 (52.5%)
Missing	0/15	2/15	4/16	6/46
Number of UTIs in the past year:				
Zero	5/15 (33.3%)	7/13 (53.9%)	4/13 (30.8%)	16/41 (39.0%)
One	3/15 (20%)	2/13 (15.4%)	5/13 (38.5%)	10/41 (24.4%)
Two	2/15 (13.3%)	2/13 (15.4%)	1/13 (7.7%)	5/41 (12.2%)
Three or more	2/15 (13.3%)	1/13 (7.7%)	1/13 (7.7%)	4/41 (9.8%)
Not applicable *(Have never had a previous UTI)*	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6%)
Missing	0/15	2/15	3/16	5/46
Were you expecting antibiotic treatment?				
Yes	13/15 (86.7%)	10/13 (76.9%)	8/13 (61.5%)	31/41 (75.6%)
No	0/15 (0%)	1/13 (7.7%)	1/13 (7.7%)	2/41 (4.9%)
Unsure	2/15 (13.3%)	2/13 (15.4%)	4/13 (30.8%)	8/41 (19.5%)
Missing	0/15	2/15	3/16	5/46
Were you expecting tests/investigations?				
Yes	12/15 (80%)	10/13 (76.9%)	8/13 (61.5%)	30/41 (73.2%)
No	3/15 (20%)	3/13 (23.1%)	4/13 (30.8%)	10/41 (24.4%)
Unsure	0/15 (0%)	0/13 (0%)	1/13 (7.7%)	1/41 (2.4%)
Missing	0/15	2/15	3/16	5/46
Were you expecting advice?				
Yes	12/15 (80%)	11/12 (91.7%)	13/13 (100%)	36/40 (90%)
No	2/15 (13.3%)	1/12 (8.3%)	0/13 (0%)	3/40 (7.5%)
Unsure	1/15 (6.7%)	0/12 (0%)	0/13 (0%)	1/40 (2.5%)
Missing	0/15	3/15	3/16	6/46
Were you expecting something else?				

Yes	0/15 (0%)	1/13 (7.7%) - *Information and prescription (1 participant)*	0/13 (0%)	1/41 (2.4%)
No	15/15 (100%)	10/13 (76.9%)	11/13 (84.6%)	36/41 (87.8%)
Unsure	0/15 (0%)	2/13 (15.4%)	2/13 (15.4%)	4/41 (9.8%)
Missing	0/15	2/15	3/16	5/46
Was your last UTI treated with antibiotics?				
Yes	8/15 (53.3%)	9/13 (69.2%)	10/13 (76.9%)	27/41 (65.9%)
No	4/15 (26.7%)	3/13 (23.1%)	1/13 (7.7%)	8/41 (19.5%)
Not applicable	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6%)
Missing	0/15	2/15	3/16	5/46
Was your last UTI treated with something other than antibiotics?				
Yes	2/15 (13.3%) - *Cystitis sachets (2 participants)*	1/13 (7.7%) - *Cystitis sachets (1 participant)*	0/13 (0%)	3/41 (7.3%)
No	10/15 (66.7%)	11/13 (84.6%)	11/13 (84.6%)	32/41 (78.1%)
Not applicable	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6%)
Missing	0/15	2/15	3/16	5/46
Did you receive no treatment for your last UTI?				
Yes	1/15 (6.7%)	0/13 (0%)	0/13 (0%)	1/41 (2.4%)
No	11/15 (73.3%)	12/13 (92.3%)	11/13 (84.6%)	34/41 (82.9%)
Not applicable	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6%)
Missing	0/15	2/15	3/16	5/46
Unable to remember how last UTI was treated				
Yes	1/15 (6.7%)	1/13 (7.7%)	1/13 (7.7%)	3/41 (7.3%)
No	11/15 (73.3%)	11/13 (84.6%)	10/13 (76.9%)	32/41 (78.1%)
Not applicable	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6%)
Missing	0/15	2/15	3/16	5/46

Treatments tried before consulting primary care				
Cranberry products				
Yes	2/15 (13.3%)	3/13 (23.1%)	3/13 (23.1%)	8/41 (19.5%)
No	13/15 (86.7%)	10/13 (76.9%)	10/13 (76.9%)	33/41 (80.5%)
Missing	0/15	2/15	3/16	5/46
Other fruit juice				
Yes	1/15 (93.3%)	1/13 (7.7%)	0/13 (0%)	2/41 (4.9%)
No	14/15 (93.3%)	12/13 (92.3%)	13/13 (100%)	39/41 (95.1%)
Missing	0/15	2/15	3/16	5/46
Bicarbonate solution				
Yes	0/15 (0%)	0/13 (0%)	0/13 (0%)	0/41 (0%)
No	15/15 (100%)	13/13 (100%)	13/13 (100%)	41/41 (100%)
Missing	0/15	2/15	3/16	5/46
Sodium/potassium citrate (cystitis sachets)				
Yes	3/15 (20%)	7/13 (53.9%)	1/13 (7.7%)	11/41 (26.8%)
No	12/15 (80%)	6/13 (46.2%)	12/13 (92.3%)	30/41 (73.2%)
Missing	0/15	2/15	3/16	5/46
Uvacin/Uva ursi (bearberry)				
Yes	0/15 (0%)	0/13 (0%)	0/13 (0%)	0/41 (0%)
No	15/15 (100%)	13/13 (100%)	13/13 (100%)	41/41 (100%)
Missing	0/15	2/15	3/16	5/46
Pain relief (e.g. paracetamol/Ibuprofen)				
Yes	6/15 (40%)	7/13 (53.9%)	4/13 (30.8%)	17/41 (41.5%)
No	9/15 (60%)	6/13 (46.2%)	9/13 (69.2%)	24/41 (58.5%)
Missing	0/15	2/15	3/16	5/46
Other treatment used?				
Yes	2/15 (13.3%) – *Water (2 participants)*	2/13 (15.4%) – *Tea tree in bath (1 participant) Sachets (1 participant)*	2/13 (15.4%) – *Water (2 participants)*	6/41 (14.6%)
No	13/15 (86.7%)	11/13 (84.6%)	11/13 (84.6%)	35/41 (85.4%)

Missing	0/15	2/15	3/16	5/46
None				
Yes	7/15 (46.7%)	2/13 (15.4%)	5/13 (38.5%)	14/41 (34.2%)
No	8/15 (53.3%)	11/13 (84.6%)	8/13 (61.5%)	27/41 (65.9%)
Missing	0/15	2/15	3/16	5/46
Number of days symptomatic				
0 days	1/15 (6.7%)	2/13 (15.4%)	1/13 (7.7%)	4/41 (9.8%)
1 day	3/15 (20%)	1/13 (7.7%)	2/13 (15.4%)	6/41 (14.6%)
2 days	4/15 (26.7%)	3/13 (23.1%)	5/13 (38.5%)	12/41 (29.3%)
3 days	2/15 (13.3%)	2/13 (15.4%)	4/13 (30.8%)	8/41 (19.5%)
>3 days	5/15 (33.3%)	5/13 (38.5%)	1/13 (7.7%)	11/41 (26.8%)
Missing	0/15	2/15	3/16	5/46
Belief that cranberry can help symptoms				
Yes	10/15 (66.7%)	7/13 (53.9%)	8/13 (61.5%)	25/41 (61%)
No	1/15 (6.7%)	0/13 (0%)	0/13 (0%)	1/41 (2.4%)
Unsure	4/15 (26.7%)	6/13 (46.2%)	5/13 (38.5%)	15/41 (36.6%)
Missing	0/15	2/15	3/16	5/46
Belief that symptoms can get better without antibiotics				
Yes	5/15 (33.3%)	1/13 (7.7%)	4/13 (30.8%)	10/41 (24.4%)
No	4/15 (26.7%)	4/13 (30.8%)	2/13 (15.4%)	10/41 (24.4%)
Unsure	6/15 (40%)	8/13 (61.5%)	7/13 (53.9%)	21/41 (51.2%)
Missing	0/15	2/15	3/16	5/46

3.4.2. Primary Outcomes

Forty-six women were recruited to the trial, surpassing the target of 45 (see Figure 3. 1). Of the 21 women who were eligible but declined to take part, the most common reason was not wishing to be randomised to receive delayed antibiotics (42.9%, 9/21) (see Table 3. 2). The first participant was recruited on 11th July 2019 and the final participant was recruited on 2nd

December 2019, with the final follow-up taking place on 30th December 2019. The findings of qualitative interviews, including interviews with 14 trial participants and eight trial recruiters, are presented in chapters 4 and 5, respectively.

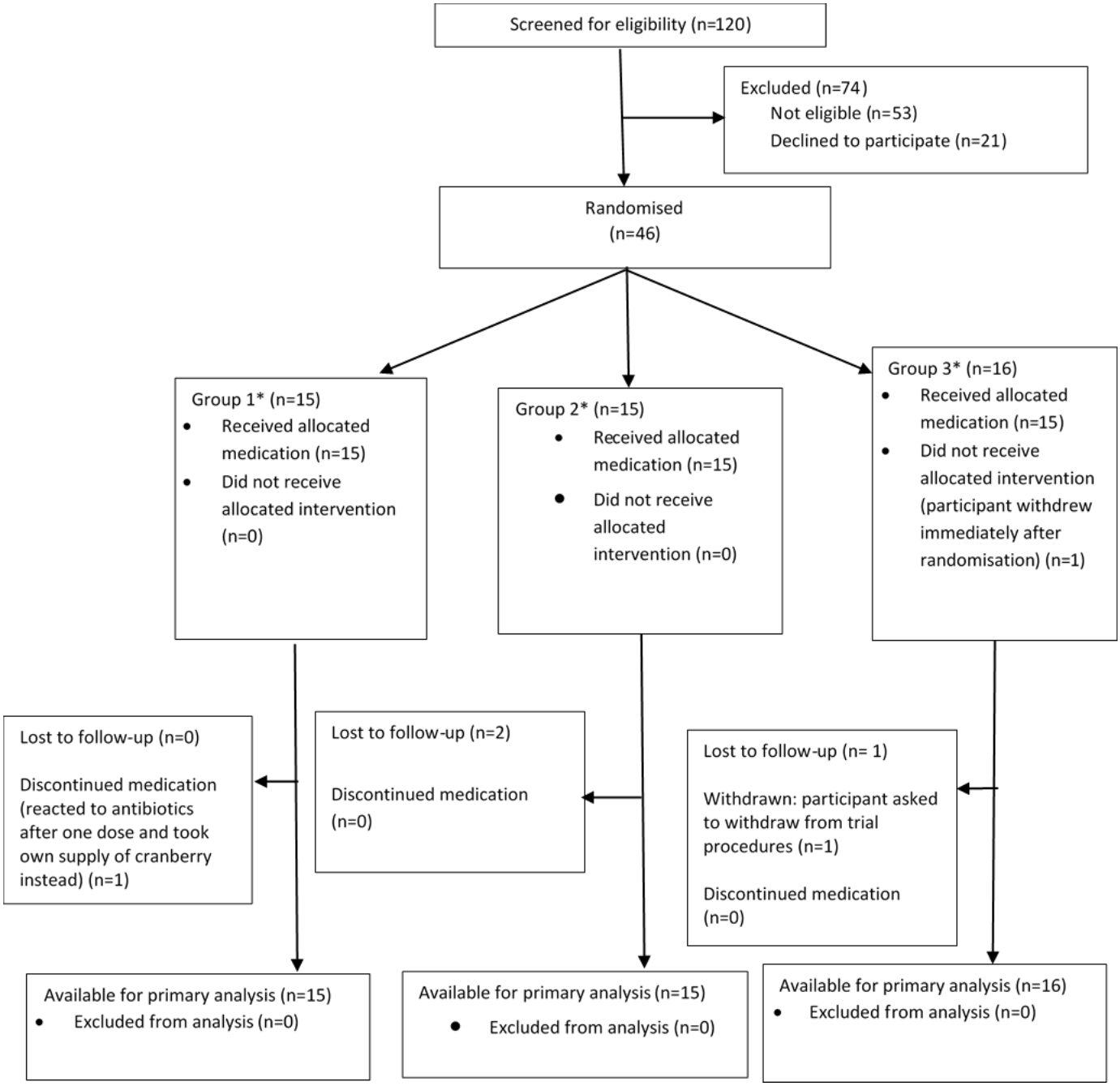


Figure 3. 1 CONSORT diagram showing the flow of participants through the trial

*Group 1 – Immediate antibiotics alone (control); Group 2 – Immediate antibiotics and immediate cranberry capsules; Group 3 – Immediate cranberry capsules and delayed antibiotics

Table 3. 2 Reasons for patients declining to take part in the CUTI feasibility trial

Reason	**n =**
Didn't want to be randomised to receive delayed antibiotics	9
Not interested/'declined'	6
Too busy	3
Had surgery the preceding day	1
Wanted to await Mid-stream Urine result before starting antibiotics	1
Due to go on holiday	1
Total	21

In total, 89.1% (41/46) of electronic diaries had some data entered by participants, whilst 69.6% (32/46) of electronic diaries were fully complete (see Table 3. 3). There were no electronic diary failures necessitating the issue of paper diaries. A mean of 9.2 participants were recruited per month, which exceeded predicted recruitment of eight participants each month (see Figure 3. 2 and Figure 3. 2). All General Practices that were invited to recruit to the trial agreed to participate (100%, 5/5), however, one General Practice withdrew prior to site opening as they predicted that they would no longer have capacity to support the trial (see section 3.3.5).

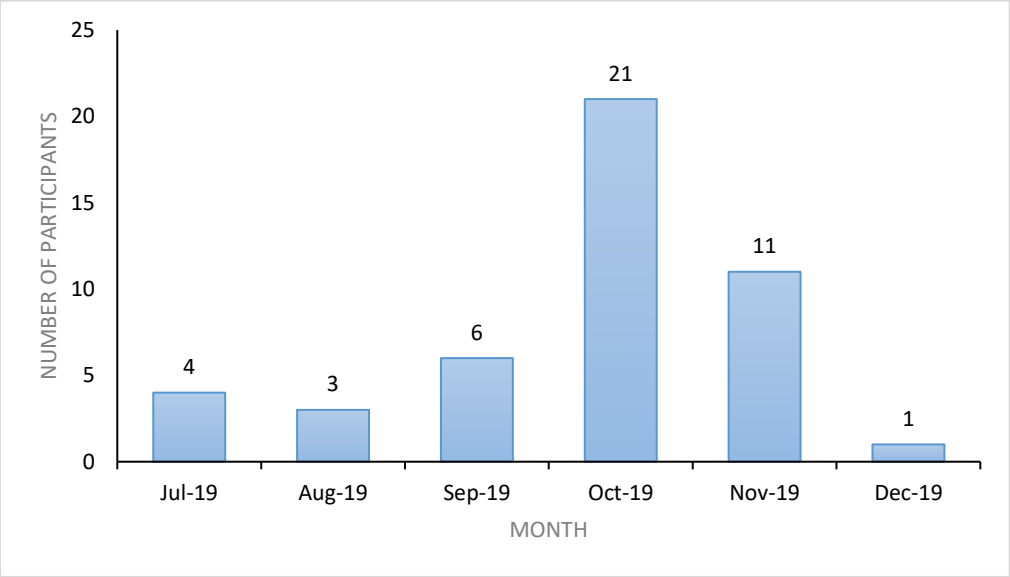


Figure 3. 2 Number of participants recruited per month

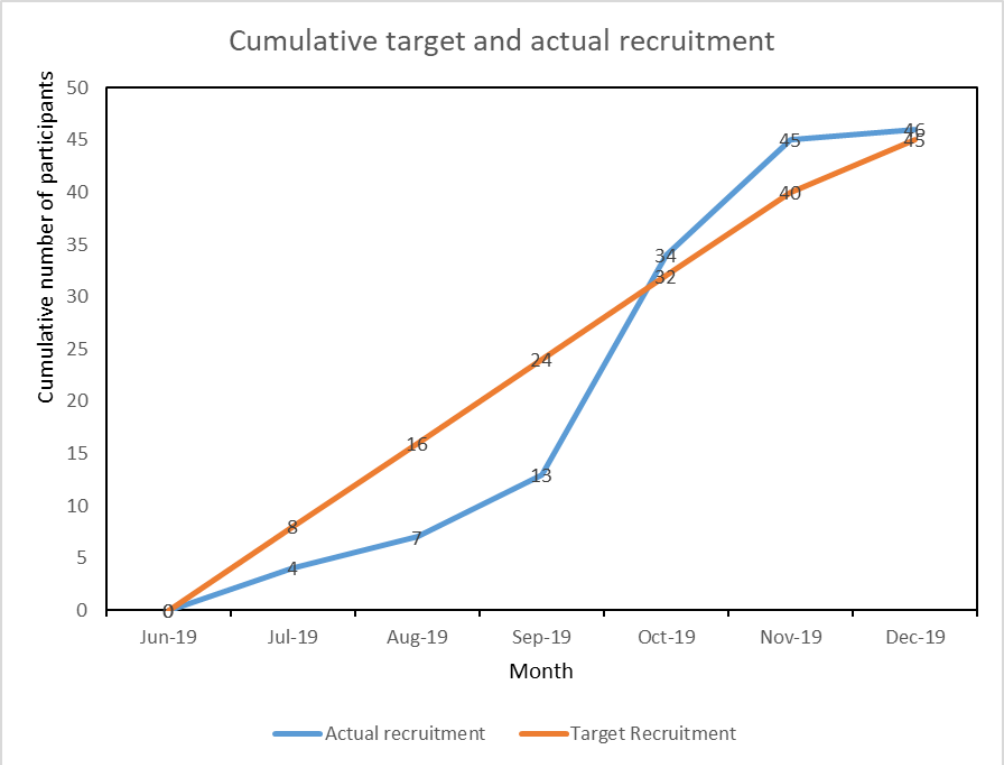


Figure 3. 3 Actual and target cumulative recruitment

Table 3. 3 Primary outcomes

Proportion (%), unless otherwise specified	Immediate antibiotics alone (n=15)	Immediate antibiotics and immediate cranberry (n=15)	Immediate cranberry and delayed antibiotics (n=16)	Total (n=46)
Number of diaries with some data points entered by participant by end of participant follow-up	15 (100%)	13 (86.7%)	13 (81.3%)	41 (89.1%)
Number of diaries fully completed by participant by end of participant follow-up	13 (86.7%)	10 (66.7%)	9 (56.3%)	32 (69.6%)
Paper diaries issued due to failure of electronic diary	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number randomised as a proportion of the target recruitment number	46/45 (102.2%)			
Number randomised as a proportion of invited participants	46/120 (38.3%)			
Number randomised as a proportion of eligible participants	46/67 (68.7%)			
No. patients invited				120
No. patients eligible				67
No. participants enrolled	15	15	16	46
No. participants randomised	15	15	16	46
No. recruited per month (n)				9.2
Number of participants lost to follow-up	0 (0%)	2 (13.3%)	1 (6.3%)	3 (6.5%)
Number of participants withdrawing from study	0 (0%)	0 (0%)	2 (12.5%)	2 (4.4%)
Side effects or problems related to cranberry consumption				
Yes	0/13 (0%)	0/10 (0%)	1/11 (9.1%)	1/34 (2.9%)
No	1/13 (7.7%)	10/10 (100%)	10/11 (90.9%)	21/34 (61.8%)
Not applicable	12/13 (92.3%)	0/10 (0%)	0/11 (0%)	12/34 (35.3%)
Missing	2/15	5/15	5/16	12/46
Problems completing the electronic diary				
No problem	14/14 (100%)	9/10 (90%)	9/11 (81.8%)	32/35 (91.4%)
Some problems	0/14 (0%)	1/10 (10%)	2/11 (18.2%)	3/35 (8.6%)
Lots of problems	0/14 (0%)	0/10 (0%)	0/11 (0%)	0/35 (0%)
Missing	1/15	5/15	5/16	11/46

Problems using the scale of 0-50				
No problem	12/14 (85.7%)	9/9 (100%)	10/12 (83.3%)	31/35 (88.6%)
Some problems	2/14 (14.3%)	0/9 (0%)	2/12 (16.7%)	4/35 (11.4%)
Lots of problems	0/14 (0%)	0/9 (0%)	0/12 (0%)	0/35 (0%)
Missing	1/15	6/15	4/16	11/46
Proportion of invited GP practices agreeing to participate in the trial	5/5 (100%)			
Proportion of invited GP practices opened and recruiting to the trial	4/5 (80%)			
Acceptability of the study to participants and recruiters, participants' experience of having a UTI and thoughts on self-help for UTIs.	Interviews with trial participants and recruiters are reported in chapters 4 and 5			

Only one participant reported a side effect or problem related to consuming cranberry capsules in the electronic diary (see Table 3. 3); she reported feeling sick, but she was unsure whether this was due to the cranberry capsules or the UTI. Few participants reported experiencing problems completing the electronic diary (8.6%, 3/35) or rating their symptoms using the scale of 0 to 50 (11.4%, 4/35).

Three participants were lost to follow-up (see Figure 3. 1). Loss to follow-up was determined to have occurred when a participant did not make any electronic diary entries and I was not able to contact them at the two week follow-up call. Two participants withdrew from the study (see Figure 3. 1). One participant was consented and randomly assigned to immediate cranberry capsules with delayed antibiotics. As soon as she received this assignment, she decided to withdraw from the study and she did not receive the cranberry capsules. Another participant was consented and also randomised to immediate cranberry and delayed antibiotics. The day after being enrolled, she emailed the trial team asking to be removed

from the mailing list (links to the electronic diary were sent by email). In light of this request, the participant was withdrawn from the trial.

3.4.3. Secondary Outcomes

Approximately one third of respondents reported contacting a healthcare practitioner within two weeks of being enrolled (36.4%, 12/33). Most contacted their General Practice (GP or nurse at their surgery) - one woman reported liaising with a pharmacist, and another contacted an out of hours GP. No participants reported requiring Accident and Emergency or secondary care input. Just over half (54.3%, 25/46) of the urine samples at the time of enrolment were positive (organism growth greater than 10^5 CFU/ml).

Exploratory analyses of effectiveness were conducted (see Table 3. 4). As this trial was not powered for these analyses I have not reported p values, and any differences detected between groups are inconclusive.

Table 3. 4 Exploratory effectiveness outcomes

	Proportion (%) of participants consuming a course of antibiotics (or part thereof) at 2 weeks [risk ratio (95% CI)]‡	Proportion (%) of participants consuming a course of antibiotics (or part thereof) at 4 weeks [risk ratio (95% CI)]‡	Mean (SD) number of courses of antibiotics consumed at 2 weeks [adjusted incidence rate ratio (95% CI)] ‡†	Mean (SD) number of courses of antibiotics consumed at 4 weeks [adjusted incidence rate ratio (95% CI)] ‡†	Median (IQR) number of days of symptoms rated moderately bad or worse [adjusted incidence rate ratio (95% CI)] ‡†	Mean (SD) symptom burden from day 2 to 4 inclusive [adjusted mean difference (95% CI)] ‡†¥	Median (IQR) days to feeling fully recovered [adjusted hazard ratio (95% CI)] ‡†	Proportion (%) of participants experiencing double sickening up to 2 weeks [risk ratio (95% CI)]‡
Group 1* (Control) n=15	15/15 (100%) Missing: 0/15	15/15 (100%) Missing: 0/15	1.5 (0.5) Missing: 0/15	1.6 (0.6) Missing: 0/15	2 (1 to 2) Missing: 0/15	6.3 (3.4) Missing: 1/15	5 (4 to 6) Missing: 0/15	6/14 (42.9%) Missing: 1/15
Group 2* n=15	13/13 (100%) [1 (1 to 1)] Missing: 2/15	13/13 (100%) [1 (1 to 1)] Missing: 2/15	1.1 (0.3) [0.7 (0.4 to 1.4)] Missing: 2/15	1.2 (0.4) [0.7 (0.4 to 1.4)] Missing: 2/15	2 (1 to 3) [1.2 (0.7 to 2.1)] Missing: 2/15	6.2 (8.0) [0.6 (-4.0 to 5.3)] Missing: 4/15	4 (3 to 6) [1.7 (0.7 to 4.1)] Missing: 2/15	3/11 (27.3%) [0.6 (0.2 to 2.0)] Missing: 4/15
Group 3* n=16	11/14 (78.6%) [0.8 (0.6 to 1.0] Missing: 2/16	11/14 (78.6%) [0.8 (0.6 to 1.0] Missing: 2/16	0.9 (0.6) [0.6 (0.3 to 1.2)] Missing: 2/16	0.9 (0.6) [0.6 (0.3 to 1.2)] Missing: 2/16	4 (2 to 8) [2.9 (1.7 to 5.1)] Missing: 4/16	11.2 (8.5) [7.9 (2.6 to 13.2)] Missing: 7/16	6 (5 to 9) [0.6 (0.2 to 1.4)] Missing: 3/16	0/12 (0%) [0 (N/A)] Missing: 4/16

*Group 1 – Immediate antibiotics alone (control); Group 2 – Immediate antibiotics and immediate cranberry; Group 3 – Immediate cranberry and delayed antibiotics.
‡Group 2 and group 3 were compared with Group 1 (controls).
†Model adjusted for site
¥ The mean symptom burden for each participant was calculated by summing the total ratings for all symptoms between day 2 and day 4 (inclusive) and dividing this by the number of symptom ratings made by the participant between day 2 and day 4 (inclusive).
Abbreviations: SD: Standard Deviation; %: Percentage

There was a 20% reduction in the risk of consuming a course of antibiotics (or part thereof) in the immediate cranberry and delayed antibiotics group (group 3), compared with the immediate antibiotics alone group (group 1- controls). This was the case at both 2 weeks and 4 weeks (risk ratio 0.8; 95% CI: 0.6 to 1.0). The number of courses of antibiotics consumed at 2 weeks and at 4 weeks was reduced in groups 2 (immediate antibiotics and immediate cranberry) and 3 (immediate cranberry and delayed antibiotics), compared with the control group (adjusted incidence rate ratios: 0.7; 95% CI: 0.4 to 1.4 and 0.6; 95% CI: 0.3 to 1.2 for group 2 and group 3, respectively). Participants in groups 2 and 3 had a longer duration of symptoms rated moderately bad or worse, compared with those in the control group (adjusted incidence rate ratios: 1.2; 95% CI: 0.7 to 2.1 and 2.9; 95% CI 1.7 to 5.1 for group 2 and group 3, respectively). The mean symptom burden (from day 2 to day 4 inclusive) was reduced in group 2 participants (adjusted mean difference: 0.6; 95% CI: -4.0 to 5.3) and increased in group 3 participants (adjusted mean difference: 7.9; 95% CI 2.6 to 13.2), compared with the control group. Similarly, the time to feeling recovered was reduced in group 2 (adjusted hazard ratio 1.7; 95% CI: 0.7 to 4.1) but increased in group 3 (adjusted hazard ratio 0.6; 95% CI: 0.2 to 1.4), compared with controls (see Appendix 3. 9 for Kaplan Meier plot). Of women randomly assigned to take antibiotics alone (controls), one third of respondents reported consuming cranberry products (33.3%, 4/12) (see Table 3. 5). The tests of model assumptions that I carried out are presented in Appendix 3. 10.

An exploratory analysis was conducted to compare the proportion of participants experiencing ‘double sickening’ between groups at two weeks (that is, feeling fully recovered and then subsequently feeling unwell within two weeks of trial enrolment). Given the short period of time over which this was assessed (two weeks), it is likely that these double sickening episodes represented incompletely treated infection, rather than a new infection.

Compared with the control group, group 2 participants had a reduced risk of experiencing double sickening (risk ratio 0.6; 95% CI: 0.2 to 2.0), whilst none of the group 3 participants experienced double sickening.

Table 3. 5 Secondary outcomes

Proportion (%), unless otherwise specified	Immediate antibiotics alone (n=15)	Immediate antibiotics and immediate cranberry (n=15)	Immediate cranberry and delayed antibiotics (n=16)	Total (n=46)
Any of the following treatments used in the past 2 weeks (not including study medication)				
Cranberry products				
Yes	4/12 (33.3%)	2/9 (22.2%)	2/9 (22.2%)	8/30 (26.7%)
No	8/12 (66.7%)	7/9 (77.8%)	7/9 (77.8%)	22/30 (73.3%)
Missing	3/15	6/15	7/16	16/46
Other fruit juice				
Yes	0/12 (0%)	0/9 (0%)	0/9 (0%)	0/30 (0%)
No	12/12 (100%)	9/9 (100%)	9/9 (100%)	30/30 (100%)
Missing	3/15	6/15	7/16	16/46
Bicarbonate solution				
Yes	0/12 (0%)	0/9 (0%)	0/9 (0%)	0/30 (0%)
No	12/12 (100%)	9/9 (100%)	9/9 (100%)	30/30 (100%)
Missing	3/15	6/15	7/16	16/46
Sodium/potassium citrate (cystitis sachets)				
Yes	0/12 (0%)	0/9 (0%)	1/9 (11.1%)	1/30 (3.3%)
No	12/12 (100%)	9/9 (100%)	8/9 (88.9%)	29/30 (96.7%)
Missing	3/15	6/15	7/16	16/46
Uvacin/Uva ursi (bearberry)				
Yes	0/12 (0%)	0/9 (0%)	0/9 (0%)	0/30 (0%)
No	12/12 (100%)	9/9 (100%)	9/9 (100%)	30/30 (100%)
Missing	3/15	6/15	7/16	16/46

Pain relief (e.g. paracetamol/Ibuprofen)				
Yes	5/12 (33.3%)	1/9 (11.1%)	5/9 (55.6%)	11/30 (36.7%)
No	7/12 (58.3%)	8/9 (88.9%)	4/9 (44.4%)	19/30 (63.3%)
Missing	3/15	6/15	7/16	16/46
Other				
Yes	0/12 (0%)	0/9 (0%)	0/9 (0%)	0/30 (0%)
No	12/12 (100%)	9/9 (100%)	9/9 (100%)	30/30 (100%)
Missing	3/15	6/15	7/16	16/46
None				
Yes	5/12 (41.7%)	6/9 (66.7%)	3/9 (33.3%)	14/30 (46.7%)
No	7/12 (58.3%)	3/9 (33.3%)	6/9 (66.7%)	16/30 (53.3%)
Missing	3/15	6/15	7/16	16/46
Time off paid work or normal activities				
Yes	5/13 (38.5%)	2/10 (20%)	3/9 (33.3%)	10/32 (31.3%)
No. of days, median (IQR)	1 (1-2)	5 (2-8)	2 (1-2)	2 (1-2)
No	8/13 (61.5%)	8/10 (80%)	6/9 (66.7%)	22/32 (68.8%)
Missing	2/15	5/15	7/16	14/46
Healthcare professional consulted at GP practice				
Yes	6/13 (46.2%)	1/8 (12.5%)	5/12 (41.7%)	12/33 (36.4%)
No	7/13 (53.9%)	7/8 (87.5%)	7/12 (58.3%)	21/33 (63.6%)
Missing	2/15	7/15	4/16	13/46
GP at surgery				
Yes	3/13 (23.1%)	0/8 (0%)	2/12 (16.7%)	5/33 (15.2%)
No. of times, median (IQR)	1 (1-1)	N/A	1 (1-1)	1 (1-1)
No	3/13 (23.1%)	1/8 (12.5%)	3/12 (25%)	7/33 (21.2%)
Not applicable	7/13 (53.9%)	7/8 (87.5%)	7/12 (58.3%)	21/33 (63.6%)
Missing	2/15	7/15	4/16	13/46
Nurse at surgery				
Yes	2/13 (15.4%)	1/8 (12.5%)	1/12 (8.3%)	4/33 (12.1%)

No. of times, median (IQR)	1 (1-1)	2 (2-2)	1 (1-1)	1 (1-1.5)
No	4/13 (30.8%)	0/8 (0%)	4/12 (33.3%)	8/33 (24.2%)
Not applicable	7/13 (53.9%)	7/8 (87.5%)	7/12 (58.3%)	21/33 (63.6%)
Missing	2/15	7/15	4/16	13/46
GP at home				
Yes	0/13 (0%)	0/8 (0%)	0/12 (0%)	0/33 (0%)
No. of times, median (IQR)	N/A	N/A	N/A	N/A
No	6/13 (46.2%)	1/8 (12.5%)	5/12 (41.7%)	12/33 (36.4%)
Not applicable	7/13 (53.9%)	7/8 (87.5%)	7/12 (58.3%)	21/33 (63.6%)
Missing	2/15	7/15	4/16	13/46
OOH doctor				
Yes	1/13 (7.7%)	0/8 (0%)	0/12 (0%)	1/33 (3.0%)
No. of times, median (IQR)	1 (1-1)	N/A	N/A	1 (1-1)
No	5/13 (38.5%)	1/8 (12.5%)	5/12 (41.7%)	11/33 (33.3%)
Not applicable	7/13 (53.9%)	7/18 (87.5%)	7/12 (58.3%)	21/33 (63.6%)
Missing	2/15	7/15	4/16	13/46
Other				
Yes	0/13 (0%)	0/8 (0%)	2/12 (16.7%) – *Pharmacist (1 participant), Phoned GP (1 participant)*	2/33 (6.1%)
No. of times, median (IQR)	N/A	N/A	1 (1-1)	1 (1-1)
No	6/13 (46.2%)	1/8 (12.5%)	3/12 (25%)	10/33 (30.3%)
Not applicable	7/13 (53.9%)	7/8 (87.5%)	7/12 (58.3%)	21/33 (63.6%)
Missing	2/15	7/15	4/16	13/46
Healthcare professional consulted at A&E				
Yes	0/13 (0%)	0/10 (0%)	0/12 (0%)	0/35 (0%)
No	13/13 (100%)	10/10 (100%)	12/12 (100%)	35/35 (100%)

Missing	2/15	5/15	4/16	11/46
No. of times, median (IQR)	N/A	N/A	N/A	N/A
Seen by a specialist (excluding hospital admission)				
Yes	0/13 (0%)	0/10 (0%)	0/12 (0%)	0/35 (0%)
No	13/13 (100%)	10/10 (100%)	12/12 (100%)	35/35 (100%)
Missing	2/15	5/15	4/16	11/46
No. of times, median (IQR)	N/A	N/A	N/A	N/A
Admitted to hospital				
Yes	0/13 (0%)	0/10 (0%)	0/12 (0%)	0/35 (0%)
No	13/13 (100%)	10/10 (100%)	12/12 (100%)	35/35 (100%)
Missing	2/15	5/15	4/16	11/46
No. of nights, median (IQR)	N/A	N/A	N/A	N/A
Positive mid-stream urine culture				
Yes	10/15 (66.7%)	7/15 (46.7%)	8/16 (50%)	25/46 (54.3%)
No	5/15 (33.3%)	8/15 (53.3%)	8/16 (50%)	21/46 (45.7%)
Missing	0/15	0/15	0/16	0/46
Proportion with a positive mid-stream urine culture	54.3%			

All outcomes reported in relation to the two weeks following trial enrolment.

3.4.4. Harms

Seven adverse events occurred (see Table 3. 6). Adverse event numbers three and four occurred in the same participant. Two adverse event descriptions sounded like possible pyelonephritis (numbers three and seven). However, one of these adverse events occurred in a participant whose Mid-stream urine (MSU) was negative, who reported feeling fully recovered on day five of the trial, and who did not contact a healthcare practitioner up to 28 days after enrolment. The second occurred in a participant whose clinical syndrome was not reported as pyelonephritis by the consulting healthcare practitioner and whose symptoms settled with increased fluid intake alone. There were no SAEs.

Table 3. 6 List of Adverse Events

Adverse Event Number	Group	Adverse Event	Outcome	Severity	Relationship to study product	Comments
1	Immediate antibiotics alone	Tummy upset that started 3 days after starting Ciprofloxacin (second course of antibiotics)	Resolved	Mild	Not related	Not applicable
2	Immediate antibiotics alone	Reaction after taking one dose of antibiotic	Resolved	Uncertain	Not related	Not applicable
3	Immediate antibiotics and immediate cranberry	Suprapubic pain, dysuria, backache, cloudy urine and single vomit	Resolved	Moderate	Possibly related	Possible pyelonephritis from description of symptoms, although not reported as such by healthcare practitioner. MSU positive - E.coli 10^5 CFU/ml.
4	Immediate antibiotics and immediate cranberry	Vomiting after second course of Nitrofurantoin started	Resolved	Mild	Possibly related	Vomit after second course of antibiotics started. Antibiotics stopped and participant encouraged to push fluids. Symptoms settled without further antibiotics being prescribed.
5	Immediate cranberry and delayed antibiotics	Feeling unwell, ache in lower back	Resolved	Moderate	Possibly related	Symptoms unlikely to be related to the study product, as the participant was recruited in the morning and the symptoms started the same day in the afternoon. Participant reported feeling fully recovered on day 2 and did not contact healthcare practitioner up to 28 days. MSU positive > E.coli 10^5 CFU/ml
6	Immediate cranberry and delayed antibiotics	Felt sick	Resolved	Mild	Possibly related	Participant mentioned that she was unsure whether the sickness symptom was related to cranberry or her UTI.
7	Immediate cranberry and delayed antibiotics	General feeling of being unwell, terrible back ache and stomach ache at times. Headache and nausea	Resolved	Moderate	Possibly related	Possible pyelonephritis, however, no growth on MSU, reported feeling fully recovered on day 5, and the participant did not contact a healthcare practitioner up to 28 days.

Abbreviations: MSU: Mid-stream urine; CFU: Colony forming unit

The difference in the proportion of adverse events between groups was compared, although the feasibility trial was not powered to detect differences between groups. At two weeks, the point estimates indicated an increased risk of experiencing an adverse event for participants in group 2 (risk ratio 1.2; 95% CI: 0.1 to 16.7) and group 3 (risk ratio 3.5; 95% CI: 0.4 to 29.4) compared with the control group, although the 95% confidence intervals were wide. At four weeks, the risk of experiencing an adverse event in group 2 was lower than for the control group (risk ratio 0.6; 95% CI: 0.1 to 5.7). The risk remained higher for participants in group 3 compared with controls at four weeks (risk ratio 1.7; 95% CI: 0.3 to 8.8) (see Table 3. 7)

Table 3. 7 Estimate of the difference in proportions of adverse events between groups

	Proportion (%) of participants experiencing an adverse event at 2 weeks [risk ratio (95% CI)]	Proportion (%) of participants experiencing an adverse event at 4 weeks [risk ratio (95% CI)]
Group 1 - Immediate antibiotics alone (Control) n=15	1/15 (6.7%) Missing: 0/15	2/15 (13.3%) Missing: 0/15
Group 2 – Immediate antibiotics and immediate cranberry n=15	1/13 (7.7%) [1.2 (0.1 to 16.7)] Missing: 2/15	1/13 (7.7%) [0.6 (0.1 to 5.7)] Missing: 2/15
Group 3 – Immediate cranberry and delayed antibiotics n=16	3/13 (23.1%) [3.5 (0.4 to 29.4)] Missing: 3/16	3/13 (23.1%) [1.7 (0.3 to 8.8)] Missing: 3/16

Group 2 and group 3 were compared with Group 1 (controls).

3.4.5. Qualitative Findings

Participants were able to provide free-text comments on the final day of diary completion (day 14). Fourteen provided comments. Some provided general feedback, including being "happy to help" with the trial and finding the diary "very easy to complete." Two described some difficulty keeping up with filling in the diary *"Just time and keeping up with it that is all. Happy to have taken part"* (41-8, Immediate cranberry and delayed antibiotics). Another mentioned that she did not receive a link to complete the final set of diary questions, and one was unclear about the guidance regarding the need to continue completing the diary once symptoms had resolved for two consecutive days. Two women commented that the scale of 0 to 50 was "too wide a range."

One woman stated that she was sceptical about cranberry at first, but found that it "helped a lot" (32-11, Immediate cranberry and delayed antibiotics). One participant found that the combination of antibiotic with cranberry cleared her infection "quite quickly" (32-14, Immediate antibiotics and immediate cranberry), whilst another found that the antibiotic/cranberry combination resulted in her taking a shorter course of antibiotics than usual – *"Nice to only take three days of antibiotics not a week"* (23-3, Immediate antibiotics and immediate cranberry). One woman stated that despite starting with cranberry, she had to take antibiotics on day two as she was in pain (41-2, Immediate cranberry and delayed antibiotics).

Three adverse events were picked up from free-text comments (see section 3.4.4).

3.5. Discussion

3.5.1. Summary of Findings

This chapter has described the methods and findings of the CUTI feasibility trial. In this open-label, feasibility randomised trial, participant recruitment was beyond target and faster than anticipated. Overall, participants found the trial procedures and interventions acceptable; few women reported problems consuming cranberry capsules or using the electronic symptom diary. There appears to be a preliminary suggestion, albeit from under-powered effectiveness analyses, that immediate cranberry (combined with immediate or delayed antibiotics) might reduce antibiotic consumption at two weeks and four weeks, compared with controls. Preliminary analyses also suggest that symptoms may be worse in women receiving immediate cranberry with delayed antibiotics, but better in women receiving immediate antibiotics and immediate cranberry, compared with controls.

3.5.2. Strengths and Limitations

To my knowledge, this is the first trial to test cranberry capsules alone and combined with antibiotics as an acute treatment for UTI. The trial processes were designed in collaboration with PPI contributors to be minimally burdensome for participants and recruiters; this may have contributed to the faster than expected recruitment. Participant and recruiter experiences are discussed further in chapters 4 and 5, respectively.

Using a participant-completed diary led to missing data, including incomplete baseline data. Furthermore, limited demographic data were collected. Missing data means that I do not have a full picture of all of the participants' experiences and outcomes. However, insights gained from the trial combined with qualitative interviews (chapters 4 and 5) should help to optimise

the design of an adequately powered trial, minimising missing data in a future trial (chapter 6).

Some may describe the open-label design as a weakness. However, the trial was purposefully designed to be pragmatic, with procedures closely aligned with real-world practice. In a meta-epidemiological study of 142 meta-analyses (including 1153 trials), there was no significant difference in outcomes between blinded and open-label trials (163). It is increasingly recognised that clinical trials should not be blinded or incorporate placebo by default, but rather, the design of the trial should be matched to the purpose of the trial (164, 165). In the present feasibility trial, the purpose was not to ascertain the efficacy of cranberry capsules, but rather to determine the feasibility of conducting a trial of cranberry extract for symptoms of acute, uncomplicated UTI in General Practice. A placebo was therefore not required. In keeping with pragmatic trial design, I was not prescriptive about the antibiotic issued, nor the duration, recognising that clinicians' prescribing is influenced by a host of factors, including a patient's past medical history and previous UTI history. Despite this, I appreciate that there is a lack of standardisation of antibiotic prescribing between groups.

Participants who missed diary entries were able to complete the diary retrospectively; retrospective entries are likely to have been less accurate than entries completed contemporaneously. Furthermore, participants' consumption of other sources of PAC-A, namely blueberry was not controlled. However, 100 mg of blueberries contains only 1-7 mg of PAC (166). Thus, unless participants regularly consumed large amounts of blueberries it is very unlikely that this would have had a meaningful impact on the results. Despite advice not to, one third of women in the immediate antibiotics alone group reported consuming

cranberry products during the trial. This highlights the challenge of trying to control external influences in a trial, particularly when this is in conflict with a participant's usual behaviour.

Trial participants ranged from age 18 years to 81 years. However, all participants were recruited from General Practices in Oxfordshire, and limited demographic information was collected. For example, no ethnicity data were captured at baseline. It is therefore difficult to know whether the findings are representative of the wider UK population of women who suffer with acute UTIs.

3.5.3. Comparison with existing literature

No CUTI feasibility trial participants developed pyelonephritis. A number of trials of non-antibiotic treatments for acute UTI have reported higher levels of pyelonephritis in participants not assigned to an antibiotic arm (35-37, 40). The absence of cases of pyelonephritis in the present feasibility trial may have been due to the small sample size, but may also have resulted from all participants receiving a prescription for antibiotics, whether immediate or delayed. In a trial of 382 women with uncomplicated UTIs evaluating the use of ibuprofen and the herbal extract *uva ursi*, all participants received delayed antibiotics and there were no cases of pyelonephritis (39).

The proportion of participants lost to follow-up or withdrawing from this feasibility trial (11%) is roughly comparable with analogous trials, which report between 1.3% (34) and 16% (37). The proportion of participants with a positive urine culture (54.3%) was lower than the proportion reported in some analogous trials (range of 32% (39) to 80% (34)). The present feasibility trial used a cut-off threshold for urine culture positivity of 10^5 CFU/ml, whilst

most other trials were aligned with European guidance and used a threshold of greater than 10^2 or 10^3 CFU/ml.

Whilst this feasibility trial was not powered to detect differences between groups, in line with the findings of similar trials, participants not receiving immediate antibiotics (group 3) consumed fewer antibiotics but had worse symptoms. However, participants in group 3 were less likely to experience double sickening. Gagyor and colleagues (35) found that significantly fewer participants receiving ibuprofen compared with immediate antibiotics experienced UTI recurrence between days 15 to 28 [percentage mean difference -5.3% (95%CI: -10.2% to -0.4%), p = 0.049]. However, the difference between groups did not reach statistical significance when all recurrent UTIs from day 1 to day 28 were assessed [percentage mean difference -2.8% (95%CI: -8.7% to 3.1%), p = 0.41].

A Cochrane review in 2012 found that overall, cranberry extract did not significantly reduce *recurrent* UTIs (13 studies meta-analysed; risk ratio 0.86; 95% CI: 0.71 to 1.04) (56). This was also the case in a sub-group analysis that focused on women with UTI (4 studies meta-analysed; risk ratio 0.74; 95% CI: 0.42 to 1.31). However, the review authors acknowledged that many included studies had high rates of participant withdrawal/loss to follow-up of up to 55%, largely attributed to difficulty adhering to drinking large volumes of cranberry juice on a daily basis. Furthermore, there was a lack of standardisation and poor reporting of the amount of cranberry extract - and specifically of proanthocyanidin (PAC) - in the interventions used. In this feasibility trial, the cranberry capsules contained a standardised amount of PAC and were consumed short-term in the context of acute UTI. These key differences may have contributed to better adherence of participants to the trial intervention.

3.5.4. Implications for Clinical Practice

This feasibility trial was not powered to detect differences between groups, thus, no definite inferences about the effectiveness or safety of cranberry in the context of acute uncomplicated UTI can be made. If cranberry extract is found to be safe and effective for managing acute UTIs through robust and adequately powered trials, it could represent an important health intervention for this common condition and has the potential to significantly reduce antibiotic consumption. Cranberry extract could be used as an initial, symptomatic treatment for women with UTI symptoms. Furthermore, immediate antibiotic treatment could be routinely combined with immediate cranberry extract if future trials find that this combination results in better outcomes (symptoms and antibiotic use) compared with immediate antibiotics alone.

3.5.5. Implications for Research

There is a need for adequately powered, randomised clinical trials to provide definitive evidence of whether cranberry extract is effective in reducing antibiotic use and managing symptoms of acute UTI. Whilst this feasibility trial does not provide evidence of the effectiveness or safety of cranberry extract in the context of acute UTI, the exploratory analyses suggest that it would be worthwhile to explore these as yet unanswered questions through an adequately powered trial. In chapter 6 (see section 6.6.1), I outline the design of an adequately powered trial of cranberry extract for acute UTI that I plan to conduct at a post-doctoral level. In order to increase the chances of success of an adequately powered trial, it is critical to understand the barriers and facilitators to women taking part in such research, as well as the challenges faced by recruiters to such trials. I have explored this using qualitative methods in chapters 4 and 5.

3.6. Conclusions

These results show that it is feasible to conduct a randomised trial of similar design to assess whether cranberry extract can help reduce antibiotic use for symptoms of acute, uncomplicated UTI. The exploratory, underpowered analyses in this feasibility trial suggest that cranberry (alone and combined with antibiotics) *may* have a beneficial impact on certain measures of antibiotic usage and symptom burden. These findings support the conduct of further, definitive research in this area to confirm or refute these preliminary results. Should cranberry extract be proven to be effective through rigorous trial, understanding women's beliefs about the intervention and the circumstances in which they would, or would not, be happy to take it, would be critical to its appropriate and successful implementation in clinical care. I have explored this through qualitative methods in chapters 4 and 5, respectively.

4. Chapter 4 – Women's perceptions and experiences of using cranberry extract for acute UTI, and of taking part in the CUTI trial: A Qualitative study

4.1. Summary

In chapter 3, I established that it is feasible to conduct a randomised clinical trial of cranberry extract for symptoms of acute UTI in primary care. Embedded within the feasibility trial were two interview studies. First, I conducted interviews with women who participated in the trial, as well as women who were not part of the trial but who had recent experience of an acute UTI. I present these findings below, with some UTI patient insights also presented in chapter 5. Second, I interviewed recruiters to the feasibility trial, and present their findings principally in chapter 5, but with some triangulation of recruiter insights in this chapter.

4.2. Introduction

Qualitative research involves the study of people or objects in their natural settings, and developing an understanding of phenomena in terms of the meanings that they bring to them (167). Whilst rigorous clinical trials can establish that a particular treatment improves clinical outcomes, they cannot tell us how, or why, a patient might consider using the medication in future (168). Incorporating a qualitative study into the CUTI feasibility trial was necessary for me to gain a deeper understanding of women's experiences of having a UTI, and how this might impact on: their views on using cranberry extract in the context of acute UTIs; the situations in which they might find a delayed antibiotic approach acceptable; and, their willingness to take part in clinical trials of cranberry extract for acute UTI. These questions cannot be meaningfully answered through quantitative methods alone.

Delayed antibiotic prescribing can be operationalised in several ways, but usually involves prescription of an antibiotic to a patient, with advice to take the antibiotic only if symptoms do not get better after a certain period of time, or if symptoms deteriorate (169). This approach has been found to be effective in reducing antibiotic consumption for acute respiratory tract infections (RTIs), whilst not compromising recovery from symptoms (170). If cranberry extract is found to be an effective acute UTI treatment, it could be incorporated into a delayed antibiotic prescribing strategy. However, there is a dearth of published evidence exploring the acceptability of a delayed antibiotic strategy for managing symptoms of acute, uncomplicated UTIs (171, 172), and none has focused on the use of cranberry extract as part of a delayed antibiotic strategy. Nor have my searches identified qualitative studies that have explored in detail the use of cranberry extract in combination with antibiotics.

The aim of this study was therefore to explore women's views on treating acute UTIs with cranberry extract, as well as women's thoughts on and experience of taking part in a trial evaluating cranberry extract in primary care.

4.3. Methods

4.3.1. Ethical approval

In accordance with the Declaration of Helsinki, I sought ethical approval for this interview study. It was approved by the South Central Oxford B Ethics Committee (REC reference: 18/SC/0673) and the Health Research Authority (IRAS Project ID: 249672) prior to patients entering into the study.

4.3.2. Participants

I interviewed some CUTI trial participants, as well as some women who were not part of the trial but had experienced a UTI in the preceding 12 months. I had also hoped to invite women who declined to take part in the CUTI trial to be interviewed, however, permission for this was not granted by the ethics committee. In keeping with National Centre for Research Methods guidance, I aimed to conduct 20 to 30 interviews (173). This guidance takes into account that interview study sample sizes are influenced by many factors, such as the purpose and topic of the interviews, as well as practical issues such as time constraints (173). The final number was determined by achieving data saturation, that is, reaching a stage at which any new data from the interviews would not meaningfully add to, or change, the developing analysis (174).

4.3.3. Eligibility criteria

All women taking part in the CUTI feasibility trial were eligible to be interviewed. Women who were not part of the CUTI trial were suitable for inclusion if they were aged 18 years and above, had experienced an acute, uncomplicated UTI in the preceding 12 months, and were registered at the General Practice conducting interview study mail-out invitations. I excluded women who were immunosuppressed (e.g. active cancer), with underlying urological abnormalities, and who were receiving palliative care; such women are more likely to have complicated UTIs and therefore to require immediate antibiotic treatment.

4.3.4. Recruitment

Recruitment to the interview study occurred through the CUTI trial and also through mailed invites from a separate, non-trial General Practice.

4.3.4.1. CUTI trial participants

A CUTI interview study PIL (see Appendix 4. 1) and a reply slip (see Appendix 4. 2) were posted to CUTI trial participants who were interested in being interviewed. Upon receiving reply slips, I contacted women and arranged to interview them at a time and location of their choosing.

4.3.4.2. Non-CUTI trial UTI patients

Interviews were additionally conducted with non-CUTI trial UTI patients. I considered that interviewing women who were not part of the CUTI trial would afford me insights from people who might be less amenable to taking non-antibiotic treatments for UTI - like cranberry extract - and therefore a wider range of voices.

The Clinical Research Network (CRN) sent a Research Information Sheet for Practices (RISP) with details of the study on my behalf to six candidate General Practices that were not involved with the CUTI feasibility trial, and four expressions of interest were received. As the General Practices recruiting to the CUTI trial were in areas with low ethnic diversity, I selected the General Practice with the highest mix of patient ethnicities to maximise the chance of achieving ethnic diversity within the sample. The General Practice that I proceeded with had a patient population ethnicity estimate of 4.2% mixed ethnicity, 14.1% Asian, 6% black and 1.3% other non-white ethnic groups (175). Having conducted electronic searches based on the study's eligibility criteria, a General Practitioner (GP) at the practice sent interview study packs to 143 eligible patients. These packs included an invitation letter (see Appendix 4. 3), a PIL (see Appendix 4. 1), a reply slip (see Appendix 4. 2) and a freepost return envelope. Upon receipt of reply slips, I contacted potential participants, confirmed eligibility, and arranged a date/time and location for interview. At this stage, I excluded two

patients because they met exclusion criteria (one had active cancer and one had experienced a UTI over one year ago).

I also placed posters advertising the study in the General Practice to try to recruit people who were not picked up through the mail-out procedure. These posters also had the potential to bring the study to the notice of people who had recently experienced a UTI, but had not necessarily presented to a healthcare practitioner with their symptoms.

4.3.5. Sampling

I endeavoured to employ a purposive maximum variation sampling strategy (176). I wanted to include participants from within and outwith the trial, hence the two separate recruitment methods that I employed (see section 4.3.4). Within this sampling strategy, I hoped to achieve variation with respect to age, ethnicity and trial groups. There was a degree of convenience to the samples, in that I had a limited sample of patients to select from (especially trial participants). However, by the end of the twenty-fourth interview, data saturation was achieved (174); no new concepts from the data were identified that would have further developed, or changed, my analysis. This was confirmed in the next three interviews that were conducted (interviews 25 to 27).

4.3.6. Materials and Procedures

I created a topic guide (see Appendix 4. 4) to facilitate interviews with patients. A narrative, semi-structured interview format (177) was used to explore participants' experiences of having a UTI and of the CUTI trial. The interview guide began with an opening narrative, asking participants to describe their experiences from the point at which they first became unwell. Additional questions elicited further details about self-care strategies that they may or

may not have employed, and what influenced their help-seeking behaviour. CUTI feasibility trial participants were asked about their experience of taking part in the trial. I described the trial design to non-CUTI trial UTI patients, asking them to consider barriers and facilitators to them participating in such a trial. The aim of the interview guide was to facilitate and prioritise the participants' stories; it did not aim to dictate the course of the interview. I explored each participant's experience in-depth on an individual basis. Understanding participants' illness beliefs and symptom representations provided the necessary context for me to understand the way that they would, or would not, consider engaging with an intervention like cranberry extract (168). I modified the interview guide iteratively in light of new information that arose as the trial and interviews proceeded.

4.3.7. Data collection

All interviews were conducted face-to-face and at a time and location of participants' choosing. Most interviews took place either in participants' own homes or in the Nuffield Department for Primary Care Health Sciences (NDPCHS). I first checked whether the participant had any further questions, and gave them time to look over the PIL (see Appendix 4. 1) again as needed, to refresh their memory. Written, informed consent was gained from participants before proceeding with the interview (see Appendix 4. 5). At the end of the interview, each participant received a £10 voucher as a token of thanks.

Interviews were audio recorded with participants' permission and consent. Audio recordings were encrypted, password-protected, and sent securely via OxFile to an independent, professional transcriptionist. Once transcribed, the transcriptionist returned encrypted, password-protected transcripts to me using OxFile. OxFile is a secure web tool, which allows secure file transfer with people outside of the University of Oxford. Each transcript was

labelled with a unique participant number and omitted any participant-identifiable data. Names of participants were only recorded on ICFs (see Appendix 4. 5), which were stored securely at NDPCHS. Once I received transcripts, I read through them, redacting any names or places mentioned by the participant, checked them against the audio recording for accuracy, and filled in any gaps in the transcription where the transcriptionist had been unsure what was said.

4.3.8. Safety procedures

4.3.8.1. Participant considerations

I did not anticipate that the topic I was discussing with participants would cause emotional distress; UTI tends not to be an emotive topic. However, at the start of each interview I reassured participants that they did not have to answer any questions that made them feel uncomfortable, and that they could ask me to stop recording at any time.

Had a participant appeared particularly nervous or uncomfortable, I would have asked her whether she wished to stop the interview or not answer a particular question. If a participant had become distressed, I would have offered the option of taking a break, continuing the interview on another day, or terminating the interview altogether. I would also have encouraged distressed participants to speak to their GP for support.

4.3.8.2. Personal safety

As I frequently travelled to participants' homes, I ensured that I followed the University of Oxford's lone-working policy. I let one of my supervisors know in advance when I had an interview outside of NDPCHS, or at NDPCHS outside of normal working hours. I sent my supervisor a text message before and after interviews.

4.3.9. Philosophical Approach

4.3.9.1. Ontology

I took an interpretivist approach to conducting the participant interviews (178). Interpretivism is commonly associated with qualitative research. The interpretivist approach acknowledges that there are multiple truths, thereby facilitating a more complete understanding of truth by appreciating how subjective experience affects the construction of reality for participants (179). For example, a person's beliefs about UTI and non-antibiotic treatments is dependent on their prior experiences, their context, and interactions that they have had. These beliefs are also changeable in light of new experiences, contexts and interactions (e.g. moving to a different country with a different healthcare system).

The interpretivist ontology recognises that the researcher and the researched are inextricably linked (179). This is in direct contrast to positivist approaches, typically used in quantitative research, in which the researcher is a "detached observer" (180). I recognised that my background (as a GP and researcher) would necessarily influence and inform the lens through which I asked questions and made observations (see reflexivity statement – section 4.3.10). Due to my interactions with the participants through asking questions, it would be impossible for there to be no influence of me, as the researcher, on the researched. This being said, I tried to limit my influence on participants (see section 4.3.10). I situated the participants as the experts, introducing myself as a researcher (not as a clinician), and I explained that I was trying to learn from them. I asked open questions as far as possible, and avoided interjecting.

4.3.9.2. Epistemology

I took an inductive (data driven), pragmatic epistemological approach to understanding the data (181). The pragmatic approach is often used in mixed methods research (182). The focus of the pragmatic approach is not to develop new theory, but rather to gather information that can be used to tackle real-world problems (181). My aim was to gain insights from the data that could be used to inform the design of a future trial (see chapter 6) and clinical/research practice (see sections 4.5.4 and 4.5.5).

4.3.10. Reflexivity

Reflexivity is the process of reflecting on how the researcher and the processes used to collect data may influence the findings (183). In this process, consideration should be given to the prior assumptions and background of the researcher (183).

My DPhil was my first experience of conducting qualitative research. However, prior to starting my DPhil, I attended a week-long course on qualitative research. Thus, despite being a novice, I had a good grounding in the key steps required to collect and analyse qualitative data. Furthermore, I had two qualitative supervisors who were able to guide me through the process.

In some ways, being a GP by background helped me with the interview process. It meant that speaking to people about medical problems in their own homes was not an alien concept; home visits are commonplace in General Practice. I received communication skills training during medical school, and have been able to develop these skills over the years.

However, whilst some skills were transferable, others required honing. For example, one typically has ten minutes for a General Practice consultation. It is often advocated to give patients a "golden minute" at the start of the consultation to talk without interruption (184), followed by asking a series of closed questions with the purpose of refining ones differential diagnoses and arriving at a final diagnosis. A completely different approach is required for qualitative interviews. I needed to ensure that the interviews were driven by the participant, not by me. The focus was not on problem-solving or shared decision making, but rather, on allowing participants to tell their stories. I therefore ensured that I asked open questions, avoided interjecting, and I tried to remain as neutral as possible in my verbal and non-verbal responses to what was said. Prior to interviewing study participants, I conducted two mock interviews (one with a friend and another with one of my qualitative supervisors). My friend gave consent for me to record and transcribe our discussion; I was able to share the transcript with one of my qualitative supervisors (Dr Anne-Marie Boylan), allowing us to discuss what did, and did not, go well, and for me to take this learning forward to the real interviews. Early interview transcripts were also reviewed by Dr Boylan, allowing me to receive feedback early on in the interview process.

In clinical consultations, there can be a perceived power imbalance between the patient and the doctor, with the doctor being positioned as the 'expert' (185). It was important in the qualitative interviews for patients to be situated clearly as the experts; I was there to learn from their experiences. I therefore ensured that I stated at the outset of each interview that the participants were the experts. Furthermore, all interviews were conducted at a location of the participant's choosing, to help them feel as comfortable as possible.

As a clinician, I have received medical training that has shaped my knowledge of UTIs, both in terms of my understanding of the illness, but also the way that I consider that it should be managed. As a GP, I also already had first-hand experience of diagnosing and managing women presenting with acute UTIs. These patient interactions informed my DPhil programme of research, and were therefore important. However, my prior clinical knowledge and experiences could have led me to have certain pre-conceived ideas about what I would find, and could also have led to me being dismissive of concepts arising in the data that were contrary to my previous experiences/expectations. Ensuring that the interviews were directed by the participants (not by me), and also that the analyses were developed in discussion with my supervisors, helped to negate this.

Participant knowledge that I was a clinician may have influenced their responses. It could have led to participants to adopt a 'patient' role and to give more 'clinical' information, rather than other insights that they may have perceived that I would consider less useful. Research suggests that participants open up less about "broader, non-health-related topics" to people who introduce themselves as a clinician, compared with those introducing themselves as a researcher (186). I therefore made sure that I introduced myself to participants as a researcher, not a clinician.

I conducted the interviews as well as running the feasibility trial. I believe that this was necessary, not only for my development as a qualitative researcher, but also to help me to immerse myself in the research and to draw links between different quantitative and qualitative elements. However, participant awareness of my dual role (running the trial and interview study) may have biased their feedback towards being more positive. I tried to

overcome this by ensuring that I asked specifically about things that participants perceived did not go well in the trial, or could be improved.

As I hope to conduct future research on the use of cranberry extract for UTI, one might consider that I could have sought out and presented only favourable interview insights. To guard against this, I tried to sample diverse women and capture a range of views, including from women who might be less amenable to taking non-antibiotic treatments. Furthermore, I took a data-driven (inductive approach), ensuring that my analyses were grounded in the data. As is common in qualitative research practice, I discussed the developing analysis regularly with my qualitative supervisors in a bid to further safeguard against me imposing myself on the data.

Finally, participants were offered a £10 voucher to take part in the interview study. Some could see this as a form of coercion, and a way of exerting undue pressure on women to take part in the study. However, I considered that this was a morally appropriate way of thanking participants for giving up their time. I also ensured that this was run by the ethics committee, and they considered that this was ethically acceptable.

4.3.11. Data analysis

I used thematic analysis to develop themes from the interview transcripts (187). Thematic analysis involves constructing and analysing patterns (or themes) within data (187). More specifically I used *reflexive* thematic analysis, rather than *coding reliability* thematic analysis or *codebook thematic* analysis. In contrast to coding reliability or codebook thematic analysis, reflexive thematic analysis is underpinned entirely by qualitative ideology, and themes are

generated as the final step in an iterative process of careful reflection on the data (188). This allowed me to bring an inductive and interpretive approach to data analysis (see section 4.3.9) (189).

Thematic analysis was conducted in keeping with the process described by Braun and Clarke (187), and my analyses and data collection took place concurrently. I ensured that I was very familiar with the data in a number of ways. Immediately after each interview, I created an A4 'mind-map' to summarize key comments and concepts from the interview. I also read over interview transcripts and listened to the audio recordings several times, which helped me to immerse myself in the data. I subsequently labelled the data with codes. Codes represent the smallest unit of meaningful data that pertain to a particular phenomenon (190). I used NVivo 12 software to help organise the data and facilitate the coding process. I grouped codes relating to similar phenomena into categories. I subsequently started an iterative process of generating themes and sub-themes to describe the data. This involved me going back and forth several times between my coded data and my developing theme structure, to ensure that I was capturing the essence of the data. This iterative process was facilitated by my qualitative supervisors. I discussed the themes that I constructed with my supervisors to ensure that they agreed that the analysis adequately described the data and highlighted concepts that were novel and of interest. Once the thematic structure was finalised, I refined the theme labels to comprehensively describe the data within, and chose selected supporting quotes to illustrate the themes and sub-themes (187).

4.3.12. Triangulation

Triangulation involves the exploration of insights on phenomena that have been obtained from different data sources (191), and is sometimes employed in mixed methods research

(192). Triangulation of data can help to provide deeper insights into phenomena that are being explored (193). Through triangulation of qualitative insights captured through interviews with UTI patients and recruiters, in combination with insights obtained from the feasibility trial (quantitative data and white space answers), I was able to identify, compare and contrast insights that related to common constructs (191). In triangulating data, it is important to recognise that there may be divergence in the findings (191). When this occurred, I took into account the way the data were collected to help determine the 'weight' given to insights from a particular source (191). For example, I considered that in certain instances, interview data may afford fuller, more contextualised insights into phenomena than checkbox responses in the electronic diary. In this way, triangulation can also help to avoid falsely drawing wrong conclusions from data (191).

4.3.13. Patient and Public Involvement (PPI)

Four PPI contributors were involved with the study from its outset. During an early meeting, they shared their lived experiences of UTI. This suggested that the qualitative study would provide rich insights into patients' UTI experiences. They scrutinised all public facing documents (e.g. the PIL and ICF – see Appendix 4. 1 and Appendix 4. 5), and their feedback was incorporated. Whilst I was developing the interview themes, I shared interview insights with PPI contributors, allowing them to give their thoughts on the findings, which I incorporated into my analyses.

4.4. Results

Twenty seven interviews were conducted with CUTI trial participants (n=14) and non-trial UTI patients (n=13) between August 2019 and January 2020. One interview with a non-trial

UTI patient was not analysed as I realised during her interview that she met an exclusion criterion (immunosuppressed). Interviews ranged from 28 - 72 minutes (mean 54 minutes). Participant characteristics are described in Table 4.1. I developed five themes from the participant interviews:

Theme 1 - Perceived symptoms of UTI have the potential to significantly compromise usual activities

Theme 2 - Treatments, cures, symptom control, and the role of the healthcare practitioner

Theme 3 - Taking part in research and women's response to changing the treatment paradigm

Theme 4 - CUTI trial procedures and electronic systems were largely perceived as par for the course – the UTI patient perspective

Theme 5 - Reflections on the CUTI trial and shaping future research

In the first theme, I describe the symptoms that women reported experiencing with a UTI, as well as the impact that these symptoms can have on their daily lives. In theme two, I discuss the way that women reported managing their UTIs, the strategies that they did (and did not) consider to be UTI treatments, and their expectations and experience of seeking healthcare practitioner input. In theme 3, I describe the barriers and enablers that women gave for taking part in the CUTI trial and interview study, their thoughts on and experience of the three CUTI trial groups, and their thoughts on delayed prescribing for an acute UTI. Themes four and five are discussed in chapter 5 (see sections 5.4.3.2 and 5.4.4).

I have integrated relevant insights from the recruiter interviews into the patient themes presented in this chapter, however, the recruiter interviews are discussed in detail in Chapter 5.

Table 4. 1 Characteristics of interview participants

	CUTI trial group 1 participants	**CUTI trial group 2 participants**	**CUTI trial group 3 participants**	**Non-trial UTI patients**	**Nurse Recruiters**	**GP Recruiters**
Number	6	5	3	12	6	2
ID numbers	T2, T7, T10, T11, T12, T13	T4, T5, T6, T8, T14	T1, T3, T9	NT2-NT13	R1-R6	R7, R8
Mean age (years)	67	69	44	45	-	-
Age range	32-81	60-77	23-57	18-76	-	-
Ethnic Group	White, English - 6	White, English – 3 White, British – 1 White, Welsh - 1	White, English – 2 White, British – 1	White, English – 2 White, British – 4 White, Spanish – 2 White, Lithuanian – 1 White, Bulgarian – 1 White, European – 1 White, Australian - 1	-	-
Marital Status	Married – 3 Widowed – 2 Divorced - 1	Married – 4 Widowed - 1	Single, never married - 1 Separated - 1 Married – 1	Single, never married – 5 Domestic Partnership – 2 Married – 4 Widowed - 1	-	-
Employment Status	Retired – 4 Employed for wages – 1 Self-employed - 1	Retired – 4 Self-employed - 1	Employed for wages – 1 Out of work and looking for work – 1 Self-employed - 1	Retired – 3 Employed for wages – 7 Unable to work, medically – 1 Student - 1	-	-
Highest level of school/degree	GCSE level – 1 A-level – 1 College qualification	GCSE level – 2 College qualification or equivalent – 2	A-level – 1 College qualification or equivalent – 1	GCSE level – 1 A-level – 1 College qualification	-	-

	or equivalent – 2 Vocational training - 1 University Bachelor's degree – 1	University Bachelor's degree – 1	Vocational training - 1	or equivalent – 1 University Bachelor's degree – 4 Master's degree – 3 Doctorate degree - 2		

4.4.1. Theme 1 – Perceived symptoms of UTI have the potential to significantly compromise usual activities

Most women experienced 'typical' urinary symptoms such as frequency, urgency and dysuria. Abdominal pain and back pain were also commonly reported. The precise nature and severity of women's symptoms often changed from one UTI episode to the next. Despite this, women were well versed in the symptoms suggestive of a UTI, having almost all experienced more than one UTI, and were usually able to make a quick self-diagnosis.

I knew, I just remembered exactly the feelings and I thought, 'This is definitely an infection'…. (T2)

Women with more severe UTI symptoms often described global feelings of being generally unwell in addition to localised urinary tract symptoms.

When I initially got the infection, wow I didn't know you could be so ill from urinary tract infection because I've never been that ill before ever and I was bad, really bad. (T13)

Some older women perceived that their symptoms had changed over time due to older age, and also due to the trigger for their UTI changing over time.

I don't get the burning, when you're young and you have sex and you get cystitis, it's not the same. What I've got now isn't the same; so it was sort of urgency, frequency but not the terrible burning. (NT3)

Women perceived haematuria as a red flag and confirmation that their symptoms were serious. This finding usually prompted further investigation in older women.

The impact of symptoms on women's lives varied from having little impact through to being "debilitating." This was dependent not only on the perceived symptom severity of the illness episode, but also on the circumstances of the individual. Some women described being unable to leave home whilst in the throes of a UTI. For younger, working-aged women, not being able to work could have financial repercussions. For older women, the impact of their UTI was typically worse if they had upcoming engagements, such as an outing or a holiday.

I couldn't go to work for three days…I mean, for me when I have a very bad UTI, it's completely debilitating (NT12)

I have a mortgage and my job's very active so if I'm sick it does really impact me…(T12)

A few women discussed the detrimental effects of UTIs on their relationships. They saw UTIs as a burden that women, not men, must shoulder, hinting at the unfairness of the differential impact on women compared with men.

There's a mixture of psychologically, like, 'God, you know, this is really annoying…I don't feel like, you know, I can have fun with my partner without getting a urinary tract infection,'… women feel, you know, they have sex and they're the ones that have to deal with the sort of consequences of it more than men…(NT5)

Almost exclusively, women talked about precautions that *they* took to avert having a UTI following sexual intercourse, such as washing themselves before and after sex. Only one woman talked of actions that both she and her husband took before sexual intercourse.

Typically, symptoms that women perceived as severe or highly inconveniencing were triggers for seeking medical attention.

4.4.2. Theme 2 – Treatments, cures, symptom control, and the role of the healthcare practitioner

4.4.2.1. Antibiotics – a cure? Or, an imperfect treatment?

Women often spoke of finding a "cure" for their UTI, and for many women antibiotics represented a cure. Most women reported that they found antibiotics to be an effective treatment for UTIs, which they perceived worked quickly, usually noticing a definite improvement in their symptoms within a few days.

I don't want to sort of lose my day and feel bad for like a whole day when I can just sort of get the antibiotics and get some, you know, something sorted. (NT8)

Women described antibiotics as a "precious" resource that should be reserved for when they are clearly indicated. Women felt differently about whether antibiotics were always needed for a UTI. Some women had only ever recovered from a UTI after taking antibiotics. Others felt that the need for antibiotics was dependent on a number of factors, including the severity of the UTI and characteristics of the patient (e.g. their age and fitness levels).

Okay, so I, I feel that some people require antibiotics however I feel that the majority of people that have a UTI you know, it could be dealt with, with home remedies…. perhaps it's heavier UTI you know, perhaps they don't have the antibodies to fight it off; they're weaker. You know, if it was an elderly person perhaps, they would need antibiotics more than a younger fitter person that would be able to recover without them.(T12)

Interviewees often expressed a tension between finding antibiotics effective and sometimes necessary, whilst wanting to avoid taking them if possible. A recurring sentiment expressed was fear of antibiotic resistance resulting from the overuse of antibiotics. They frequently reported fears of becoming "immune" to antibiotics if they took them too often. The majority of women being interviewed had experienced more than one UTI, and some had experienced multiple UTIs over the years and may therefore have perceived themselves as high antibiotic consumers. Most women spoke of concerns that antibiotics would not work for them personally in future if they over-used them; fewer women talked of the wider societal consequences of antibiotic over-use.

You don't sort of want to, you know, take too many of them [antibiotics] and then like the next episode you have, you cannot sort of treat it well, well enough, you know. (NT8)

Some women talked of antibiotic side effects and allergies, as well as times when they had required more than one course of antibiotics due to resistance. Others spoke of the disruptive effect of antibiotics on the body's microbial flora, and reported taking probiotics to help restore the balance. Women sometimes described antibiotics as weakening their own immune system.

I don't want to use them [antibiotics] because they say, they weakens the immune system…killing off good bacteria as well, so, so better to try to avoid it if it's possible. (NT11)

For some women, antibiotics did not represent a cure. Women expressing this view had typically experienced protracted urinary symptoms, had an early recrudescence of symptoms despite antibiotic treatment, or had experienced frequent UTIs. For these women, a cure implied a permanent end to their symptoms, which went above and beyond their perceived capabilities of an antibiotic.

It's [antibiotics] a quick fix. It doesn't get to the root of it, but nothing does. (NT4)

OG: …when you then contacted your GP practice…what were you sort of hoping for?
NT6: I think I was…hoping for a cure but knowing that perhaps I would only get antibiotics.

4.4.2.2. Non-antibiotic measures were variably considered as treatments, treatment adjuncts and means of symptom control

Over-the-counter (OTC) remedies, such as cystitis sachets and cranberry products, were generally seen as more "natural," and consequently less likely to cause unintended harm or an adverse reaction. They were also considered more easily accessible than antibiotics, not necessitating a General Practice appointment or prescription. Women described mixed experiences with OTC remedies; some saw them as holding measures to provide some symptom relief when it wasn't possible to get a General Practice appointment. However, other women used these measures as a treatment for their UTI in their own right, particularly when their symptoms were milder, in the earlier stages of their illness, and if they didn't have an important upcoming engagement (e.g. going on holiday).

They're [cystitis sachets] quite effective if you, if you get it early but once an infection takes hold, they're, they're not very, in my, from my experience, not very effective.(NT12)

I think mostly I've, I've used the potassium citrate and I suppose if the problems got any worse then, then I do go for antibiotics….It's very dependent on how I'm feeling at the time (T6)

Few women had tried cranberry capsules/tablets, or indeed were aware that cranberry extract existed in this formulation prior to taking part in the trial/interview study. Women usually felt that cranberry capsules/tablets would be preferable to consuming cranberry juice, due to

concerns about the taste and sugar content of cranberry juice. Those women who had used cranberry tablets usually reported using them as a means of preventing UTI, rather than as a way of managing an acute UTI. This may be driven by cranberry tablet/capsule brands that tend to promote their products for use as a preventative, rather than as an acute UTI treatment (194).

I've been taking the cranberry tablets just sort of daily (NT13)

Most women did not naturally consider combining OTC remedies with antibiotics; if initial OTC treatment did not work, then they would stop taking it and seek antibiotic treatment. Women reported that the advice given with OTC treatments was typically to use them only for a short period (3-5 days). Once on antibiotic treatment, some women felt that there was no point in combining antibiotics with OTC treatments, given that antibiotics are usually effective.

I think there's no need [to combine treatments] if you get antibiotics then it helps… (NT11)

However, other women were willing to consider using a combined treatment strategy, if proven to be effective.

Yeah, if, I thought it would help [combining treatments], yeah, absolutely (NT5)

Yes, if they have a synergistic effect that would be great. I'm fine with, whatever works basically, I'd be happy to do (NT12)

Although women did not necessarily find that OTC treatments reliably treated UTIs, they reported few concerns about taking them. On occasion, the expense of OTC products was

mentioned. A few women had a degree of scepticism about OTC remedies. These were usually women who had previously tried OTC remedies with limited success.

If there is something that is proven to be good, why aren't they prescribing it? …nothing of the alternative remedies are backed by the NHS. (NT4)

Some of the over the counter/not prescribed remedies are… flogged to women, particularly to women… they've got a cocktail of stuff in them and you don't know what they are. (NT6)

Only two women raised concerns about UTIs escalating to something more serious if OTC remedies were used instead of antibiotics; of note, both women had previous experience of a complicated UTI (pyelonephritis).

Either you have to have it treated early or you leave it…like once I did thinking that I could cure it and you end up on very, very strong antibiotics or the threat of going into hospital where you have the antibiotic put in via a drip…and I have to avoid those things at all costs because I don't like needles and I don't like hospitals, so I'm just, just get to the doctors as soon as I can.(T4)

I wouldn't want it [UTI] to escalate into something more...(T1)

Women frequently reported that they would increase their fluid intake as an early part of their UTI management. Similarly to OTC remedies, increasing fluid intake was viewed by some as a holding measure.

I drank loads of fluids because I know there was no doctors open across the weekend. (T1)

However, unlike OTC remedies, women often continued increased fluid intake alongside taking antibiotic treatment, perceiving it as a treatment adjunct and a way to flush out the

infection. Some women felt that a mild UTI could even be treated through increased fluid intake alone.

If it's [the UTI] really mild… you can flush it out with water…. (T10)

Whilst some women talked of drinking water and teas, cranberry juice was the fluid most commonly reported in this context. Many women perceived that cranberry juice might have specific therapeutic properties over and above other fluids, even if they had not personally found cranberry juice to be effective. This perception may well have been shaped by the fact that cranberry extract, in various forms, has been used a means of managing urinary symptoms for many decades, well before the introduction of OTC remedies, and so people may commonly associate cranberry extract with UTIs.

I've heard cranberry mentioned so much over the past years, going back from my own GP who is saying, you know, "Drink, drink cranberry juice and whatever." So it's always been in the loop…(T7)

I know that once I've, I've drunk…cranberry juice, it feels a lot better... I'm not sort of desperate for weeing so much, so I always keep two now in my fridge. (NT2)

Whilst cranberry juice was perceived as a 'natural' treatment compared with antibiotics, many women expressed concern about the taste of cranberry juice, and particularly the sugar content.

I haven't tried cranberry juice very much because I can't stand the stu-, I really don't like the stuff. I'm quite happy to chew cranberries.(NT3)

*It [cranberry juice] was awfully sweet and I'm not terribly good with a lot of sugar.(*NT4)

A number of women described self-help measures that they took to try to relieve the symptoms of their UTI. Women commonly described that sources of warmth (such as hot water bottles and baths) were comforting.

Most women did not naturally link analgesia (e.g. paracetamol/ibuprofen) with treating a UTI. For some, it was because they did not have painful UTIs. However, women did not perceive that analgesia would treat the cause of their symptoms. Women who reported taking analgesia saw it as a means of alleviating certain symptoms (e.g. abdominal/back pain), but not as a way of treating their UTI.

It [taking analgesia] wasn't something I really thought or associated really… I was thinking really more about actually making what was causing it better rather than actually taking the painkillers to mask it (T3)

I've taken paracetamol which will help with the stomach pain but doesn't help with the peeing side of things. (T5)

To be perfectly honest I wouldn't even have put, it wouldn't have entered my head to have taken pain relief for it… Because it wasn't what I would term a pain. (T14)

4.4.2.3. Functional and formulaic - UTI consultations in General Practice

Most of the participants had set expectations when contacting their General Practice, namely, to be seen in a timely fashion and to receive a prescription for antibiotics. They often hoped to have their urine sample tested through a urine dipstick; this was viewed by some as an important way of confirming the diagnosis and validating the need for antibiotics. Most

expected a face-to-face consultation; enabling them to have a urine dipstick performed. However, some, usually younger women were happy to have a telephone consultation, describing this as a more convenient approach.

[I expected] to get an appointment to get antibiotics because these are the only, the only thing that has made me feel much better in a short, short period of time…(NT10)

I think I thought it would just be a urine sample so I would have probably been surprised if they had requested other tests given the nature of the symptoms.(NT13)

I think I would have liked to have seen somebody face to face because I feel that you need to do that test, that urine test so I, I feel more comfortable knowing exactly that that's what it was…(T13)

Focusing on non-CUTI trial UTI patients, their most recent UTI consultation had usually met with their expectations. Women reported having a mixture of telephone and face-to-face consultations, usually on the day that they had contacted their General Practice. Consultations tended to be focused and fast, which women generally found acceptable.

Most women reported that they provided a urine sample for dipstick testing during their consultation, or that they dropped off a urine sample at their General Practice after a telephone consultation. Other than having a urine sample dipped and sent to the laboratory, most women did not have any other tests or examination. Women sometimes sensed that healthcare practitioners seemed to be following an algorithm, for which the outcome was usually an antibiotic prescription, which in turn typically met with their expectations.

They will just say, infection yes or no; antibiotics, yes or no. (NT13)

I think I made it quite clear what I wanted. I wanted to speak to a doctor because I wanted to, wanted to have a prescription. (NT6)

Only one woman did not receive an immediate antibiotic prescription, following an equivocal urine dipstick and symptoms that were perceived to be early and non-severe. She perceived this mismatch between her expectation and the consultation outcome as the doctor thinking that he knew her body better than she did.

I went to the doctor and they said, "It wasn't that bad yet and to just." They didn't give me antibiotics and they told me just to go, so I went home… I gave them a sample… they said they couldn't detect anything…So, they said, "Oh it will probably go away on its own if it's starting." (NT12)

CUTI trial recruiters were able to provide insights into UTI consultations from a clinician's perspective. Overall, recruiters to the CUTI trial felt that there was a tendency amongst clinicians to "over treat" UTIs, and that clinicians often had a "knee jerk" reaction to prescribing antibiotics. Reasons given for this included the risk of an uncomplicated UTI developing into pyelonephritis, and local UTI management guidelines that support antibiotic prescription.

We all know that we over treat UTIs, lots and lots of stuff about over treating them and maybe this is bladder inflammation not infection… (R6 – nurse recruiter)

There's always this concern, 'Will this develop from a bladder infection into a kidney infection?' So it's often just knee jerk, antibiotic, antibiotic, give an antibiotic. (R2 - nurse recruiter)

The advice given by healthcare practitioners usually focused around drinking plenty of fluids and safety netting in case of worsening symptoms.

I think they says, "If you take the antibiotics and still you feel like pain or your pain is sort of going up to your kidneys or something like that,"…"to ring us back straight away, or actually probably go to A&E"… (NT8)

Outside of the CUTI feasibility trial, most women had never had a discussion about non-antibiotic treatment options with a nurse or GP; the perceived binary choice between antibiotics or no antibiotics did not appear to leave much room for these wider discussions. When these conversations did take place, it was usually with women who experienced frequent UTIs.

Of those healthcare professionals promoting non-antibiotic options, cranberry juice was most commonly suggested. Women described that healthcare professionals tended to express negative sentiments (stating that non-antibiotic options did not work) or neutral feelings (stating that non-antibiotic options were unlikely to help, but unlikely to do harm). Women also suggested that different healthcare professionals provided conflicting advice about OTC treatments.

I said…"I can recover without antibiotics?" but he said, "No," so. So was very clear. He said, "Antibiotics or nothing, but nothing, make sure you are going to get worse." He didn't mention about there is another method. (NT9)

A doctor that I saw in X when I was having symptoms and I think I even said, "Oh, you know, I heard cranberry can be quite good," and she was very dismissive and said, "No, no it doesn't work," or, you know, just didn't seem open to alternatives… there have been other doctors who have, you know, said, 'Oh, you know, there are things like cranberry and other things you can try'…(NT13)

These varied views about the potential benefit of cranberry extract were voiced by recruiters to the CUTI trial. Whilst they were keen on the idea of an antibiotic alternative that could help to "de-medicalise" UTIs, they had mixed thoughts about the potential benefits of cranberry extract in the context of an acute UTI. Some cited inconclusive evidence of its effectiveness, which they in turn communicated to their patients.

I think anecdotally I've always thought that it was a good idea to try it [cranberry] … the evidence has always been a bit inconclusive at the moment, so it, it's I kind of find myself saying to patients that you're not going to harm yourself by drinking cranberry juice and if you feel it helps that's good but the evidence is just a bit inconclusive at the moment rather than I can say, 'Yes, you should be taking this because it is going to help.'(R5 - nurse recruiter)

There's been lots of information over the years hasn't there about the use of cranberry and, 'Is it useful? Is it not? Is it an old wives' tale? Is it really actually got something going for it? (R6 - nurse recruiter)

Women usually stated that their view of OTC remedies would be influenced by the views of their healthcare practitioner.

As a non-medical person you, you trust what people are talking to you about if they have got that medical expertise (T14)

I trust my doctor if I was talking to him, if he advised something, I would take it because I trust him. I know him very well and he knows me (T10)

Whilst many women had great trust in the judgement of their healthcare practitioner, some women stated that they would do additional research to supplement what they had been told. Furthermore, whilst women usually stated that a positive message from their healthcare practitioner would encourage them to try non-antibiotic options, they were less likely to be put off trying non-antibiotic options if their healthcare practitioners had an unfavourable view - this was also the case for some women who had tried OTC remedies with limited success. This might reflect a combination of: A strong desire for women to find effective, non-antibiotic treatments; a move away from paternalism in medicine; ready access to alternative information sources (internet, friends and family); as well as perceived healthcare practitioner uncertainty/hesitancy about non-antibiotic treatment options.

If they felt positive it, it would definitely affect how I felt about them, yes…But... I'm not needy of what they say. I'm just supportive of a new development. (T9)

If they [GP] didn't think that they actually worked, if I wanted them that's what I would have. I wouldn't be persuaded that antibiotics were the best option if I felt that the cranberry tablets were better for me. No it's my body, my choice. (T5)

4.4.3. Theme 3 – Taking part in research and women's response to changing the treatment paradigm

4.4.3.1. Barriers and facilitators to taking part in the CUTI trial and interview study

Altruism played an important part in women's reasons for taking part in the CUTI trial. They perceived taking part as a way of advancing research in this field, and felt that exploring non-antibiotic treatments for UTI, like cranberry, was "worthwhile."

The majority felt that the study sounded "interesting," "positive" and was "long overdue." They were pleased that a non-antibiotic approach to treating UTIs was being researched.

I thought it was long overdue if I'm honest and, and I really thought, 'Wow, yes how come because it's widely known certainly like I've heard it for years that you should take cranberry juice…so yeah I was like yeah, that's good, that's good.' (T13)

Often antibiotics is the first line of treatment and it's very readily prescribed by doctors, you are not always given that opportunity to see if something else could work... So, I think it sounds like it would be a good study and it's, you know, with the three different groups, it sort of gives you that scope to test it. (NT13)

Recruiters similarly perceived that most women had a positive initial reaction to the trial. They felt that women were interested in the trial, were open to discussing what taking part would entail, and were disappointed if they could not take part (e.g. due to ineligibility).

I think the majority of them were interested in it and like would, wanted to be involved... then they would be quite disappointed if they couldn't be involved. (R5 - nurse recruiter)

Many women felt that it was important to take part in research studies, recognising that it was a necessary part of generating new knowledge, and also a way of 'giving something back' to the National Health Service.

*I think I was hoping that it could throw some more light on the subject, understand what was going on and hope that there was another cure other than antibiotics**….**I just felt that it was a worthwhile thing to do.*(T6)

I mean if people don't volunteer, you're not going to get any knowledge are you? (T11)

Whilst altruism played a big part for many women, some women also perceived that they derived personal benefits from taking part in research – such as avoiding antibiotics. Women felt that the results of the research could have beneficial implications for the future management of their own UTIs, as well as for their friends and relatives.

I think it's just the fact that you're helping, you know, if you can get away from antibiotics all well and good. (T4)

And I said, "Yes," because, because I would like to be proactive in this kind of, I know about cranberry, we've taken, my daughter drank cranberry for years. We know that cranberry can be helpful but I'm not saying it could eradicate it, but I was anxious to see if it would because that's a great development. (T9)

Few women reported initial concerns. One non-CUTI trial UTI patient envisaged that it might be difficult to recruit women during the narrow window of an acute UTI episode.
A CUTI trial participant had initial concerns about the level of commitment that taking part in the trial would involve.

When I was sitting waiting to see the nurse, I was thinking about it and I suppose I first thought, 'Gosh if this involves a whole lot of time and energy…'... I asked her that, I said, "Is this, what sort of involvement, is this going to be arduous in any way?"(T2)

Recruiters to the trial stated that common reasons for women declining to take part in the trial were: Lack of time; not wishing to be assigned to the delayed antibiotic group; not being able to get to the General Practice (either because they were feeling unwell or were at work); or having an upcoming event/holiday for which they wanted a treatment that would guarantee a quick resolution of their symptoms – namely, immediate antibiotics.

I explained to her over the phone what the study was about but I think she was the one that said, "Oh no, I don't want to delay treatment," (R1 - nurse recruiter)

I think it was just that there's almost, there's that programmed, 'an antibiotic will sort this out.' (R2 - nurse recruiter)

The majority of people who couldn't do it because they were at work, they, they were really apologetic and they said, "Oh it sounds really interesting but I can't come out." (R4 - nurse recruiter)

Recruiters had differing perceptions of the characteristics that made women either more or less likely to agree to participate in the trial, and they usually focused on the age of participants. Some felt that older adults were less likely to want to take part; they perceived that older adults were more likely to have experienced recurrent UTIs for which antibiotics had been effective, and therefore might be more reluctant to try an antibiotic alternative.

Conversely, others perceived that older adults were more open to taking part, whilst younger adults were more likely to want a "quick fix" for their UTI.

I thought the youngsters were a bit more enthusiastic so I would say perhaps 20, 30 something's…I think the longer somebody had had symptoms for, you know, if you're, if you're perhaps in your 50s plus and you'd had recurrent symptoms over a few years, you may well have already tried something like over the counter treatments or cranberry…(R2 - nurse recruiter)

I think the the over 50s are possibly more likely to take part…I think they're perhaps just a little bit more not open minded as such but I think, you know, young people with babies or whatever, they just want to feel well don't they?...They want a quick fix maybe…(R3 - nurse recruiter)

We had a mix of patients and all, you know sort of educated and less so, young people, older people. No, we had a real mix of people. (R4 - nurse recruiter)

When asked, UTI patients most commonly cited lack of time as a reason that they perceived people might not wish to take part in research. This was especially the case with taking part in an interview study; interviews took roughly an hour and required some advance planning, whereas daily electronic diary entries (completed as part of the CUTI feasibility trial) took approximately five minutes.

It [being interviewed] does kind of change your day… for instance I might have kind of gone out after lunch and walked into town, you know, but I had prior commitment so that's fine…I can see where it might impinge a little bit, you know what I mean?...Because things happen and on the day, you might feel differently…(T13)

Some women saw being interviewed as part of a research study as something of an unknown entity, and they consequently considered that some people might find the idea anxiety-provoking. Furthermore, the word 'interview' has negative connotations for some people and may be linked to being in a stressful situation.

They might feel nervous about it… people associate interviews with nerves and fear and I think it would be that association. (T12)

I suppose some people might be worried about what you were going to ask, whether that was probing into their personal, I don't know, their, their body maybe or, or, you know, whether or not they thought they had to have an examination or answer some more questions.(T14)

I thought about it [being interviewed] longer than I did initially think about going into the [CUTI] study but I thought an hour's questions [laughs] could be quite interesting…there's always a slight query over what you're going to be asked…There's always that little, little bit thought in your head that it might be difficult but no, no I've, I've enjoyed the process…Well only because it's unknown, you know, it's just the, the constant query you might have about not knowing what you were going to be asked…(T6)

A suggestion was made for a different name to be used for the interview process, such as a 'discussion,' to make the process sound less daunting.

4.4.3.2. CUTI trial groups- meeting treatment expectations and going against the grain

Women in the CUTI trial were randomly assigned to one of three groups (see section 3.3.2). Whilst women within and outwith the trial reported that they were happy, or would have been happy, to be randomly assigned to a group, most had preferences. These preferences were dependent upon perceived personal benefits of the trial group in question (the ability to try cranberry and/or the ability to recover quickly) as well as their perceived ability of the trial group to meaningfully contribute to research.

Most women were hoping to be prescribed antibiotics for immediate use when they contacted their General Practice. Group one of the trial (immediate antibiotics alone) aligned with what

they had originally hoped for, was a known entity, and was therefore the preference for some women.

I have to say when she said, 'Oh you're in the antibiotics only,' inside I went, 'yes.' (T10)

This was particularly the case for women who were experiencing perceived severe symptoms, or who had already delayed seeking medical attention; the desire to make a swift recovery from their symptoms weighed heavily on their preference.

On the other hand, some women were drawn to the study because they were keen to try cranberry capsules. Receiving immediate antibiotics alone was therefore their least favourite option, as it was the only arm of the trial in which women did not receive cranberry capsules. Recruiters to the trial reported that many women seemed disappointed if they did not receive cranberry capsules.

[In group 1- antibiotics alone] I don't have the chance to, to see if cranberry capsules help me… (NT7)

I found when we randomised them, a number of them dropped into the 'just an antibiotic,' category and they were like, 'Aw I was hoping to take some cranberries away.'" (R2 - nurse recruiter)

Some of the patients who got randomised to the not taking cranberry arm of the study seemed a little bit disappointed that they weren't taking it… (R5 - nurse recruiter)

Some women also perceived that being in the immediate antibiotics alone group would provide less meaningful information to the researchers, as it reflected the status quo.

I don't know if I could have given you as much feedback today because that's [immediate antibiotics alone] my normal experience; antibiotics is what I've always been given, and I

don't know any different. I do now…. I would choose cranberry first over antibiotics, but I wouldn't know that if I'd been in the first group [immediate antibiotics alone]." (T5)

Okay, that's [immediate antibiotics alone] not probably really so crucial for the research. (NT8)

There were similarly differing schools of thought about being assigned to group 2 of the trial (immediate antibiotics and immediate cranberry capsules). Many women perceived this group as the 'best of both worlds,' allowing them to experience the benefit of taking an antibiotic along with any potential additional beneficial effect of cranberry. They perceived that they might recover faster in this group, and even referred to it as the 'safest' group.

Probably the safest one would be the immediate antibiotics and the cranberry capsules because you get both basically, so that's like a, you know, a full force attack…(NT8)

However, other women primarily saw the utility of cranberry as a way of *avoiding* antibiotics. These women were keen to establish whether cranberry extract would help them personally, and they felt that combining cranberry with antibiotics would make this more difficult to ascertain. From a research perspective, some women also felt that this group represented an unfair test of any possible effect of cranberry, as it would not be possible to unpick the effects of antibiotics from the effects of cranberry.

I don't know what you prove by that one [immediate antibiotics and immediate cranberry]… you have both and you get better, how do you know what helped? (T9)

I suppose if I'd been chosen for option two [immediate antibiotics and immediate cranberry], I think I would have felt a little bit disappointed because I wouldn't have then myself known if the cranberry capsules were making a difference (T12)

Despite this, women who were assigned to this group often reflected that they perceived an additive benefit to taking cranberry alongside antibiotics. They compared their UTI

experience within the trial with their previous UTI experiences that had been managed with antibiotics alone. They often reported that their symptoms cleared up faster, and that they were able to take less antibiotic than usual. This is in keeping with the preliminary, under-powered feasibility trial effectiveness analyses (see chapter 3, Table 3. 4), in which there was a suggestion that women receiving immediate antibiotics and immediate cranberry capsules recovered faster and had a lower symptom burden compared with women receiving immediate antibiotics alone.

Between the two [antibiotics and cranberry capsules], it cleared it up very quickly…it was really, really helpful.. (T8)

I was a bit sceptical taking sort of the antibiotics and the cranberries…but it worked so that was the main thing for me…I've said to several of my friends I did feel that the cranberries really helped, really helped were you not taking quite so much antibiotic. (T4)

I took the cranberry tablets alongside [antibiotics] and I thought the symptoms had gone but within a couple of days, I felt they were coming back again. [I]Took some cranberry tablets because I hadn't sent them back to you, so I took another two days' worth and I think I knocked it on the head. But I think that probably if I hadn't had the cranberry tablets I would have had to go back to the GP for more antibiotics.(T5)

I only had three [days of antibiotics] this time…whether it was the cranberry tablets with it, they might have helped to, to reduce the quantity of antibiotics.(T6)

For women who were keen to determine whether cranberry might work for them personally, potentially enabling them to avoid taking antibiotics, group three (immediate cranberry with delayed antibiotics) was their preference. Women were reassured that they would receive back-up antibiotics, which one woman described as a "parachute," giving confidence to try a new intervention. Indeed, another woman felt that this group offered women more treatment "choices;" the ability to try cranberry first, then antibiotics, if needed.

Immediate antibiotics… it's just one choice…Whereas, group three have two choices…and then you see which one works for you. (NT7)

I felt I had nothing to, to lose really because I'd rather try something first before I had antibiotics anyway…(T3)

It's the way to see if cranberry can really help on its own to relieve the symptoms. But, of course, having the backup antibiotics, it's like safe option that you have in case it doesn't get better (NT10)

However, the immediate cranberry with delayed antibiotics arm of the trial was the least favourite group for some women. Typically, these women's primary concern was with making a quick recovery. Some had already waited before contacting their GP to get an antibiotic prescription, and so they did not wish to incur further delays to taking antibiotics, which they perceived to be a fast and effective treatment.

I didn't consider if you like that the cranberry capsules would work as quickly as the antibiotics…my immediate thought is just get rid of my, my problem…and I didn't know that that [cranberry] would. It may well have done but my first thoughts were, 'No not that one first. I'll go to that one [immediate antibiotics] first. (T7)

People who've, who've got lesser symptoms, I think that [immediate cranberry with delayed antibiotics] would probably appeal to them wouldn't it more…(T2)

Many women perceived this group to be the most useful from a research perspective, as women felt it would be providing researchers with new knowledge. However, this did not necessarily equate to it being women's preferred group. Depending on perceived symptom severity and timing of presentation to General Practice, the balance could still be tipped in favour of preferring one of the immediate antibiotic groups.

The only one I can see that benefits your study is number three [immediate cranberry and delayed antibiotics] which is the one I got…. I wanted the [immediate] antibiotics. I'd been ill for four/five days anyway, so I wasn't looking to delay my recovery. (T9)

Of the women interviewed who were in the delayed antibiotic group, all ended up needing to take their back-up antibiotic prescription. However, there was a suggestion that cranberry had *some* effect, albeit not as potent as antibiotics, and seemed to prevent symptom deterioration.

I felt that actually just taking the tablet, the cranberry tablets it was just like, it didn't get rid of it, but it helped, I think it prevented it from getting any worse. So, the actual like burning feeling and needing to go for a wee, I felt like it was a steady level. (T1)

I can't remember how many days I took them [cranberry capsules] for before I started the antibiotics. So, I didn't feel, I didn't feel worse. I can't say I felt better to start with either but then after a couple of days I asked advice again whether I should perhaps take the antibiotics… (T3)

Whilst some women reported that they had encountered a delayed antibiotic approach for managing other infections, none explicitly reported that this approach had been used in the management of their UTIs outside of the CUTI trial. Some women considered that the delayed antibiotic strategy provided an often welcome opportunity to avoid consuming antibiotics for an acute UTI. However, women weighed this potential benefit against the severity of their symptoms, their present circumstances (e.g. whether they had an upcoming important event), and the timing of their presentation to General Practice. A few women, typically those who had previously experienced an upper UTI, also factored in the potential risk of developing a complicated UTI if antibiotic treatment was delayed.

I might be a bit grumpy about it. I think it would depend how awful I felt…(NT3)

It's going to be an indiv-, very individual and, you know, people's lifestyle and their circumstances. I mean, if you're suffering from cystitis and you've got three kids coming

home from school and you've got to look after them, you're in a different situation than if you're just looking after yourself…(NT6)

If my infection was bad and I would, had to wait to take the antibiotics. I would feel like, I would not be annoyed at it, but I would just be worried about them getting worse. (T1)

Shortening the time to delaying antibiotics usually tipped the balance towards a more favourable view of the delayed antibiotic approach. Many women felt that a delay of 3-5 days (as suggested in the CUTI trial) was too long. They worried about having ongoing disabling symptoms and becoming more unwell if cranberry was not effective. Most women suggested that a shorter delay of 2-3 days would be more acceptable to them.

I think that [3-5 days] would be too long, definitely too long …I think the…maximum is two days…because once it gets a hold it can really go (T4)

In the past that my infections have progressed…to take the delayed antibiotics three to five days, I would be in a terrible state by then and for, for a severe infection… that would be really difficult... that would just mean, just staying home for me (NT12)

Some women, on the other hand, particularly those experiencing milder symptoms, felt that a 3-5 day delay would be acceptable, and perhaps even important in order to give cranberry a chance to be effective. Ultimately, whether women would be prepared to delay antibiotics, and the time that they might be prepared to wait was very much dependent on the features of the UTI episode in question. Some women described that changes in symptoms and circumstances from one day to the next could influence whether they would find a delayed antibiotic approach acceptable. For many women, it was important that they were in charge of the delay - they were the experts in their own body's and of their symptoms, and so were best placed to make this decision.

The antibiotics were always there if needed anyway…I wasn't concerned at all [about delaying antibiotics in the trial] because I was still in control of what I wanted to do…(T3)

I think if you've had a few of these [UTIs], you really know the direction of travel that your body's going and so usually by the second day I will know if it's going to be really severe or not…(NT12)

Alternative trial designs were discussed with women. Women were asked to consider a trial that incorporated placebo, in which there would be a chance of being randomly assigned to receive immediate placebo with delayed antibiotics. The idea of adding an immediate placebo arm gave many women pause for thought. They often recognised that placebo designs were an important part of scientific study. However, the notion that they might be assigned to initially receive no active treatment tipped the balance of agreeing to a delayed antibiotic approach in a negative direction. For those who would be willing to engage, receiving a delayed antibiotic prescription was a deal-breaker.

If it has placebo and delayed antibiotics, that's, I would go for it but if it doesn't have antibiotics, I wouldn't go for it because it has no treatment. (NT7)

Knowing that I've got the delayed antibiotics I knew at any point I could start taking them… I would have felt in control enough to have been happy to have taken the placebo.(T3)

I described another study design, in which there was a chance that women would be randomly assigned to receive delayed antibiotics alone. Women expressed once again that having contacted General Practice it was important for them to receive *something* by way of treatment in the interim.

I'm not sure why you'd just delay antibiotics without doing anything because the whole reason for going to your doctor is that you've reached a decision, a big decision that you want to go the doctor to get it sorted out and the fact that the doctor says we'll just wait another couple of days, you might already have waited three, four, five days before you made that decision to go to the doctor… (T14)

If they did not receive treatment from their healthcare practitioner, then they would seek treatment through other means.

If it was random and I ended up with this one [delayed antibiotics alone] and then was asked not to take the antibiotics for a few days I would probably then supplement myself. I would probably still just take the cranberry. (T13)

4.5. Discussion

Women generally considered antibiotics to be a reliably effective treatment and expected to receive an antibiotic prescription when presenting to General Practice. UTI consultations appeared to be set up to meet this expectation, with a quick, algorithmic approach to management. Women were aware of the potential pitfalls associated with antibiotic consumption, including antibiotic resistance (specifically becoming 'immune' to antibiotics), and so expressed a degree of dissatisfaction with the status quo; many women were keen to find a non-antibiotic treatment that would effectively manage their symptoms.

Whilst most women saw antibiotics as an effective treatment for acute UTI, or indeed a cure, OTC remedies were usually viewed as a less reliable treatment. Typically, women's experience of OTC remedies was that they could be effective if taken early in the illness course and with milder symptoms, but not if taken when infection was well established or with severe symptoms. Increasing fluid intake, including cranberry juice consumption, was often an initial response to an acute UTI and was used as a treatment adjunct, rather than a standalone treatment. Analgesia, when used, was generally viewed as a way of controlling pain, but not as a treatment for an acute UTI. Women's views of what was, and was not, considered a treatment for UTI seemed to be shaped by both the ability of the strategy to

effectively alleviate their symptoms, and also the capacity for the strategy to facilitate removal of what they perceived to be the root cause of their symptoms – for example, killing bacteria with antibiotics, or flushing out bacteria with fluids. The use of analgesia typically failed this test on both counts.

Prior to taking part in this interview study and/or the CUTI trial, cranberry capsules were an unknown entity to most. For those familiar with cranberry capsules, the idea of using them in the context of an acute UTI was generally novel. Most women were open to trying cranberry capsules a way of managing acute UTIs, with provisos, both within and outside the context of a trial. Receiving a back-up antibiotic prescription was important to women; it reassured them that if their symptoms did not get better or worsened, they had ready access to a treatment that they had previously found effective.

Agreeing to a delayed antibiotic approach was not a fixed decision in time; it was dependent on the stage of their illness, their perceived symptom severity and prevailing personal circumstances. Delaying antibiotics was more acceptable to women if they were receiving *something* in the interim that they perceived had therapeutic potential.

4.5.1. Strengths and Limitations

A strength of this study is that views were sought from different stakeholder groups. I interviewed non-CUTI trial UTI patients to increase the chance of capturing the views and experiences of women who might be less amenable to trying non-antibiotic treatments. The recruiters to the trial were able to bring a wealth of knowledge from their experiences of speaking to women with acute UTIs in the context of both clinical and research work. In

addition, trial recruiters were able to provide some insights from people that I was not able to reach, such as women who declined to take part in the CUTI trial.

Triangulation of insights from CUTI trial participants, non-CUTI trial UTI patients, CUTI trial recruiters, and quantitative findings, allowed multiple perspectives on the same phenomena to be explored. For example, both UTI patients and recruiters suggested that the outcome of UTI consultations is usually a prescription for immediate antibiotics (see section 4.4.2.3). Furthermore, the positive experience reported by women who took both immediate antibiotics and immediate cranberry capsules, is in keeping with the preliminary and exploratory effectiveness outcomes of the feasibility trial (see section 3.4.3).

Whilst I tried to capture UTI patients with diverse views, it is possible that non-CUTI trial UTI patients agreeing to be interviewed were women who were more likely to have an interest in non-antibiotic treatments. Thus, the views of women in my interview sample may be biased towards having a more favourable view of non-antibiotic treatments, and potentially also towards accepting a delayed antibiotic approach. I had hoped to invite women who had declined to take part in the CUTI trial to be interviewed, however, I did not receive approval from ethics for this. Interviewing CUTI trial decliners may have provided additional, useful insights from women who are less inclined to try non-antibiotic treatments.

As a result of my recruitment methods (through General Practices) I am less likely to have captured women with acute UTIs who typically manage their symptoms without seeking healthcare practitioner input. The use of posters in the mail-out study General Practice was one method used to try to overcome this (see section 4.3.4.2). However, given that I am ultimately trying to reduce antibiotic consumption for acute UTIs, it could be considered

more helpful to seek the views of women who are more likely to consume antibiotics and/or contact a healthcare practitioner for their symptoms.

I conducted interviews with CUTI trial participants and non-CUTI trial UTI patients of a range of ages and backgrounds (see Table 4. 1). However, despite my best efforts (see section 4.3.4.2), there was limited ethnic diversity in the sample (Table 4. 1). These results may therefore be less reflective of the experiences of women with UTIs from non-Caucasian backgrounds.

I conducted all of the interviews. The process of conducting the interviews, listening to and reading the transcripts several times, and conducting the analyses, allowed me to immerse myself in the data. However, women being interviewed were aware that I was the Chief Investigator (CI) of the CUTI trial, and I had interacted with CUTI trial participants during the trial at their two-week follow-up call. This may have influenced the responses given by the CUTI trial participants, predisposing them to give a more favourable account of their trial experiences. I tried to mitigate this by positioning interviewees as the experts, and explaining that I would be guided by them. Furthermore, I explained that the purpose was to gather information to help shape the design of a future trial, as opposed to gathering positive feedback.

4.5.2. Comparison with existing literature

When women present to a healthcare practitioner with symptoms of an acute UTI, they almost always receive a prescription for antibiotics for immediate use (15). In a prospective, observational study of women presenting with symptoms of uncomplicated UTI to primary

care in England, Wales, Spain and the Netherlands, only 2% (13/702) of women received a delayed antibiotic prescription for their symptoms (195).

The present interview study findings suggest that in certain situations, many women are prepared to delay antibiotics for an acute UTI. Other research studies similarly suggest that women would find the delayed antibiotic approach acceptable. In a Dutch mixed methods study in primary care, a questionnaire administered to 231 women with an acute UTI revealed that 66% of respondents would be willing to delay antibiotics for their symptoms (196). In a prospective cohort study in the Netherlands, women presenting to participating General Practices with symptoms of an acute UTI were asked by their GP whether they would be willing to delay antibiotics (197). With this approach, 37% (51/137) of women were willing to delay antibiotics, and of these women, 55% (28/51) reported that they had not used antibiotics by one week (197). Whilst this was a small study that reported only short-term outcomes, the findings suggest that a proactive approach by healthcare practitioners to offer women delayed antibiotics is likely to be accepted by a proportion of women.

Awareness of the delayed antibiotic approach for acute UTI appears to be low amongst the public. In an English household survey of 1,625 people aged 15 years and above, 72% (1,181/1,625) were unaware of the name, or the practice, of 'delayed antibiotic prescribing' (198). Those who were fully aware of the term and practice were more likely to report being strongly in favour of its use for UTIs, compared with those who were not aware of the term or practice (51% versus 35%, respectively). Through randomised clinical trial, offering a delayed antibiotic prescription has been found to significantly reduce the proportion of women with acute UTIs consuming an antibiotic compared with those receiving an

immediate antibiotic prescription [77% versus 97% antibiotic use, respectively (odds ratio 0.12; 95% CI: 0.03 to 0.59)] (33).

In an interview study that explored GP and patient experiences of delayed prescribing for UTIs, the authors conclude that the decision to delay antibiotics should depend on whether self-management strategies have already been tried before seeing the GP, and on symptom severity (172). In a German study, women taking part in a trial of immediate antibiotics versus immediate ibuprofen for acute UTI were interviewed (199). Many suggested that they considered that it was safe to take part in the trial because UTI is "not a serious condition." Indeed, four of the five trial decliners interviewed had refused trial participation on the basis that they wished to *avoid* immediate antibiotics. This contrasts with the findings of the present study, in which many women reported significant, disruptive symptoms associated with UTI. Furthermore, CUTI trial recruiters reported that wishing to receive immediate antibiotics was a reason for some women declining to take part (see section 4.4.3.1 and Table 3. 2). This may represent cultural differences in the way that UTIs and antibiotics are perceived. Of note, outpatient antimicrobial prescription in Germany is lower than in the United Kingdom (200).

Leydon *et al* (171) explored women's thoughts on and experiences of delayed antibiotics for UTIs, and found that women would be prepared to delay antibiotics if their symptoms were not severe. The authors also suggest that GPs should be mindful that women may not always want immediate antibiotics, and that giving a delayed antibiotic prescription is often sufficient to validate women's symptoms and help-seeking. The present interview study builds on these findings, and provides additional insights suggesting that the acceptability of

a delayed antibiotic strategy for UTI may be increased by receiving a non-antibiotic option with perceived therapeutic properties in the interim.

A number of studies have evaluated the use of non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen, as an alternative treatment for acute UTIs; these studies have found that NSAIDs reduce antibiotic consumption but result in a higher symptom burden and more cases of pyelonephritis (34-36). In the present interview study, women did not typically perceive analgesia as a UTI treatment, but rather a means of combatting pain. Thus, whilst NSAIDs have been shown to reduce antibiotic consumption through clinical trials, they may not necessarily be widely accepted by women as a treatment strategy for their acute UTIs. Women wanted to take something that they perceived treated the root cause of their symptoms. This is in keeping with a questionnaire study of women with UTI, which found that most women take antibiotics because they want to "combat bacteria." (196) The nature of pain that women experience with a UTI may also play a part in their thoughts on NSAIDs; whilst women felt that analgesia could help with abdominal pain, they tended not to see it as a way of helping with the pain experienced on passing urine/urethral discomfort. Furthermore, not all women experience pain when they have a UTI; urinary frequency or urgency may be the predominant symptoms.

The need to "combat bacteria" may also be prevalent amongst healthcare practitioners. In an interview study exploring GPs' experiences of delayed antibiotic prescribing for a UTI, GPs felt that a firm UTI diagnosis warranted antibiotics (172). They might consider a delayed antibiotic approach for equivocal UTI symptoms, but were more used to using the delayed antibiotic approach in the context of acute respiratory tract infections (172). Urine samples sent for culture are the commonest specimens sent to microbiological laboratories (201).

Healthcare practitioners routinely receiving urine culture results showing bacterial growth may serve to reinforce immediate antibiotic prescribing behaviour. In contrast, throat swabs/sputum cultures are not routinely sent to laboratories from primary care (202, 203), thus, the same positive reinforcement of antibiotic prescribing behaviour may not be present for acute respiratory tract illnesses.

Women in the present interview study did not typically combine over the counter treatments with antibiotics. In vitro research suggests that alkalinisation of urine may render Nitrofurantoin less effective against *E.coli* and *Proteus mirabilis*; with a rise in pH from 5.0 to 8.0 leading to a twentyfold increase in the minimum inhibitory concentration of Nitrofurantoin against *E.coli* (204). By contrast, the purported mechanism of action of cranberry extract suggests that there could be synergy with antibiotics. Given that PAC-A in cranberry extract is believed to reduce the ability of *E.coli* to adhere to the uroepithelium (50), this could potentially render antibiotics more effective, enhancing their ability to attach to and kill pathogenic microorganisms.

Factors influencing the decision to participate in research trials have previously been evaluated (205-208). In a survey study of 198 patients who were approached to take part in clinical trials in the Netherlands, the authors found that for patients with acute conditions, people were less likely to participate in a trial if the trialled treatment appeared risky, but more likely to participate if the trialled treatment was perceived to be better than their usual care (207). The idea of 'competing interests' was examined in an interview study of people who had been invited to take part in a range of trials, including trial decliners and withdrawers (209). The authors identified anticipated personal benefit as a major theme, as well as a weighing up of the wish to help others against any potential risks to self (209).

McCann *et al* use the term 'conditional altruism;' people are initially interested in taking part in trials because they want to help others and additionally perceive potential personal benefits, but disengage if there are too many negatives or risks associated with taking part (205). A similar theme emerged in the present interview study; women wished to take part in the CUTI trial because they wanted to help progress research in this area, and additionally perceived potential personal benefits (e.g. access to a novel treatment – cranberry capsules, and the potential to avoid antibiotics). The incorporation of a delayed antibiotic trial arm was generally considered acceptable unless the balance tipped too far towards potential personal harm (e.g. receiving immediate placebo or no initial treatment – see section 4.4.3.2).

4.5.3. Comparison with existing theory

Self-regulation theory was proposed by Leventhal and colleagues in 1980 (210). Central to this theory is the patient as an active problem solver, generating hypotheses on the basis of their symptoms (211). Patients' illness representations are strongly influenced by 'the individual personal context,' that is, their previous experiences of the illness (211). Their illness representations then influence their action (or inaction) to avoid a perceived threat. The worse the perceived threat, the more likely the patient is to take action. The need to additionally take into account the impact of external influences on patient behaviour, such as the impact of healthcare professionals, has also been highlighted (212); understanding patients' illness representations provides a window for healthcare professionals to intervene.

The present interview study suggests that women make a quick self-diagnosis of an acute UTI on the basis of their symptoms and previous experiences. However, when patients present to a healthcare professional, the outcome is almost always an immediate antibiotic

prescription. It may be the case that a patient has already tried self-management strategies, or that they have perceived severe symptoms, however, recruiter insights suggest that immediate antibiotics is the default request from many UTI patients. There appears to be a degree of conditioning of patient behaviour; receiving an immediate antibiotic prescription is what always happens when women present to a healthcare practitioner. The expectation to receive immediate antibiotics may also be compounded by a lack of awareness of potential alternatives, or a prior bad UTI experience (e.g. developing pyelonephritis).

There is potential for the healthcare practitioner to intervene, and when appropriate, to offer a delayed antibiotic approach. However, the suggestion from the present interview study (and others (15)) is that this approach is rarely offered by healthcare practitioners. This may be due to: A perception of a lack of robust evidence for alternative options; a perception that giving immediate antibiotics will lead to greater patient satisfaction; a desire to reduce the risk of an adverse outcome; and a perception of a faster/more straightforward consultation (213). A healthcare practitioner's actions may therefore perpetuate and reinforce a patient's belief that immediate antibiotics are always needed for an acute UTI.

In an open-label trial evaluating the effectiveness of five different approaches to managing acute UTIs in women, the authors found that women assigned to a delayed antibiotic approach re-consulted with UTI significantly less than women receiving immediate antibiotics [odds ratio 0.44 (95% CI:0.21 – 0.95)] (33). This result points to the potential for advice from healthcare practitioners to influence patients' future behaviour.

4.5.4. Implications for research

The CUTI trial (see chapter 3) has demonstrated that it is feasible to conduct a trial of cranberry extract for acute UTI in primary care (67). The present interview study has confirmed that women are receptive to exploring non-antibiotic treatments for acute UTI, and they are willing to take part in trials of cranberry extract in this context. In light of this, the efficacy of cranberry extract as a way of managing acute UTI should be explored through a rigorous clinical trial (see chapter 6, section 6.6). Such a trial should test cranberry extract in capsule/tablet formulation; women have indicated that this would be preferable to using cranberry juice (due to concerns about the volume, taste and sugar content).

In order to determine the efficacy of cranberry extract, it should ideally be compared with placebo. Whilst the integrity of trial design to determine this should not be compromised, it is important that the design gives due consideration to women's thoughts on and feelings surrounding receiving placebo-only treatment in the context of an acute UTI (see section 4.4.3.2). Women's views on trial designs that incorporate placebo are discussed further in chapter 5 (see section 5.4.4).

Women indicated that, in addition to a sense of altruism and perceived personal benefits, an important factor contributing to their decision to take part in a trial was whether they felt that their contribution would make a meaningful difference to advancing research. It was important that they understood the research benefit of each arm in a trial, whether they were assigned to a usual care arm or a novel intervention. Highlighting the rationale behind the different treatment groups, and their equal importance in providing an answer to the research question being addressed, should be emphasized in participant literature e.g. PILs.

A future trial should include an embedded qualitative evaluation. These interviews will provide rich insights into women's experience of taking part in a trial of acute UTI that incorporates placebo. Furthermore, ethical approval permitting, capturing the views of women declining to take part in the trial would provide additional, useful insights into the reasons that women might decide not to take part in UTI trials that incorporate cranberry extract and placebo. Both a future trial and future interview study should ideally incorporate the views of people from diverse ethnicities, making the voices heard more reflective of the wider population. The use of alternative language to describe the interview process, such as a 'discussion,' may make the process seem less daunting to prospective participants and could lead to higher levels of participation.

4.5.5. Implications for clinical practice

The current National Institute for Health and Care Excellence (NICE) guidance suggests that a delayed antibiotic prescription can be considered for women with acute UTIs, taking into consideration various factors such as symptom severity, the risk of developing complications and patient preference (156). In the present interview study, women did not report that the delayed antibiotic approach had been used for managing their UTIs, which is largely in keeping with the findings of previous studies (171, 172). The present interviews suggest that women would accept this approach in certain circumstances. However, the decision to delay should be principally guided by the patient.

NICE guidance advises simple analgesia and increased fluid intake as self-care measures (156). The current Scottish Intercollegiate Guidelines Network (SIGN) guidelines for management of acute UTI mention that a three day course of an NSAID can be used as first-

line treatment for women who describe mild symptoms, with advice to seek medical attention if their symptoms do not improve in three days (214). Women commonly describe increasing their fluid intake early in their illness course, but were less likely to consider taking analgesia to manage their symptoms and did not consider analgesia as a UTI treatment. Whilst women were happy to try a delayed antibiotic approach, this was usually made more palatable by receiving an interim treatment with perceived therapeutic potential. The current consultation model, described by most women, does not leave much scope for wider discussions about non-antibiotic treatments. Healthcare professionals may also be constrained by the lack of robust evidence for, or against, certain non-antibiotic options, such as cranberry extract. Compared with analgesia, women view cranberry extract as a potential UTI treatment, with cranberry juice already commonly used as a UTI treatment adjunct. This highlights the need to establish evidence for or against the safety and effectiveness of cranberry extract in the context of an acute UTI. Having a firm evidence base in this area may well facilitate healthcare professional discussions with women, allowing them to give firm advice about whether they should, or should not, use cranberry extract as a way to manage acute UTIs.

If cranberry extract is found to be effective through a future clinical trial, it could be incorporated into a delayed antibiotic prescription strategy. Cranberry extract could also potentially be used in combination with antibiotics. Women who were assigned to the immediate antibiotic and immediate cranberry group often described an additive benefit to the combination, which was also seen in the preliminary and under-powered CUTI trial analyses (see section 3.4.3).

4.6. Conclusions

There is an appetite amongst women for safe and effective non-antibiotic treatments for acute UTI. In certain circumstances, many women are willing to try a delayed antibiotic approach, made more acceptable by concurrently receiving an interim non-antibiotic treatment. There is therefore a need to ascertain the efficacy of non-antibiotic treatment options, such as cranberry extract, in the context of acute, uncomplicated UTIs.

In order to establish this evidence base, further rigorous clinical trials of cranberry extract are needed. Recruiting to trials of opportunistic conditions is commonly recognised as one of the most challenging recruitment models. Furthermore, retention of participants minimises missing data and enhances the veracity of quantitative trial findings. In chapter 5, I explore the experiences of recruiters to the CUTI trial, as well as women's experiences of CUTI trial practical processes (e.g. using the electronic diary), with the aim of using this information to maximise the chance of a future trial recruiting to target, and of participant retention.

5. Chapter 5 –Experiences of opportunistic recruitment to the CUTI trial and of CUTI trial processes: A qualitative study with CUTI trial recruiters and UTI patients

5.1. Summary

In chapter 4, I established that in certain situations many women would find it acceptable to use cranberry extract as a way of managing acute UTIs. Before cranberry extract is considered for use in routine clinical practice, it is important to establish its efficacy/effectiveness through clinical trials, and the exact niche and/or combination. In order to gain meaningful results from said clinical trials, it is imperative to be able to recruit and retain participants. In this chapter, I explore insights gained from interviews with recruiters about opportunistic recruitment, and integrate these insights with women's views on and experiences of CUTI trial processes.

5.2. Introduction

Well-conducted randomised clinical trials (RCTs) are critical to answering important research questions and advancing clinical practice. However, it is well documented that recruitment to RCTs can be difficult, and around two thirds of clinical trials do not achieve their target sample size (215, 216). Inadequate sample sizes, and consequently under-powered trials, lead to equivocal results. In the face of inadequate recruitment, further trials may need to be conducted in order to tackle research questions that remain unanswered, with the ensuing considerable expense and time incurred.

Opportunistic recruitment is recognised as one of the most challenging forms of recruitment in General Practice, given its inherent unpredictability, coupled with the high existing workload in primary care and short appointment times (217). However, opportunistic recruitment is unavoidable for trials of incident conditions, such as acute UTI. Whilst some research has sought to address these challenges (218, 219), few studies have done so through the lens of primary care recruiters (220, 221).

The aim of the present interviews with recruiters was to learn from their experiences, good and bad, and to take this learning forward to the planning for a main trial. Learning from the experiences of feasibility trial recruiters should increase the chances of successfully recruiting to target in a future trial, and therefore of producing research that usefully adds to the current, limited evidence base of the use of cranberry extract for managing symptoms of acute UTI (65).

In addition to successfully recruiting patients, participant retention and data completeness help to ensure that research generates meaningful results, reducing attrition bias (222). This can be particularly challenging when outcome reporting is participant dependent, and participants are asked to do something above and beyond taking an intervention (e.g. completing a symptom diary). I therefore wanted to understand women's thoughts on and experiences of the practical procedures required of CUTI trial participants, such as using the electronic diary and the scale of 0-50 to rate symptoms.

I present the findings and lessons learned from both recruiters and UTI patients of their experiences of the practical procedures/processes involved with the CUTI trial, with the aim

of using this learning to guide future trial design (see chapter 6 section 6.6 and Appendix 6. 2).

5.3.Methods

Below, I focus on the methods used for conducting interviews with recruiters to the CUTI trial. The methods for conducting interviews with UTI patients, both participants and non-participants of the CUTI trial, have been described in chapter 4 (see section 4.3)

5.3.1. Ethical Approval

In accordance with the Declaration of Helsinki, I sought ethical approval for the recruiter interview study. It was approved by the South Central Oxford B Ethics Committee (REC reference: 18/SC/0673) and the Health Research Authority (IRAS Project ID: 249672) prior to recruiters being invited to participate in the interview study.

5.3.2. Participants and eligibility criteria

Recruiters were eligible to take part in this interview study if they were involved in recruitment to the CUTI trial and provided written, informed consent to be interviewed. I invited all recruiters (thirteen in total) to take part in the interview study. Eight recruiters accepted the invitation, with representation from different recruiter roles (six nurses and two GPs), from each of the four recruiting General Practices, and from the Clinical Research Network (CRN).

5.3.3. Recruitment

Electronic invitations, including an invitation letter (see Appendix 5. 1) and a participant information leaflet (PIL) (see Appendix 5. 2), were sent to recruiters. Recruiters opting for a telephone interview were posted an informed consent form (ICF – see Appendix 5. 3), and were asked to sign and date it, before posting it back to me.

5.3.4. Materials and Procedures

A semi-structured interview guide (177) was used to explore recruiters' experiences (see Appendix 5. 4). I began by asking recruiters about their initial thoughts on the CUTI trial. Additional questions and prompts elicited details about recruiters' experience of approaching participants and recruiting them to the trial, and their thoughts on recruiting participants to a subsequent, adequately powered trial. The aim of the interview guide was to facilitate and prioritise the recruiters' experiences; it did not aim to dictate the course of the interview. I modified the interview guide iteratively in light of new information that arose as the trial and participant/recruiter interviews proceeded.

5.3.5. Data Collection

I conducted a mixture of face-to-face and telephone interviews with recruiters. Face-to-face interviews took place in a private location, chosen by the recruiter. Locations included recruiters' residences, recruiters' places of work (General Practices), and the Nuffield Department for Primary Care Health Sciences (NDPCHS). All interviews took place at a date and time of the recruiter's choosing. At the outset of the interview, I checked whether the recruiter had any questions, and gave them time to look over the PIL (see Appendix 5. 2) again, as needed, to refresh their memory. I gained written, informed consent from

participants before proceeding with the interview (see Appendix 5. 3). At the interview conclusion, recruiters received a £20 voucher as a token of thanks.

Each interview was audio recorded with recruiters' permission and consent. Audio recordings were encrypted, password-protected, and sent securely via OxFile to a professional transcriptionist who returned the transcripts to me, encrypted and password-protected, using OxFile (see section 4.3.7). Each transcript was labelled with a unique recruiter identification number and omitted any recruiter-identifiable data. Names of recruiters were only recorded on ICFs (see Appendix 5. 3), which have been stored securely at NDPCHS. I read through transcripts upon receipt, redacting any names or places mentioned by the participant, filling in any gaps in the transcription where the transcriptionist had been unsure what was said, and checking them for accuracy against the audio recording.

5.3.6. Safety Procedures

5.3.6.1. Recruiter considerations

I did not anticipate that the topic that I was discussing with recruiters would cause emotional distress. Despite this, at the start of each interview I reassured recruiters that they did not have to answer any question that made them feel uncomfortable, and that they could ask me to stop the audio recorder at any time.

5.3.6.2. Personal considerations

As the recruiters were all healthcare professionals, with whom I had been working on the CUTI trial, I considered that my personal risk was very low. Despite this, I followed the University of Oxford's lone-working policy and I let a supervisor know in advance when I had an interview off-site, for example, in a recruiter's home.

5.3.7. Philosophical Approach

As with the UTI patient interviews (see section 4.3.9), I took an interpretivist approach to conducting the recruiter interviews (178). I recognised that each recruiter's beliefs and experience of the trial would be shaped by their past experiences (of recruitment to trials, clinical practice and otherwise), as well as by their context (e.g. their current workplace). I also recognised that my background, as a GP and researcher who had led the CUTI trial, would necessarily inform the lens through which I asked questions, and would also inform my observations and my understanding of the data.

I took an inductive (data-driven), pragmatic approach to understanding the data (181). My primary concern was with gaining insights from the data that could be used to inform future research (see section 5.5.3) and the design of a future trial (see chapter 6).

5.3.8. Reflexivity

I have discussed my approach to reflexivity in detail in chapter 4 (see section 4.3.10). A specific consideration with the recruiter interviews was that I was interviewing people that I had worked with throughout the trial. This may have biased them towards giving favourable views of their trial experience. To help guard against this, I ensured that I had many question prompts within the topic guide about things that they perceived did not go well or could be improved. Furthermore, the recruiters were aware that the goal of the interview study was to learn from their feedback (positive and negative) in order to shape a future trial. There would therefore have been less incentive for them to paint an overly favourable picture of their experience.

5.3.9. Data Analysis

The approach that I took to data analysis has been described in detail in chapter 4 (see section 4.3.11). In brief, the steps of thematic analysis described by Braun and Clarke were followed (187). This involved familiarisation and deep immersion in the data, coding of the data, and then using the data to develop overarching themes through an iterative process, and in discussion with my qualitative supervisors.

5.4. Results

I conducted eight interviews with recruiters in February and March of 2020. The duration of these interviews ranged from 20 to 33 minutes (mean 26 minutes). Recruiter characteristics are described in Table 4. 1. I developed four themes from the recruiter interviews:

Theme 1 – First impressions count – recruiters' initial perceptions of CUTI trial utility and achievability

Theme 2 – Opportunistic recruitment to the CUTI trial – channelling patients into research clinics and overcoming expectations for immediate antibiotics

Theme 3 – CUTI trial procedures and electronic systems were largely perceived as par for the course – *the recruiter perspective*

Theme 4 - Reflections on the CUTI trial and shaping future research

In the first theme, I describe recruiters' initial thoughts on the CUTI trial and their experiences prior to sites opening to recruitment, including partaking in the Site Initiation Visit (SIV). In the second theme, I discuss the recruiters' perceived barriers and facilitators to opportunistic recruitment of acute UTI patients in the CUTI trial. In the third theme, I discuss recruiters' thoughts on and experience of the practical procedures required of them in the

trial. In this theme, I integrate UTI patients' thoughts on and experience of trial processes and procedures, such as using the electronic symptom diary (*the UTI patient perspective*). In theme four, I integrate the reflections of recruiters and UTI patients on their CUTI study experience, and their thoughts on ways to improve future trials of cranberry for acute UTI - including trials that incorporate placebo.

5.4.1. Theme 1 – First impressions count – recruiters' initial perceptions of CUTI trial utility and achievability

Recruiters took a number of factors into account when weighing up whether it would be appropriate for them to recruit to the trial. It was important that: they felt the research would help to answer an important question, namely, the avoidance of antibiotic treatment for acute UTIs; they perceived that the research study would be acceptable to their patients; and, that the research seemed achievable – that is, that research procedures did not appear too onerous and that it would be possible to recruit to target. Recruiters predominantly reported positive sentiments when asked their initial thoughts of the CUTI trial.

It was, sounded like a good, yeah a good idea, a useful research study. (R1 - nurse recruiter)

I thought it was achievable. I thought that patients would like it. I didn't think it would be particularly difficult to recruit to… (R3 - nurse recruiter)

Some recruiters sensed that there was a change in the way that patients perceive antibiotics, no longer seeing them as a 'panacea.' They felt patients would be open to trying a non-antibiotic treatment. Furthermore, recruiters perceived that the acceptability of the trial to participants would be helped by the fact that using cranberry in the context of a UTI was likely to be familiar to patients.

People's awareness is changing now about the resistant thing and that there are alternative ways to treat all sorts of conditions… (R6 - nurse recruiter)

We have lots of patients a) would want to, be happy to try something different and may be put off the idea of having antibiotics and also b) who like the holistic approach and what they might deem as being homeopathic but would like to try something slightly different. (R8 – GP recruiter)

One recruiter perceived that an additional benefit of recruiting to the trial might be a reduction in the workload of clinical staff, given that acute UTI consultations are common (12) and such presentations would be diverted to their research nurse.

Few initial concerns were expressed by recruiters. Two recruiters wondered how acceptable patients would find the idea of delaying antibiotics, alluding to the perception that women typically contact General Practice with the expectation of receiving a prescription for immediate antibiotics (see section 4.4.2.3).

Some people come in with an agenda. A lot of people come in and, you know, plonk themselves down and say, "I've got a urinary tract infection. I need antibiotics" (R6 - nurse recruiter)

Consideration was also given to the potential impact of different UTI consultation models on the ability to recruit, particularly remote consultation by telephone.

Working people…they wouldn't always have time to come into the surgery to be recruited…younger people that UTIs normally affect tend to be at work. So that was the only thing I thought…Although I was pleasantly surprised actually people did come in… (R4 - nurse recruiter)

Overall, recruiters found the Site Initiation Visit (SIV - see section 3.3.6) comprehensive and clear, and most felt that it provided them with the information that they needed to proceed

with trial recruitment and to cascade information to clinical colleagues. In particular, recruiters appreciated the live demonstrations of the electronic systems that they would use for recruitment, namely REDCap and Sentry (see section 3.3.10).

It fleshed out the trial to us to explain what you're doing, and why you're doing it and how you're going to do it. It's a useful, you know, SIVs are always useful for us for understanding the trial especially where there's opportunistic recruitment so if I have a thorough understanding then I can tell my colleagues and we did that at the SIV (R7 – GP recruiter)

Due to a delay in me receiving feedback from ethics about a substantial amendment, there was a longer than planned interval between the SIV and General Practices receiving the green light to open to recruitment. Recruiters highlighted the importance of SIVs taking place as close as possible to sites opening to recruitment, so that trial procedures are fresh in their minds, obviating the need for re-training.

The only problem with site initiation visits; they should always be as close to the starting date as possible…. Because what happens, what often happens then is people forget about the study when it goes into the long grass for a while and then people then need a refresh…(R8 – GP recruiter)

5.4.2. Theme 2 – Opportunistic recruitment to the CUTI trial – channelling patients into research clinics and overcoming expectations for immediate antibiotics

At most sites, the majority of acute UTI patients were consulted in minor illness clinics, which were often run by nurse practitioners. The minor illness clinics usually offered face to face appointments, although one site used an initial telephone triage system. UTI patients

were also commonly consulted by the 'duty doctor' (on-call General Practitioner), and some UTI patients were seen in routine GP clinics.

Some recruiters found it harder to recruit to the CUTI trial than they had anticipated. The main difficulty experienced by recruiters was channelling patients from their usual clinical pathway through to the research team. Opportunistic recruitment seemed to work best when there was co-ordination between minor illness practitioners and trial recruiters; the recruiter could identify potential UTI patients from the minor illness clinic list and book them directly into one of their research slots. Close proximity between the two clinics was also reported to be beneficial, facilitating communication.

When she's in minor illness, I'd look through her list and I'd be able to spot the urine infections because they're identified on the, the patient on the patient appointment system online…I would… message her instantly and say, "There's a number of UTIs so I'll, I can take them."(R2 - nurse recruiter)

The receptionist was often the first person to speak with a potential UTI patient, and there was potential for them to triage UTI patients directly into research slots. However, this was not necessarily a straightforward process, in part, due to low awareness of ongoing research studies amongst reception staff, in addition to frequent changes in reception staff during the day as a result of shift working.

I had a bit of a, an issue with the receptionist…I'd go down, I'd say, "let, can you let me know if there's any urine specimens," and then I'd get down there and they'd, someone else would test them and they'd already been put on the triage…the problem is, you know, when you've got more than one receptionist and they change shift… so it's constantly kind of reminding them (R3 - nurse recruiter)

Various methods were used at the different sites to try to improve awareness of the trial amongst clinical (non-research) colleagues, in the hope that this would encourage clinical

staff to direct eligible patients to their research colleagues. I created desk prompts (see Appendix 5. 6) and distributed these to recruiting sites. The idea was for them to be placed on the desks of clinical staff (e.g. General Practitioners and nurses). Whilst some recruiters perceived that their clinical colleagues saw them as helpful, real-time aides memoires, they did not necessarily perceive that this translated into a meaningful diversion of eligible patients to research staff. There was potential for desk prompts to be ignored, exacerbated by the desk prompts being perceived as insufficiently prominent or "eye catching."

They [desk prompts] were a bit small and blended into the background a bit I think a bit too much. So, they my colleagues accepted them but I don't know that anyone actually recruited or that it made a significant difference to our recruitment to be honest. (R7 – GP recruiter)

Egton Medical Information System (EMIS) prompts - prompts that automatically appeared on-screen in response to trigger words typed into the electronic patient record, suggesting that a patient may be eligible for the trial - were used by some of the recruiting sites. These prompts similarly received a mixed reception; whilst they had the potential to keep the study in the minds of clinical staff, they could also become a source of "irritation."

Some of them [EMIS prompts] are not always appropriate for the moment and so sometimes they get, they can cause a wee bit of irritation and amongst all our colleagues…(R6 - nurse recruiter)

Typing CUTI trial reminder messages at the top of duty doctor or minor illness clinic electronic lists, where patients with an acute UTI would usually be found, was perceived as a useful way to encourage clinical staff to divert appropriate patients to the research clinic. Sending direct, on-the-day messages to clinicians working in these clinics was similarly perceived to be useful. Whilst these messages were not automated and therefore more manually intensive than EMIS prompts, these targeted and personalised alerts were perceived

to be more effective.

What I found quite useful was if we have, we have like a booking system for urgent on the day appointments, I'd kind of put a reminder on, on that if anyone had symptoms of UTI please send to X for research kind of thing, that seemed to work better than the desk prompts, I think. (R5 - nurse recruiter)

The inherent unpredictability of opportunistic recruitment was also commonly mentioned as a barrier to recruitment. The inability to plan ahead for when potentially eligible patients would present meant that such patients could not always be booked into research slots. Furthermore, recruiters had reduced capacity to conduct CUTI research activity on busy clinical days.

A barrier experienced uniquely by the CRN nurses was the inability to make first contact with patients. This was for confidentiality reasons, as they were not members of staff employed by the General Practice site. They were therefore dependent on members of staff within the General Practice to make first contact with potential participants about the trial, before potential participants could be directed to a CRN nurse recruiter.

Once patients had entered the research pathway, recruiters generally found that the CUTI study was straightforward to explain to participants, facilitated by the simple trial design.

It was a lot simpler than some of the other studies that I've been involved in where there's an awful lot of information to give… (R1 - nurse recruiter)

Recruitment to the trial was initially slower than I had anticipated (see Figure 3. 3). Screening and enrolment log information suggested that the commonest reason for women declining to take part in the trial was not wishing to receive a delayed antibiotic prescription (see Table 3. 2). On the advice of the Trial Steering Committee, I created a script that recruiters could use

to explain the delayed antibiotic group (see Appendix 5. 5). The goal of the script was to positively frame this group as a way to potentially avoid taking antibiotics, whilst knowing that antibiotics were close to hand if needed. Most recruiters found that the script facilitated their discussions with participants about the delayed antibiotic group, which some women viewed less favourably. They perceived that women found the script persuasive, and that it helped recruitment.

I did use it [the script] and it is nicer and easier to because you can get a little bit tongue tied sometimes when you're explaining something, when you've just got that, you know, with very, with clarity as to, to what is being said…so that was useful...(R4 – nurse recruiter)

One recruiter felt that receiving the script to help explain the delayed antibiotic group earlier in the trial could have aided recruitment.

Having that [the script] at the very beginning to have said would have been I think probably, probably missed a couple at the very beginning because they just said, "I want to take antibiotics" (R3 - nurse recruiter)

5.4.3. Theme 3 – CUTI trial procedures and electronic systems were largely perceived as par for the course

5.4.3.1. The recruiter perspective

Recruiters found it easy to navigate the site file (containing essential trial documents) and site boxes [containing ICFs (see Appendix 3. 5), participant PILs (see Appendix 3. 3), participant study packs and cranberry capsules]. They found it convenient having the cranberry capsules on site, and did not encounter any problems issuing the study product to participants.

Everything was very easy to find within the file. All the packs were together do you know what I mean? It was easy to put together. Once somebody came it was easy to get an information sheet, a consent form. It was all in that plastic envelope wasn't it? (R3 - nurse recruiter)

Recruiters found the trial recruitment processes easy to follow. A one-page, A4 flow chart summarising the recruitment process (see Appendix 3. 2) was praised as a helpful aide memoire, which recruiters used regularly – although, one recruiter felt that the flow chart could have been bigger.

…that flow chart…was perfect…that just fed you through the, the process very easily, yeah. (R4 - nurse recruiter)

The simplicity of the trial procedures meant that most recruiters were able to complete the recruitment process in 10 to 20 minutes, thus, some could fit recruitment into a routine clinical appointment slot.

Recruiters felt well supported in their recruitment efforts by the central trial team and valued regular communication by email and through a weekly newsletter (see section 3.3.19). The newsletter included recruitment numbers by practice and general recruitment tips. Recruiters generally appreciated receiving non-judgmental feedback and felt that the newsletter helped to foster healthy competition between recruiting practices, although one recruiter cautioned that some General Practices might find it 'overbearing.'

Two online systems were required for recruitment; REDCap was used to confirm eligibility and to randomise participants, whilst a separate electronic system called Sentry was used to store personal participant details such as the participants' names, email addresses and

telephone numbers (see section 3.3.10). Recruiters found both electronic systems quick and easy to use, and none experienced technical problems.

I've used REDCap…for other studies…Sentry was really straight forward as well though, so they work really well together, so it wasn't an issue at all. (R2 - nurse recruiter)

General Practice medical records reviews (see section 3.3.13) were also completed electronically using REDCap. Again, recruiters found the process straight-forward, and often commented that it was considerably less onerous than medical records reviews that they had completed for other studies. One recruiter saw the medical records review as an opportunity to reflect on patient outcomes, which would not routinely take place in usual clinical practice.

5.4.3.2. The UTI patient perspective

Overall, UTI patients found the process of being recruited to the CUTI study straightforward. They found the trial paperwork [e.g. participant information leaflet (PIL – see Appendix 3. 3) and consent forms (ICF – see Appendix 3. 5)] easy to understand, and were happy with the contents, although one woman described the trial paperwork "over the top." Women found that the information they received from the recruiting healthcare practitioner, usually a research nurse, clear and comprehensive.

She [recruiting nurse] explained everything very, very thoroughly, you know, what you were doing and why you were doing it…she was very good. She took me through the whole lot, you know, [um] handed me all the documentation and what I had to sign and let me read it and everything. (T4)

Whilst most women had an idea of their preferred CUTI trial group, they were happy to be randomly assigned to a group. They understood that randomisation is an important part of

clinical trials and of "science," and were happy to place scientific methodological integrity over their personal preferences. However, one non-CUTI trial UTI patient considered that it would be preferable for a clinician to consider the history of each individual, and to use this intelligence to allocate the participant to the group that they perceived would benefit the participant most.

Maybe there are different factors which we need to take into consideration to put one woman in one group or another one instead of doing the random. (NT9)

Women taking part in the CUTI trial completed a 14 day electronic diary (see section 3.3.12 and Appendix 3. 6), with which they rated their symptoms and recorded any treatments that they were taking for their UTI. Women found the diary intuitive and easy to use. Notably, this was also the case for women who would not describe themselves as 'tech savvy.'

I'm not very technically minded and I'm not good on the computer. I've only learnt to text and do emails and things properly over the last few years….My husband…he looked at it first and he said to me, "It's so straight forward," and I didn't have to have any more help. I'm very proud of myself….I thought it was good... especially my age group, you do need to do that because people just can't be bothered to have anything too arduous… (T2)

The simplicity of the electronic diary meant that women typically did not need to spend a long time completing it (usually around five minutes), which was acceptable to them. However, if they forgot to complete the diary on a particular day, retrospectively entering data could be time-consuming.

It only took a few minutes. It wasn't arduous at all. (T5)

I'm quite bad at remembering to do stuff, so there were days where I had like a back-log, so I was going through and trying to sit there and remember how I felt on different days…but that's just me, I'm not very good at remembering to fill stuff in… It was quite simple, easy to follow…There wasn't any hassle to it. (T1)

CUTI trial participants received a daily email reminder to complete the electronic diary. Email reminders were generally perceived to be a useful prompt, which women did not find intrusive. These prompts were often considered particularly useful in the latter stages of diary completion, when many women were no longer symptomatic or taking UTI treatments, and therefore liable to forget to complete the diary.

It was good…yeah appreciated the emails every day to remind me to do it…it would have been quite easy to have forgotten so the emails coming in were quite good. (T14)

Most women completed the electronic diary using their home computer/laptop, an iPad/tablet, or a mobile phone. Typically, women completing the diary using a mobile phone were younger. Some felt that the electronic diary functionality was better suited to being completed using a computer. Technical troubles were rarely reported. A couple of women mentioned that they had some difficulty accessing the link to the final set of diary questions, and that the link had to be re-emailed to them.

As part of my feasibility work, I developed a rating scale of 0-50, an adaptation of an existing Likert scale of 0-6 (see section 3.3.12). Some women reported that having a wide scale gave them the ability to accurately rate how they felt, and gave them more flexibility in their daily symptom ratings. However, most women felt that a smaller scale would have been easier to use, albeit perhaps not providing the researcher with as much information.

Oh there was so many categories that I could have gone forward or backward in. I thought there were too many options.(T7)

Analogous UTI trials have typically used paper symptom diaries. I was keen to find out women's preferences regarding the format of the diary, specifically comparing an electronic format with a paper diary or a mobile phone application. Women expressing a preference for

a paper diary were usually of the older generation, who did not grow up with electronic devices and were less au fait with their use.

I'm that generation where paper is the thing isn't it?... you hear it all the time where people say, "Oh paper, gosh is it, is it on paper?" as if to say, 'Oh that's so antiquated, that's so backwards,' that even I accept that it probably is backwards but if it's filling in on paper I know that I would be perfectly happy to do that. (T2)

However, paper diaries were perceived by many to be inconvenient. Concerns were expressed about finding it harder to remember to complete a paper diary, the potential for paper diaries to get lost, the added hassle of having to post the completed diary back to the research team, and the adverse environmental impact of printing multiple diaries.

Personally, I've tried that [paper diary] before and I just forget…I just don't, I don't commit to it… I just forget to write it down with a pen but when it's with a phone, like, let's say email or something, you can quickly do it, you can quickly score it. (NT7)

The electronic diary was the expressed preference for the majority of women, including older women. It was seen as something of a half-way house between a paper diary and a mobile phone application: Completing an electronic diary requires a degree of technical ability and dexterity, but not to the extent that a mobile phone application might. On the other hand, it was seen as more convenient than a paper diary. The electronic diary was also a popular option with working age women, who often reported using a computer for their work and consequently checking their emails several times a day. A number of younger women felt that older women would prefer a paper diary, yet the expressed preference of many older women was for the electronic diary.

I type more actually than I write now….(NT3)

A preference for using a mobile phone application was more typical of younger women, although not exclusively. The principal perceived advantage was the easy portability of a mobile device, allowing women to fit diary completion into their daily schedule more easily (e.g. whilst commuting). An electronic diary was perceived by these women as a comparatively more restrictive option.

Well you can have your phone whenever you are; maybe on my way to work on the bus or anywhere basically, so I think it's much easier. (NT10)

Based on their experience of mobile phone applications, women felt that an app-based diary would need to be kept very simple, making use predominantly of tick-box responses, with free text kept to a minimum.

Some women, usually older, found using mobile phone applications unfamiliar territory and consequently "daunting." Despite this, a common sentiment expressed was a willingness to give it a go, albeit with some assistance from family or friends. Whilst for some women it would simply be technically challenging, for a few women it would be technically impossible as their mobile phones were not able to support such applications.

I'm still learning how to do an App. I think if I went now and they said. "We're going to do it [the diary] all by App." I'd go, "Please, no." I probably wouldn't want to do it…unless it was unbelievably simple. But if I had cystitis and I was still unfamiliar with doing Apps, it would be a deterrent because I would not be feeling like making the extra effort of being stressed out by the bally machine. (NT6)

Women received email reminders to complete the electronic diary, and generally found this acceptable. However, when asked, many women would equally have been happy to receive a text message reminder. Most women were familiar with sending and receiving text messages, even if they couldn't use a mobile phone application. Furthermore, women were used to

receiving text message reminders in other walks of life, such as for healthcare appointments. Whilst some women felt that the reminder should use the same platform as the diary (i.e. an email reminder for an electronic diary, or a text message/phone reminder for a mobile phone application), others felt that a text message was generally more visible than an email, particularly for those women who did not routinely check their emails every day.

I feel like where I don't always check my emails every day though. I probably would have remembered maybe if it was as a text message. (T1)

CUTI trial participants were telephoned at two weeks post enrolment to invite them to be interviewed (if they had provided prior consent), to encourage completion of the diary (if incomplete), and to obtain a minimum data set. The minimum data set elicited information on: the day the participant felt fully recovered; whether they had taken antibiotics; whether they experienced problems using the electronic diary; and, whether they experienced any problems taking cranberry capsules (if applicable). Women knew in advance that the call would take place through trial literature and the recruiting clinician, and generally found the content and length of the call acceptable. Indeed, some women felt that the phone call added a "personal" touch, and was a positive acknowledgement of their contribution to the study.

It was quite reassuring actually to know that somebody out there, you know, you're not doing this in vain that people, I know that you're doing it because you want to do research and stuff but I suppose with the email diary I know it's going somewhere but it's nice to know who it's gone to… Human touch. (T5)

A minority of women taking part in the CUTI trial were telephoned on day 3 of the study if their diary was incomplete, to check that they were not experiencing technical difficulties (see section 3.3.12). Women generally considered that such a telephone call would be acceptable to them, and not an invasion of privacy.

5.4.4. Theme 4 – Reflections on the CUTI trial and shaping future research

Both recruiters and trial participants reflected positively on their experience of the CUTI trial. They felt that the trial represented valuable research and had potential to influence future clinical practice. They liked most aspects of the trial design, and did not find the trial procedures burdensome.

It was all very straight forward. I don't think there was anything really. I'm not, I didn't think, 'Oh, that's a bit silly or, you know, what do they want to know that for?' I didn't feel there was anything on that in that study that made me sort of go, 'Oh I didn't like that, no.' I think it was very good, very good. (T4)

I did really enjoy doing the study. It was straight forward. It's interesting… (R5 - nurse recruiter)

The majority of UTI patients and recruiters stated that they would be happy to take part in, or recruit to, a similar trial in future.

It was a very, from a professional point of view, a very satisfying trial to take part in and I'm looking forward to it being rolled out and getting going again really…(R6 - nurse recruiter)

UTI patients often reflected that the trial and interview process had made them consider a different approach to future UTI management; this was also the case for women who were assigned within the trial to receive immediate antibiotics alone.

It certainly made me think differently that's for sure and I think, you know, in the, in the future…if I get another infection I will do that one [take cranberry]… I wouldn't go to the doctor in the first instance like I have done. I would do that first…(T13)

Recruiting to the trial was also a potential learning opportunity for recruiters. One recruiter described "unexpected learning" about the way that urinary symptoms were managed at the recruiter's General Practice.

What this study has highlighted to us as a surgery is we actually have a lot of patients who completely try and bypass our triage system and they just bring in a urine sample…and might provide a form with some very basic information and then lots of that doesn't actually get sent through to the GPs so these patients don't get recorded if the urine dip is negative and they maybe have one mild symptom, actually we're not, we're not seeing or discussing these patients and maybe we should be. (R7 – GP recruiter)

Most recruiters and UTI patients had few suggestions for ways to improve the trial, or their trial experience. One recruiter mentioned that it would have been helpful for recruiters to have seen the electronic diary that participants received, so that they could better explain what it entailed to participants. Another recruiter suggested that a welcome change would be to allow CRN nurses to directly approach potential participants, rather than potential participants first needing to be approached by a member of the General Practice team (creating extra workload for practice staff). Yet another recruiter spoke of the "hidden" costs associated with recruiting to trials, and the importance of ensuring that participating General Practices are adequately reimbursed.

As outlined in chapter 4 (see section 4.4.3.2), some women felt that shortening the antibiotic delay in group 3 would make the trial more appealing. The need to keep trial procedures simple, to consider offering participants a choice of diary format (e.g. paper or electronic), and to show gratitude to participants, were also raised. Generally speaking, women were pleased to receive a voucher for participating in the CUTI study and/or interview study, but they tended not to suggest payment as a way of encouraging women to take part in research.

One woman felt that transparency around the role of commercial bodies/study funding was important to foster trust between participants and researchers.

I discussed the idea of incorporating placebo into a future trial with UTI patients. The prospect of being randomly assigned to receive immediate placebo with delayed antibiotics did not sit comfortably with a number of patients (see section 4.4.3.2). For some, it signalled a trivialisation of their illness.

That's a mental thing that you're thinking, they don't care…at least with the cranberry you think, 'Well it might work, you know, it might be okay.'…you got this urinary tract infection and they're just giving me a sugar pill…I want something that's going to make me feel really better.' …with sugar pills…it's a no-no for me (T4)

I described a second placebo trial design that would allow women to choose whether they received immediate or delayed antibiotics, as illustrated in Figure 5. 1.

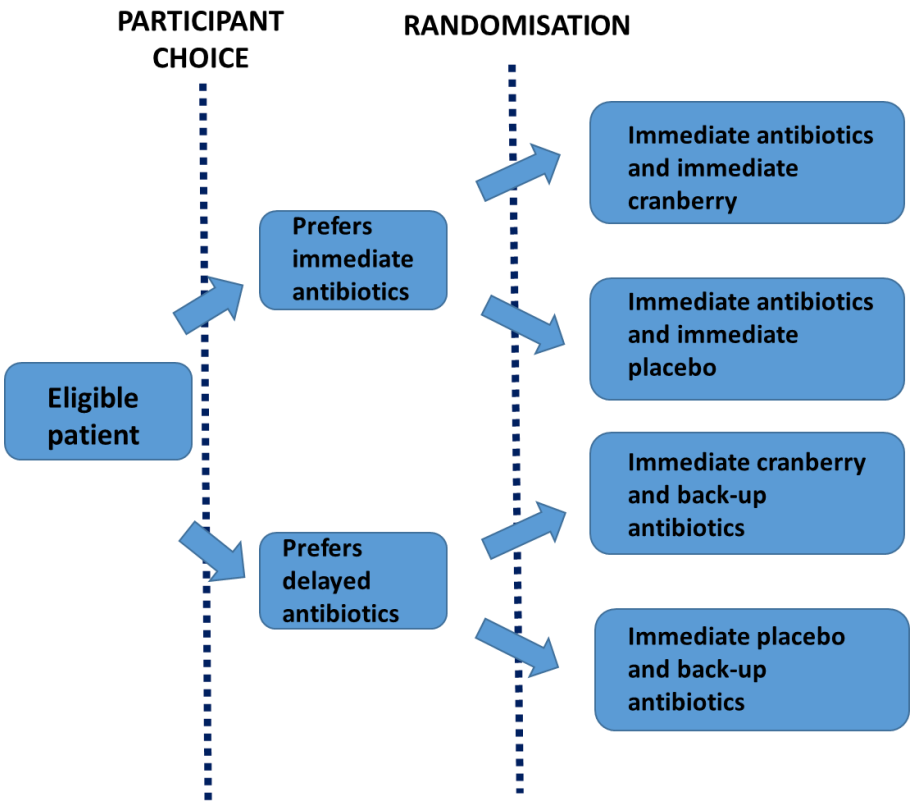


Figure 5. 1 Design of placebo controlled trial with incorporation of some participant preference

In this design, women preferring to receive immediate antibiotics would be randomly assigned to receive either immediate antibiotics with immediate cranberry or immediate antibiotics with immediate placebo. Those women preferring to delay antibiotics would be randomly assigned to either immediate cranberry with back-up antibiotics or immediate placebo with back-up antibiotics. Most women found this placebo controlled design that incorporated a degree of choice about group allocation more appealing than a placebo design without choice incorporated. The addition of choice made them feel more in control of the management of their UTI.

If you can choose that you have immediate antibiotics at least then you know that you're being treated and if you want to delay the antibiotics it's only for a couple of days… (T14)

However, some women called into question the use of immediate placebo as the only treatment in the context of managing an infection, as compared with a non-infective pain syndrome. Whilst they were aware of the placebo effect on pain symptoms, they perceived that it would not be possible for a placebo to treat a genuine infection.

If you've got an infection and you think you're getting something to make it better, I can't see how that will make it better… I really don't believe that mind of matter could clear up an infection…(T6)

Whilst incorporating choice into the placebo design (see Figure 5. 1) was generally perceived to be a more acceptable approach, the scientific implications were queried on occasion, including the risk of imbalance between the immediate and delayed antibiotic groups.

What happen if everyone want to try non-antibiotics at the beginning…all the people in one group and the other group will be empty so maybe to give the opportunity to choose is maybe not the best thing to do if you want to have a balanced groups. (NT9)

Furthermore, the possibility that women opting for delayed antibiotics might take antibiotics sooner than in an open trial design, to avoid the 50% chance of receiving no initial treatment, was raised.

For the vast majority of women, their least favourite group was immediate placebo with back-up antibiotics. Of note, this group was the expressed preference for one woman who was particularly keen to avoid taking medications/antibiotics for her UTIs; she perceived placebo as the most 'natural' intervention.

I don't like to take any medications, so if I can be in this group [immediate placebo]…if I feel at the end of the day I feel better just with sugar pill, with the placebo, will very successful. So yeah, yeah for me it will be perfect. (NT9)

Recruiters generally perceived that a placebo controlled trial would be logistically more complicated than an open design, but they understood the rationale and felt that it was a good idea. Some recruiters were unsure how a trial with an immediate placebo arm would be received by participants. Ensuring that women were given a clear explanation for incorporating placebo, as well as ensuring that women assigned to immediate placebo additionally received a back-up prescription for antibiotics, were deemed important.

I think some people might worry that they're not getting something…But on the other hand I think if they've got standby script, I think that would reassure a lot of people… probably it would put some people off I would have thought.(R4 - nurse recruiter)

Key learning points from the four interview themes, pertinent to opportunistic recruitment and acute UTI trials in primary care, are summarised below in Table 5. 1.

Table 5. 1 Key learning points for opportunistic recruitment and acute UTI trials in primary care

Theme	Learning points	Supporting quotes
Theme 1	• Recruiters are more likely to take part if they feel the research answers an important question and is achievable • Ensure that all relevant information about the trial and trial processes is given at the SIV • The SIV should take place as close as possible to site opening	*I remember thinking at that point that this was going to be a really useful study to do and it, and it seemed that it would be quite an easy one to implement.* (R6) *Fundamentally the question that's being asked is a sensible question. It's a very simple study design and simple to fulfil if you like, you know, patient comes in, gets assessed, gets a product, not too many visits, not too onerous on our staff, not too onerous on the patient and potential for great impact.* (R7) *Oh, it was, it was brilliant [the SIV]…very informative. It gave us the information we want.* (R4) *Site initiation visits; they should always be as close to the starting date as possible…. Because what happens, what often happens then is people forget about the study when it goes into the long grass for a while and then people then need a refresh and so it almost wastes time by going through the refresh period again.* (R8)
Theme 2	• Real-time communication/messages targeted at clinicians working in the clinics in which patients with incident conditions usually present (e.g. minor illness clinics) are likely to facilitate the flow of patients from their usual clinical pathway through to research clinics. • Generic prompts (such as EMIS pop-ups and desk prompts) may be less effective. If desk prompts are used, they should be large and eye-catching. • The use of a script to explain trial groups that may be considered less desirable (e.g. delayed antibiotics) can aid recruiters' interaction with potential participants, and hence also recruitment	*When I came in to do research on X's day when she's in minor illness, I'd look through her list and I'd be able to spot the urine infections because they're identified on the, the patient on the patient appointment system online…I would Sophos her, message her instantly and say, "There's a number of UTIs so I'll, I can take them. (R2)* *Some of them [EMIS prompts] are not always appropriate for the moment and so sometimes they get, they can cause a wee bit of irritation and amongst all our colleagues…* (R6) *They [desk prompts] were a bit small and blended into the background a bit I think a bit too much. So, they my colleagues accepted them but I don't know that anyone actually recruited or that it made a significant difference to our recruitment to be honest.* (R7) *Yeah, no I did use it [the script] and it is nicer and easier to because you can get a little bit tongue tied sometimes when you're explaining something, when you've just got that, you know, with very, with clarity as to, to what is being said and so yeah so that was useful, yeah.* (R4)
Theme 3	• Ensuring that trial procedures are quick and straight-forward is likely to help opportunistic recruitment, potentially enabling recruiters to recruit patients in their routine clinical slots. • Recruiters value regular communications from the central trial team.	*Well probably longer [time taken to recruit a participant] on the first couple but after that not, not really very long, fifteen minutes, twenty minutes.* (R3) *I've only got ten minutes appointments and I was managing to do it [recruit participants] in that…* (R6) *I thought, you know, we had con-, you know, constant email contact which was really good, so I don't feel at any point if we'd been struggling or anything it will, we wouldn't have been able to get hold of you, so that was really good.* (R2)

	• Participant completed symptom diaries should be intuitive, user-friendly, and daily entries should not take long to complete (ideally no more than five minutes). • If women are required to provide daily symptom ratings, it is useful for them to see their ratings on previous days. • Daily reminders to complete the diary are helpful; women do not find them intrusive. • When designing symptom diaries for studies, consider the age group of the study participants. If the participants are exclusively younger women (aged under 50 years), a mobile phone application may be the most appropriate format. If the study will include older women or women of all ages, then an electronic diary may be more appropriate. • Many older women are happy to use an electronic diary and prefer this to using a paper diary.	*Being quite time poor, it's [completing the diary], it's a little, you know, bit of something to do…I could do that for two weeks. I mean it wouldn't it would just be a few minutes a day, right so.* (NT12) *I think the fact that it's [diary completion] only five minutes, it's not really, you know, it's not, it's not going to take a long time or be a major inconvenience for people…I think that's quite acceptable.* (NT13) *I think one of the best things about it [electronic diary] is the fact that it tells, it gives you the information from before… that's what you need, to do it properly, you need to see that you put twenty or you put thirty or you put ten because then you can sit and decide exactly where from there you're going to go…It would have been very difficult I think without that. (T2)* *That [email reminder] was quite useful because if I was really busy to have the reminder, it sort of prompted me, 'Oh, yeah, I've got to do that this evening.'* (T10) *It was in my inbox, I had to do it really, so it was easy…The jog was perfect for me.*(T9) *I'm generally on my computer any given point during the day or on my tablet or something like that, it was just easy because I just would just flick into it [electronic diary] and flick out. Whereas, this [paper diary] would perhaps be a bit more of a conscious must remember to pen and paper, you know what I mean ….* (T13 – 68 years) *If you wanted my thoughts on how to improve it [the diary], you could have an App…an App would be nice and easy* (T12 – 32 years)
	• Women may find it easier to use scales that are smaller than 0-50.	*I mean it might be almost too fine a scale [scale of 0-50] maybe with, you know, ten points for every category… (NT12)* *I mean I, I'm thinking, 'Fifty, gosh that's big; that's huge, you know, am I at death's door at that point?'* (NT4) *It would have been easier to have filled in [scale of 0-6] because you didn't have to think about it quite so much.* (T14) *I think it [scale of 0-6] would be yes, better and more clear, yeah, clearer, yeah definitely.* (NT9)
	• Women are happy to receive a follow-up phone call so long as there is flexibility with respect to the time of the call. Many women look favourably upon the follow-up call and see it as a personal touch.	*Yeah, no, it [follow-up call] was fine…I felt like it was, it was fair. It didn't take up too much of my time (T1)* *As long as if it's [follow-up call], you know, calling at an inconvenient time that they're happy to call back or…* (NT12)

	• Follow-up calls should be kept as short as possible.	*I think it's just if you sit on the phone too long with anyone, they lose concentration… I think maybe just making it twenty minutes tops, if that even, I would say, ten minutes probably.* (NT5) *It was quite reassuring actually to know that somebody out there, you know, you're not doing this in vain that people, I know that you're doing it because you want to do research and stuff but I suppose with the email diary I know it's going somewhere but it's nice to know who it's gone to… Human touch. (T5)*
Theme 4	• The use of an immediate placebo arm in a UTI study is likely to dissuade some women from taking part. If used, the reason for including placebo should be carefully explained. • The provision of back-up antibiotics in an immediate placebo arm is a deal-breaker for many women. • The incorporation of some participant choice into placebo study design may also encourage participation (e.g. ability to choose immediate versus delayed antibiotics).	*I would have been angry, I think… Because it [UTI] is so painful… I think if you were in your own home that might have worked but I wouldn't have wanted it this time… I would have said no, definitely no.* (T4) *I'm not sure I'd have been as happy because the whole point of going to the doctor was that you want it to get better and if you theoretically aren't getting any treatment…theoretically you might not be getting better… I think I would have thought twice about it.* (T14) *It [placebo] would annoy me because I'd just put off the inevitable for nothing for sugar pills…Absolutely not interested.* (T9) *I really don't believe that mind of matter could clear up an infection…but I wouldn't be too worried if there were antibiotics to follow…*(T6) *That probably works [ability to choose between immediate and delayed antibiotic groups in the placebo design] better because if for whatever reason you can't get an appointment and you, you feel that you have to go into this group [immediate antibiotics] but, you know, if it's early enough and you get to the doctor early enough then I'd be happy to go into this group and just get a kind of backup antibiotic prescription…so that would give more flexibility….* (NT12)

5.5. Discussion

Recruiters described initial 'buy-in' to the trial question; they felt that it represented useful research that had potential to influence future clinical care. Both recruiters and UTI patients generally found the trial procedures and technology straight-forward. The user-friendly trial procedures facilitated opportunistic recruitment, allowing recruiters to fit research processes more easily in amongst their other (research and clinical) duties. Using an electronic symptom diary was generally acceptable to UTI patients. Some UTI patients, typically younger women, expressed a preference for a mobile phone application, which they perceived would be more convenient.

For recruiters, the main barrier to recruitment was establishing effective ways to filter UTI patients from their usual clinical pathway through to the researchers. Targeted, real-time reminders to key 'gate-keepers' in the patient pathway were reported as the most effective way to encourage opportunistic recruitment. To this end, manually typing prompts above patient lists where eligible patients were likely to present (namely, minor illness clinic and duty doctor lists); sending messages real-time to clinical colleagues; and, close communication with reception staff, all helped to direct potential patients to the research team. Less focused prompts, such as desk prompts and on-screen pop-up alerts, received a more mixed reception. Once women had been filtered through to the recruiters, they found the use of a script to explain the delayed antibiotic group facilitated recruitment of eligible women who may otherwise have declined to take part.

Recruiters and UTI patients reflected favourably upon taking part in the CUTI trial, and often stated that they would be keen to take part in, or recruit to, a future, similar trial. However,

the addition of placebo to a future trial was less favourably received by UTI patients, and indeed the premise of using immediate placebo in the context of an infection was questioned by some women. The incorporation of a degree of patient choice into the placebo trial design was welcomed by most women, allowing them to decide whether they were randomly assigned to immediate or delayed antibiotic groups (see Figure 5. 1).

5.5.1. Strengths and Limitations

One strength of the recruiter interview study is that it captures the views of seldom heard voices. Whilst incorporating qualitative elements into trials is increasingly recognised as important, the views sought are usually of patients rather than recruiters. In addition, I was able to interview recruiters from each of the sites, including a mixture of practice nurse, GP and CRN nurse recruiters. The findings are therefore likely to be representative of the experiences of recruiters to the CUTI trial. However, only eight recruiter interviews were conducted, and all were with recruiters working in Oxfordshire. This may limit the generalisability of the insights gained to primary care trial recruiters based in other geographical regions.

I was able to triangulate insights from recruiters, UTI patients and quantitative data from the feasibility trial, allowing me to capture multiple perspectives on phenomena. For example, UTI patients suggested that the electronic diary was straight-forward to complete, and represented something of a happy medium between a mobile phone application and a paper diary. This is in keeping with the largely positive way that women rated their experience of using the electronic diary through questionnaire responses (see Table 3. 3).

Triangulation of insights also shed light on divergent findings. In the CUTI feasibility trial electronic questionnaires, most women stated that they had no problems using the scale of 0-50 (see Table 3. 3), and only two women commented in free-text responses that they felt the scale was too wide (see section 3.4.5). However, insights captured through interviews suggest that women would generally find a smaller scale more user-friendly. Questionnaire data can be very useful; questionnaires are typically faster to complete, and I was able to capture questionnaire data from more women than I was able to interview. However, interviews, by their nature, allow deeper insights to be afforded. This does not mean that one insight is 'right' and another is 'wrong,' but merely that they are shedding light on different aspects of using the 0-50 scale. Taking all of the insights from women into account, it would seem that whilst women were able to use the 0-50 scale, and it did not necessarily materially compromise their trial experience or ability to rate their symptoms, a scale with fewer points may well have been easier for them to navigate. Thus, in future I would employ a smaller scale for women to rate their symptoms. This highlights the usefulness of triangulation - improving the depth of insight into a phenomenon and reducing the chance of reaching conclusions that may be further from the truth, compared with using a single data source (191).

I conducted all of the interviews, and was additionally the Chief Investigator of the trial. This may have positively biased the responses of recruiters, who may consequently have wished to present a more positive experience of being part of the trial. I tried to negate any such potential effect of me as the researcher on the recruiters by including several prompt questions within the topic guide about things that did not go well, or could have been done better. Finally, the interviews took place a long time after the initial SIV, which meant that some recruiters could not recall clearly all that had taken place.

5.5.2. Comparison with existing literature

A lack of equipoise has been highlighted as a reason for poor recruitment to trials in primary care (223, 224). If recruiters feel that a particular trial group may offer patients sub-optimal treatment, they may not be happy to recruit patients. In the present interview study, none of the recruiters expressed concern about participants being randomly assigned to receive delayed antibiotics, despite this group being the furthest deviation from usual clinical practice. It is likely that clinical equipoise of the recruiters enhanced recruitment to the CUTI trial.

Research suggests that high practice workload combined with lack of time are additional reasons that primary care recruiters may struggle to recruit to trials of incident conditions (219, 225). The importance of keeping trial procedures simple and fast, ensuring that the research topic is relevant to recruiters, and of ensuring adequate reimbursement, is in keeping with the findings of existing studies (220, 221). Generic prompts, such as ‘pop-ups’ have the potential to overwhelm clinical colleagues and can cause ‘pop-up fatigue’ (226), especially when one considers that primary care clinicians may spend around 50 minutes each day processing such alerts (227). The present recruiter interviews provide additional useful insights regarding practical ways to facilitate opportunistic recruitment through the use of a script to explain trial group that may be contrary to the expectations of patients who have contacted General Practice (i.e. delayed antibiotics), and the importance of purposefully directing reminders at the clinics in which patients with incident conditions are found (e.g. minor illness clinics).

The feasibility of using a mobile phone application to capture UTI patient treatment and symptom severity data has previously been explored (228). In a study evaluating data collection using a mobile phone application, acute UTI patients were invited by text message to download a mobile phone application, and to use the application to record their symptom data daily for seven days (228). Of the 203 women downloading the mobile phone application, 71 women (35%) completed the first day of the diary, and 31 women (15%) completed the entire diary. Furthermore whereas 52% of women responding favourably to the initial text message invitation were aged 45 years and above, only 14% of women completing at least one day of the mobile phone application diary were in this same age bracket. Whilst mobile phone applications confer certain advantages such as potential for real-time data capture (228, 229), they are less likely to be used by older women, and the ability to achieve levels of UTI diary data completion that are comparable with those attained through traditional methods is uncertain.

Placebo-controlled trials have historically been perceived as the 'gold standard' in clinical trial design, but are not without problems (230). Patient reservations about taking placebos can lead to reduced recruitment and retention of participants to clinical trials (230). In the present interview study, the possibility of being randomly assigned to receive immediate placebo with back-up antibiotics was off-putting to many women. Incorporating of a degree of choice (between immediate or delayed antibiotic groups) made the idea of a placebo trial more acceptable to women; allowing them to opt out of the delayed antibiotic group in which they had a 50% chance of receiving immediate placebo with back-up antibiotics (see Figure 5. 1). The notion of incorporating patient preference into trials is not new, and has been suggested as part of patient preference trials (231). In such trials, patients expressing a clear preference are non-randomly assigned to their preferred group, whilst those in equipoise are

randomly assigned to a group. Perceived advantages of this approach include better recruitment and the ability to overcome 'resentful demoralization'(232); people assigned to a group that they consider less desirable may engage less well with the intervention, and therefore the trial results may not be a true representation of the intervention in question when widely applied in routine practice (232). However, one must be cautious about interpreting the results of such trials, as comparisons using results from non-randomised individuals are liable to bias from measured and unmeasured confounding (233).

5.5.3. Implications for research

The main 'bottleneck' to opportunistic recruitment encountered by recruiters was the effective filtering of patients from the usual clinical pathway through to the research clinics. The findings of this interview study suggest that sending targeted prompts to clinicians based in the clinics to which the incident condition typically presents (e.g. minor illness clinic and duty doctor) may be more effective than generic prompts (e.g. desk prompts and electronic pop-ups). SIVs can be used as an opportunity to tailor the approach to the recruiting site in question, according to their existing clinic structures, optimising recruitment processes. Manually typing reminders at the top of electronic lists may be considered labour intensive; ways to automate this process should be explored in future trials. It may also be helpful for the researcher to brief the General Practice reception team about the trial, to increase their awareness and potentially improve effective triage of patients through to research clinics. The time-frame between the SIV and General Practices opening to recruitment should be kept as short as possible. These findings are applicable to trials of incident conditions in primary care, not just acute UTI trials.

The second stumbling block encountered by recruiters was overcoming some women's expectation of receiving immediate antibiotics. Incorporating a script to help explain groups that deviate furthest from usual practice, or that participants may perceive as less desirable, may facilitate patient participation.

The use of electronic systems, both for recruiters and trial participants of all ages, is considered acceptable, and often preferable to paper-based systems. Future researchers asking women to rate symptoms should be mindful that smaller scales are generally easier to use than wider scales, such as the scale of 0-50 used in the CUTI feasibility trial. Giving the option of an email and/or text message prompt to patients to complete a diary are likely to serve as acceptable and effective prompts.

The incorporation of placebo into trials of acute UTI should be done sensitively, with careful explanation of the rationale for incorporating placebo. If women are assigned to receive immediate placebo, they should additionally receive a back-up antibiotic. Despite this, women may find an immediate placebo group off-putting, and this is likely to adversely impact on recruitment. The incorporation of a degree of choice into placebo trial design may encourage recruitment; for example, allowing women to choose between immediate or delayed antibiotic groups. However, it is important to bear in mind that there will be differences, both measurable and unmeasurable, between women choosing to be in an immediate antibiotic group, and women choosing to be in a delayed antibiotic group. Thus, no direct comparisons between the immediate and delayed antibiotic groups can be made.

5.5.4. Implications for clinical practice

The learning from recruiters to the trial and UTI patients in this chapter provide critical insights that will help to shape trial procedures used in an adequately powered trial of cranberry, thereby increasing the chance that such a trial will recruit to target and retain participants. This will, in turn, increase the chance of an adequately powered trial providing definitive answers to patients and clinicians alike about the safety and effectiveness of cranberry extract in the context of an acute UTI.

Interviews with recruiters suggest that recruiting to a trial can additionally result in unanticipated learning opportunities; both a better understanding of patient pathways within the General Practice, and time to reflect upon clinical practice and patient outcomes.

5.6. Conclusions

Whilst most CUTI trial procedures were considered acceptable to both recruiters and CUTI trial participants, these interviews have provided useful insights into the areas where there is scope for improvement in future trial design and trial processes. Ensuring that the trial topic was relevant and that trial procedures were straightforward encouraged UTI patients and recruiters alike to engage with the trial. The use of targeted prompts directed at clinicians working in minor illness clinics and duty doctor clinics were generally perceived to be more useful than generic reminders such as desk prompts. The use of a script to help explain the delayed antibiotics group, perceived by some patients as less desirable, was also perceived to be a helpful recruitment aide. The incorporation of placebo into a trial of cranberry extract for acute UTI may dissuade some women from participating.

In chapter 6, I draw together the learning from this chapter, along with the results from preceding chapters. I explain how my findings inform the design of an adequately powered trial of cranberry extract for acute UTI, incorporating placebo, which I plan to conduct at a post-doctoral level.

6. Chapter 6 – Discussion

6.1. Summary

In chapter 1, I explained that the rise of antibiotic resistance has spurred efforts to discover non-antibiotic treatments for common bacterial infections, with one option being the use of cranberry extract for acute UTIs. In chapters 2 to 5, through varied methodologies, I sought to address this by establishing the existing evidence base for, and the feasibility and acceptability of testing, cranberry extract as a non-antibiotic treatment for acute, uncomplicated UTIs in primary care. In this chapter, I summarise my findings, reflect on the strengths and weaknesses of this research programme, and discuss the implications of the findings for clinical practice and research. This chapter culminates with a discussion of how this thesis supports the need for, and has shaped the design of, an adequately powered efficacy trial of cranberry extract for acute UTI that I plan to conduct at a post-doctoral level.

6.2. Principal Findings

In chapter 2, I synthesised the available evidence for using cranberry extract as an acute UTI treatment, and identified three studies suitable for inclusion (143-145) (see Table 2. 1). Whilst each study provided some information that was pertinent to the review question, none of the studies was primarily focused on the use of cranberry extract as a way of managing acute UTIs. The systematic review revealed that there is insufficient evidence for or against the use of cranberry extract as a way of managing acute UTIs. Despite this, women commonly report using cranberry extract in this way (64), and *ex vivo* research suggests that cranberry extract has anti-adhesion activity against *E.coli* (89). Taken together, this suggested that further research in this area would be addressing a crucial evidence gap.

I designed, set up and ran a feasibility, randomised trial of the use of cranberry extract in managing symptoms of acute, uncomplicated UTI in primary care, as outlined in chapter 3. The purpose of the trial was to determine feasibility outcomes, such as the ability to recruit participants, as well as the acceptability of the study product and trial procedures. The trial recruited to target, at a faster rate than anticipated (see Figure 3. 3), and with loss to follow-up comparable to analogous trials. 70% of diaries were fully completed, and 89% were partially completed (see Table 3. 3). Through questionnaire responses in electronic symptom diaries, women reported good acceptability of the study product and trial processes (such as using the electronic diary). Exploratory, under-powered secondary analyses were conducted (see Table 3. 5). These analyses provided a preliminary suggestion that women in the two cranberry groups (group 2 – immediate antibiotics and immediate cranberry, and group 3 – immediate cranberry and delayed antibiotics) consumed fewer antibiotics than controls (group 1 – immediate antibiotics alone). The preliminary analyses also suggested that women in group 2 had better symptom outcomes than controls. The feasibility trial findings indicated that conducting an adequately powered trial of cranberry extract for acute UTI in primary care is feasible, and has merit.

Interviews with UTI patients within and outwith the trial afforded deeper insights into their thoughts on and experiences of trial procedures, as well as an understanding of the situations in which they might consider using a non-antibiotic treatment - like cranberry extract (see chapters 4 and 5). Women generally found the trial procedures acceptable. Compared with using a mobile phone application or a paper diary, most women perceived the electronic symptom diary to be a happy medium. Whilst the *quantitative* feedback on the scale of 0-50 was positive (see Table 3. 3), *qualitative* insights suggested that a smaller scale would be easier to use (see section 5.4.3.2). Most women suggested that, in certain circumstances, they

would find it acceptable to delay antibiotic treatment for an acute UTI. This was dependent on factors such as the stage or their UTI (early or late presentation), the perceived severity of their symptoms, and their prevailing circumstances (e.g. having a significant upcoming engagement). However, not all antibiotic delays were considered equal; having contacted a healthcare practitioner with symptoms, it was important to women to receive *something* in the interim with perceived therapeutic potential when taking the delayed antibiotic approach. For this reason, the idea of receiving immediate placebo in a trial (with back-up antibiotics) was often off-putting.

Recruiter interviews provided valuable insights into ways to optimise opportunistic recruitment to a future trial of cranberry extract for acute UTI in primary care (see chapter 5). One of the main challenges encountered was channelling patients from their normal clinical pathway through to the research team. Targeted prompts directed at the clinics in which acute UTI patients presented (e.g. minor illness clinics and duty doctor lists) appeared to be more successful than generic prompts (e.g. desk prompts). Another challenge encountered was overcoming UTI patients' expectation of receiving a prescription for immediate antibiotics. To this end, most recruiters found it beneficial to use a script that I created to help explain and positively frame the delayed antibiotics group. Overall, recruiters and participants described a positive experience of being a part of the CUTI feasibility trial, and a willingness to contribute to similar research in future.

Table 6. 1 summarises the key learning points from the results chapters (2 to 5) of this thesis.

Table 6. 1 Summary of key findings from thesis results chapters

Research Question	Thesis Chapter	Thesis Method	Key Findings
What is the existing evidence for using cranberry extract as a treatment for acute, uncomplicated UTI?	2	Systematic Review	• Three studies met the eligibility criteria and were judged at moderate risk of bias for the outcomes of interest in the systematic review • The objective of the systematic review was not the primary focus of any of the included studies in the systematic review • Two studies were under-powered to determine the effects of cranberry on outcomes, and the third study had high attrition of 26% • The cranberry extract used in the included studies varied in formulation (juice versus capsules) and in the amount of PAC (believed to be the active ingredient) • There is insufficient evidence for or against the use of cranberry extract as a means of treating acute UTIs
Is it feasible to conduct a trial of cranberry extract for symptoms of acute, uncomplicated UTI in primary care?	3	Feasibility trial	• Four General Practices (100% of target) recruited to the feasibility trial between 1st July and 2nd December 2019 • Forty-six participants were recruited (target of 45 recruits) • Nine participants were recruited per month on average • The mean age of participants was 48.4 years (SD 19.9, range 18-81) • 89.1% (41/46) of diaries contained some participant entered data, and 69.6% (32/46) were fully completed • Three participants (6.5%) were lost to follow-up and two participants (4.4%) withdrew. • There were no serious adverse events or episodes of pyelonephritis • Exploratory, under-powered effectiveness analyses suggest that patients in the two cranberry groups consumed fewer antibiotics than controls • The preliminary effectiveness analyses also suggest that patients receiving immediate cranberry had worse symptoms compared with controls, whilst patients receiving immediate antibiotics and immediate cranberry had better symptom outcomes compared with controls • It is feasible to conduct a randomised clinical trial of cranberry extract for treating symptoms of acute uncomplicated UTIs in primary care
What are women's perceptions and experiences of using cranberry extract and of taking part in the CUTI trial?	4	Qualitative study	• UTI patients suggested that they find antibiotics reliably effective, but were also aware of potential associated harms such as antibiotic resistance. • Many women would be amenable to delaying antibiotic treatment and trying an initial symptomatic treatment (for example, with cranberry extract) for acute UTI symptoms in certain circumstances, namely, with earlier and milder symptoms and with no important upcoming engagements. • It is acceptable to UTI patients to conduct a randomised clinical trial of cranberry extract for treating symptoms of acute uncomplicated UTIs in primary care

What are recruiters' and UTI patients' experiences of trial processes and of opportunistic recruitment?	5	Qualitative study	• UTI patients and recruiters generally felt that the feasibility trial addressed an important question, and as such were happy to contribute to the research • The incorporation of an immediate placebo group in a future trial is likely to be off-putting to some women • Most patients and recruiters found the recruitment process straightforward and acceptable • The principal barriers to opportunistic recruitment were channelling patients from their usual clinical pathway through to research clinics, and overcoming patient expectations to receive immediate antibiotics • The former barrier was helped by sending targeted prompts to healthcare practitioners in clinics in which acute UTI patients commonly presented (e.g. minor illness clinics), and the latter barrier was helped by using a script to positively frame the delayed antibiotics trial group

6.3. Contribution of thesis findings in relation to existing literature and guidelines

My systematic review highlights the lack of robust evidence for or against the use of cranberry extract for the treatment of an acute UTI (65). This is important, given that up to 27% of women report using cranberry for this indication (64). Interestingly, a Cochrane review of cranberry extract as an acute UTI treatment, with searches last updated in 2020, did not find any relevant studies (97). My systematic review therefore serves as a useful update.

The CUTI feasibility trial provides a further helpful addition to the literature. To my knowledge, it represents the first published data from an *in vivo* trial that is focused on the use of cranberry extract (alone and combined with antibiotics) as an acute UTI treatment. Whilst it does not provide evidence of the effectiveness of cranberry extract (effectiveness outcomes were exploratory and under-powered), it does provide good evidence that conducting an adequately powered trial of cranberry extract for acute UTI in primary care is

feasible. The current NICE guidance for the management of acute, uncomplicated UTIs currently states that "no evidence" was found for the use of cranberry products (156). However, an absence of evidence does not equate to an evidence of absence of effectiveness. Conducting an adequately powered trial of cranberry extract will provide a much needed addition to the limited existing evidence base. The CUTI feasibility trial, with embedded interview studies, provides a solid platform for such a trial to be conducted. Whether the result of a future, adequately powered trial is 'positive' or 'negative,' dissemination of the trial's findings will help to direct the management of acute, uncomplicated UTIs. The results of such a trial will provide healthcare practitioners with the required evidence to determine whether they should, or should not, advocate the use of cranberry extract to their patients with acute UTIs. NICE guidance should also be updated in line with the results of such a trial. The systematic review in chapter 2 identified a trial registration of an ongoing trial in Spain of cranberry extract versus fosfomycin for acute UTI treatment (140) (see section 2.5.1); the results should also provide a useful addition to the literature.

Existing qualitative research suggests that the delayed antibiotic approach can be tried for an acute UTI in certain situations, such as for women with earlier and milder symptoms, and for women who have not already tried self-care strategies (171, 172). The interviews that I conducted with UTI patients are in keeping with these studies. In addition, my interview findings suggest that delaying antibiotic treatment for an acute UTI may be better received by patients if they are offered an interim non-antibiotic measure with therapeutic potential (see chapter 4, section 4.4.3.2).

NICE guidance suggests that a delayed antibiotic strategy can be used, taking into account various factors, such as symptom severity, women's preferences, the risk of developing

complications and previous antibiotic use (156). The analyses of my interviews with UTI patients and trial recruiters, as well as existing research (171), suggest that the use of a delayed antibiotic strategy for acute UTI is uncommon in General Practice, and that there is scope for more discussions about delayed antibiotic prescribing with patients.

NICE advise encouraging fluid intake and "self-care" with analgesia/anti-inflammatory drugs (e.g. paracetamol or ibuprofen) (156). Clinical trials have shown that offering non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen) to women with an acute UTI can significantly reduce antibiotic consumption, albeit with higher symptom burden and more cases of pyelonephritis (35, 36). In a German trial of ibuprofen compared with fosfomycin for acute, uncomplicated UTI, the number of courses of antibiotics prescribed for any indication within 28 days was significantly lower in the ibuprofen group compared with the fosfomycin group [283 versus 94 antibiotic courses; incidence rate reduction of 66.5% (95% CI: 58.8% to 74.4%), $p<0.001$] (35). However, the interviews that I conducted with UTI patients suggest that they tend not to perceive ibuprofen/analgesia as UTI treatments, as they do not address the "root" of the problem and may not necessarily help with their primary symptoms, if pain is not predominant. If cranberry extract was found to be effective and safe in the context of an acute UTI, it would provide women with a welcome, evidence-based alternative to the current, limited non-antibiotic treatment options.

Recruiters to the CUTI feasibility trial appreciated the low burden and ease of trial procedures; this facilitated opportunistic recruitment. The recruiters felt that the trial represented relevant research, and did not consider that patients would be receiving sub-optimal care in any of the trial treatment arms. The importance of keeping recruitment procedures simple and straight-forward has been highlighted in existing research as a means

of facilitating opportunistic recruitment (220, 221), as well as the need for recruiter equipoise and 'buy-in' to the trial concept (223, 224). The recruiter interviews in this research programme additionally highlight the importance of establishing links to the clinics in which incident conditions present (e.g. minor illness clinics), to facilitate opportunistic recruitment. The use of a script to help explain trial groups that may be considered less desirable to some patients (e.g. delayed antibiotics for acute UTI patients) may also be an effective recruitment adjunct.

6.4. Strengths, Limitations and Personal Development

6.4.1. Strengths

A key strength of this programme of research is that it addresses both a novel and important question. Acute, uncomplicated UTIs account for up to 3% of General Practice consultations (11, 12), and are almost always managed with an immediate antibiotic prescription (15). As most acute UTIs have an uncomplicated course, there is scope to potentially avoid antibiotics. The systematic review (see chapter 2) confirms that this programme of research goes some way towards filling a critical evidence gap.

The mixed methods approach employed to addressing the research question is another strength of this research. The feasibility trial provided useful quantitative insights, such as recruitment rates and completeness of outcome data. The qualitative interviews provided additional insights into *how* and *why* different elements of the trial worked. Furthermore, the interviews provided a better understanding of how cranberry extract, if found to be effective, might be incorporated into clinical practice in a way that would be acceptable to women. I was able to use quantitative data and qualitative data from various stakeholders to triangulate

insights, providing a richer understanding of various phenomena (191) (see sections 4.3.12, 4.5.1 and 5.5.1).

Conducting an initial feasibility trial (rather than an adequately powered trial), with embedded qualitative studies, lays a solid foundation for conducting future research in this area (see section 6.6). Initial feasibility work helps to ensure that a future, adequately powered trial is both acceptable and achievable, increasing the chances of such a trial successfully recruiting to target and therefore providing meaningful evidence. Many trials do not recruit to target (215, 216), and opportunistic recruitment represents a particular challenge (220). Trials that do not recruit to target, or have inadequate participant retention due to poor acceptability of the intervention or trial procedures, can lead to wasted resources and less useful contributions to existing evidence.

Another strength is that PPI (Patient and Public Involvement) contributors have been involved throughout my research. PPI is defined as "an active partnership between patients, carers and members of the public with researchers that influences and shapes research." (234). A systematic review and meta-analysis found that the involvement of PPI, and particularly of contributors with lived experience of the condition being researched, improved participant recruitment to trials (235). PPI contributors have been meaningfully involved in my research from idea conception through to results dissemination; from sharing their own personal testimonies and UTI experiences, to looking over public-facing documents, to sitting on the Trial Steering Committee (TSC). They provided insights into how participants might perceive various study procedures and documents, and regularly made suggestions for improvements. For example, I sought a freelance animator to create a video explainer of the CUTI trial findings. PPI contributors looked over the script that I wrote for the video, and

suggested changes to ensure that the language was appropriate to a lay audience. They reviewed several iterations of the explainer video, providing further useful insights. For instance, they commented that there was limited body diversity in the characters in the video. I had not picked up on this, and subsequently requested changes to be made accordingly. Such changes can make a difference to the way that people perceive and engage with such videos. The lay explainer video can be accessed via the following link:
cuti — Nuffield Department of Primary Care Health Sciences, University of Oxford
I kept PPI contributors informed about the research and key developments throughout. Providing feedback to PPI contributors about the impact of their contribution to research is likely to improve their engagement with research (236).

The strengths of individual studies have been highlighted in each of the results chapters.

6.4.2. Limitations

All of my primary research was conducted with patients in Oxfordshire. Furthermore, despite my best efforts (see section 4.3.4.2), there was limited ethnic diversity in the sample of UTI patients that I interviewed. Whilst I did not capture ethnicity data for the feasibility trial participants, they were all recruited from General Practices in Oxfordshire with predominantly white practice populations. It is difficult to know whether the findings of my research are generalizable to people of other ethnicities, and indeed people in other parts of the country. Research suggests that the under-representation of ethnic minorities in research is not because they are unwilling to take part, but rather because access to health research is more difficult (237). This may be the case in Oxfordshire. Lots of research is conducted in Oxfordshire, however, due to the ethnic make-up of the local population, it may be harder to capture people from ethnic minority groups. To try to overcome this, in a future trial, I hope

to recruit participants from different regions of the country, including places with more ethnic diversity (see Appendix 6. 2 – recruitment and participant procedures).

I employed a pragmatic feasibility trial design (238). Pragmatic trials are typically less prescriptive than explanatory/efficacy trials, and more in keeping with real-world practice (238). The results of pragmatic trials are therefore likely to be more reflective of what would happen if an intervention was introduced into clinical practice (238). In line with pragmatic trial design, the CUTI feasibility trial was open-label, and I did not specify the antibiotic that the prescribing clinician should give to each participant. Whilst these were deliberate design decisions (see chapter 3, section 3.5.2), it does introduce certain biases. If participants believed that cranberry capsules might help their symptoms, this belief (independent of any true effect of cranberry extract) may have affected the observed outcomes, introducing performance bias (239). The ability of placebos to exert a significant effect on outcomes, such as pain, has been well documented in medical literature (240). In a single-blinded study, 56 medical students were told that they would receive either a stimulant or sedative drug, and were subsequently given either pink or blue placebo tablets. The pink tablets led to significantly more stimulant effects, whilst the blue tablets caused more sedative responses (241). These effects were significantly increased in those receiving two placebo tablets compared with those receiving one placebo tablet (241).

Thus, any possible observed benefit of cranberry extract in the CUTI feasibility trial, from under-powered analyses, may have been partially, or entirely, due to a placebo effect. This is particularly important to bear in mind, given that participants were reporting many subjective outcomes, such as symptom score ratings (239). This being said, the purpose of the CUTI feasibility trial was not to establish the effectiveness of cranberry extract in the context of an

acute UTI – these analyses were purely exploratory. The primary purpose of the feasibility trial was to determine the ability to recruit to, and the acceptability of, a trial of cranberry extract in the context of an acute UTI. Performance bias is therefore unlikely to have had an effect on the primary outcomes of the feasibility trial. However, in a future, adequately powered trial, it would be necessary to establish the efficacy of cranberry extract through a double-blinded trial (see section 6.6). Such a trial would provide evidence that any observed effects of cranberry are real, and not due to a placebo effect.

Performance bias can also relate to differences in the way that the participants are managed in a trial (239). As recruiters to the trial knew the participants' group assignment, this may have influenced their management of participants. For example, knowing that a participant was randomly assigned to the delayed antibiotics group could, in theory, have made the recruiter more likely to prescribe a higher potency antibiotic. However, this did not appear to take place in the CUTI feasibility trial, as most women received a 3-day course of Nitrofurantoin, in keeping with NICE guidance (156).

Being observed, through trial participation, can lead to participants behaving differently to normal, known as the Hawthorne effect (242). In some ways, employing a pragmatic trial design can help to minimise this, as pragmatic trials are more closely reflective of usual clinical practice than explanatory trials. Furthermore, interviewing UTI patients allowed me to conduct a more naturalistic inquiry into how UTI patients would, or would not, engage with cranberry extract, if found to be effective. Interestingly, a third of women assigned to receive immediate antibiotics alone reported taking cranberry extract, despite advice not to (see Table 3. 5). This may suggest that this bias did not influence all aspects of participants' behaviour.

Another potential bias of the feasibility trial is that there was cranberry industry involvement. Indena S.p.A (an Italian company) supplied the cranberry capsules to the trial for free. There have been concerns raised about the potential impact on research findings if there is pharmaceutical industry input into trial design, conduct of analyses and control over publication of findings (243). Other than supplying the study product, Indena S.p.A had no other involvement with the CUTI feasibility trial.

I conducted the feasibility trial and all of the interviews with UTI patients and trial recruiters. Whilst a strength of this approach was the ability for me to immerse myself in the data and triangulate insights on varied phenomena, this approach may also have biased participants towards giving favourable reports of their trial experiences. I tried to negate this by including several question prompts about things that participants perceived did not go went well, or could have been done better/differently. I also tried to highlight that a key purpose of the interviews was to help shape the design of a future trial (rather than to receive positive feedback). However, in a future trial that incorporates qualitative studies, it may be useful for a researcher who is further removed from the trial to conduct the interviews.

Women responding to the invitation to be interviewed may have been more likely to have stronger views on the subject (positive or negative), and therefore perhaps less representative of the views of the wider population. Furthermore, I was unable to interview trial decliners; this may mean that the views shared with me through interviews were more positively biased towards accepting an initial non-antibiotic approach to acute UTI management. This being said, I was able to gain some insight into the reasons for women declining to take part in the trial by reviewing screening and enrolment log data (see Table 3. 2) and also through

interviews with recruiters to the trial. In addition, I interviewed non-CUTI trial UTI patients, so that I could hear from people who may have been less amenable to non-antibiotic UTI treatments. If conducting a future trial with an embedded qualitative study, I would seek permission from ethics to obtain feedback from trial decliners (for example, through a questionnaire).

The limitations of individual studies have been discussed in detail in each of the results chapters, as well as my approach to reflexivity (see sections 4.3.10 and 5.3.8).

6.4.3. Personal Development

Before my DPhil, I had never run or been a part of qualitative research or a clinical trial. Through incorporating varied research methodologies into my work, I have developed many new skills - from applying for NHS ethics approval, to writing a feasibility trial protocol with embedded qualitative studies, to writing a statistical analysis plan. Having set up a trial management group and trial steering committee, I regularly led meetings throughout the trial, creating the agenda and data reports for committee members as needed, taking meeting minutes, and circulating the minutes to members. I collaborated with the local Clinical Research Network (CRN), and developed an understanding of how they help to support research, for example, by identifying research-active General Practices.

I learned how to work effectively with the General Practices recruiting to the trial. This involved clear and effective communication and instruction throughout. For example, I created a weekly newsletter to provide updates to the recruiting General Practices. I also made sure that I was available to respond efficiently to any queries from recruiters by email or telephone. When needed, I hand-delivered trial supplies to recruiting sites that were

running low. Sound organisational skills were required to ensure that all site files and the trial master file were kept up-to-date.

Prior to this programme of research, I had not conducted any primary data analyses. I now know how to export data from Research Electronic Data Capture (REDCap) into Excel, clean the data, format it appropriately for import into a statistical package (Stata), and run statistical analyses. Conducting qualitative studies was also new territory. In addition to learning how to interview participants (see reflexivity statements in sections 4.3.10 and 5.3.8), I gained an understanding of the processes required to safeguard data and ensure personal safety. Whilst systematic review work was familiar to me, the systematic review in the present research programme helped to hone my skills in critical appraisal of studies.

In March 2020, just over halfway through my DPhil, the COVID-19 pandemic threw the world a curveball. Completing my DPhil in the throes of a pandemic has been challenging. Access to printing facilities, to a quiet workspace, and to trial/interview study documents that were on-site at the NDPCHS for data security reasons, was hampered. Working from home also reduced my interactions with other academics. However, I have learnt the importance of taking regular breaks from work, and have improved my competence with using virtual meeting platforms (e.g. Microsoft Teams).

When the pandemic struck, I paused my DPhil activities and focused almost entirely on COVID-19 related projects for two months. During this time, I became a member of the Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE) trial management group. PRINCIPLE seeks treatments to reduce ill-health in patients in the community at higher risk of an adverse outcome. Through my

involvement with the PRINCIPLE trial, which continues to date, I have learned about the mechanics of setting up and running a national trial - in the midst of a pandemic. Furthermore, PRINCIPLE has provided in-pandemic results that have meaningfully impacted patient care (244-246).

During my DPhil, I have been lead author of ten peer-reviewed publications, and have co-authored six peer-reviewed publications (see Appendix 6. 1). At the outset of my research programme, I successfully led two grant bids to secure funding for the CUTI feasibility trial and interview studies (see Appendix 6. 1). Presenting my research internationally during my DPhil has helped me to develop my IT skills (using PowerPoint), to practice my presenting skills, and to gain confidence in fielding questions from experienced researchers (see Appendix 6. 1). Alongside supervision, attending training courses, such as week-long courses in 'Statistics for Clinical Trials' and 'Clinical Trial Management,' served to buttress my learning (see Appendix 6. 1). Developing these skills, which are critical to an ongoing career in academia, has stood me in good stead for conducting research at a post-doctoral level.

6.5. Implications for clinical practice and policy

If cranberry extract is found to be effective through future clinical trials, it could lead to a radical change in acute UTI management and clinical guidance. There is potential for cranberry extract to be used in two ways. First, it could be incorporated into a delayed antibiotic treatment strategy. Women have indicated that in certain situations, they would be happy to initially try a non-antibiotic treatment. At present, there are limited, evidence-based non-antibiotic treatments to use in this way. Clinical trials have established that NSAIDs, such as ibuprofen, reduce antibiotic consumption for acute UTIs (35-37). However, as

previously discussed, women may not necessarily consider NSAIDs/analgesia to be an adequate UTI treatment (see sections 4.4.2.2 and 4.5.2). If cranberry extract is found to be effective, it could be used as an initial treatment for women in some instances, potentially averting the need for them to take antibiotics. Cranberry extract could be made available on prescription in addition to being available to purchase over the counter. The latter option might facilitate easier and earlier access to cranberry extract, particularly out-of-hours, and could reduce General Practice consultations/contacts.

Secondly, if cranberry extract is found to provide an additive benefit to antibiotics, it could be used in combination with immediate antibiotic treatment. The exploratory, under-powered analyses of the CUTI feasibility trial suggest that this approach could improve some symptom measures and reduce antibiotic consumption at two weeks and four weeks, compared with immediate antibiotics alone (see Table 3. 4). If this is proven through an adequately powered trial, immediate antibiotic treatment with immediate cranberry capsules could become the routine, first-line treatment for managing acute UTIs. However, before considering any of these changes to current clinical practice, further, adequately powered clinical trials are required. To this end, below I describe the design of a trial that I hope to conduct at a post-doctoral level (see section 6.6).

The qualitative research studies suggest that there is latitude for broader discussions to take place in UTI patient consultations. Stott and Davis (247) discuss the ‘exceptional potential’ in each General Practice consultation, and the importance of not only managing presenting problems, but also modifying help-seeking behaviour. There is scope for more discussions between clinicians and UTI patients about considering a delayed antibiotic approach, with interim self-help strategies, which would be in keeping with NICE guidance (156). These

discussions may currently be hindered by a perception that women want immediate antibiotics, the limited existing evidence for non-antibiotic treatments, and the time pressures faced by General Practitioners (213). Improving the evidence base for non-antibiotic treatments, through further research on the use of cranberry extract for acute UTIs, may facilitate these discussions with UTI patients in primary care.

6.6. Implications for future research

6.6.1. An efficacy trial

The present programme of research suggests that not only is it feasible to conduct a trial of cranberry extract for managing symptoms of acute, uncomplicated UTI in primary care, but also that incorporating cranberry extract into acute UTI management would be acceptable to many women. The next step is therefore to determine the efficacy of cranberry extract in the context of an acute UTI. In so doing, any potential beneficial effect of cranberry extract established through a future effectiveness trial can be attributed to cranberry extract, rather than to a placebo effect.

6.6.1.1. Design considerations

The 'purest' way to test the efficacy of cranberry extract would be to randomly assign women with symptoms of an acute UTI to receive either immediate cranberry or immediate placebo, with no recourse to antibiotics, and to compare symptoms between women in the two groups (see Figure 6. 1). However, it would not be morally/ethically acceptable to deny women access to antibiotics; interviews that I have conducted with women also confirm this (see chapter 4, section 4.4.3.2). It would therefore be necessary to incorporate back-up antibiotics into such a trial design (see Figure 6. 2).

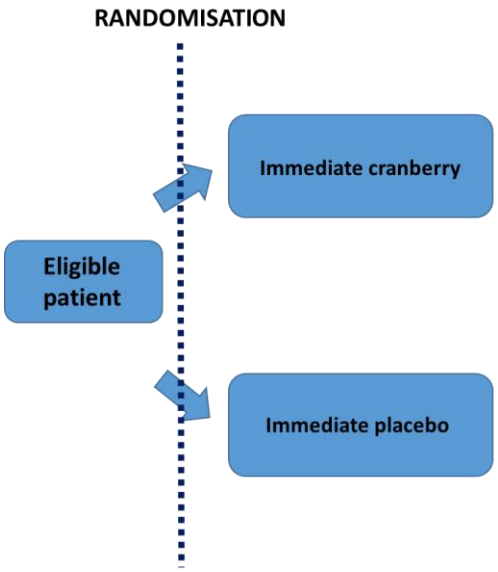


Figure 6. 1 Efficacy trial design 1 – head to head comparison of cranberry extract and placebo alone

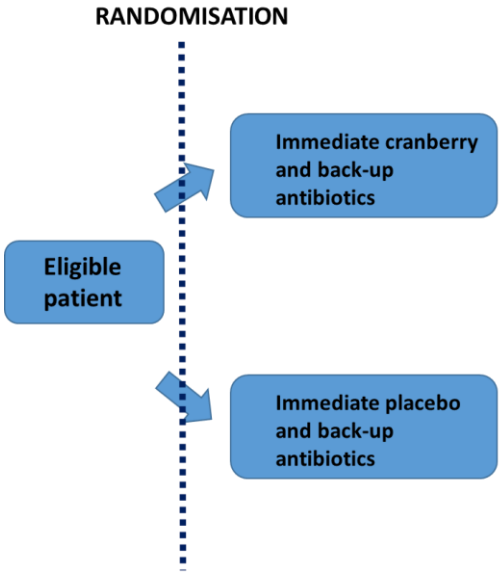


Figure 6. 2 Efficacy trial design 2 – incorporating back-up antibiotics

However, the introduction of back-up antibiotics to both groups would make analysis of the results problematic. Given that antibiotic use would vary between groups, and antibiotics have a significant impact on women's UTI symptoms, the primary outcome would need to take into account both antibiotic use and a measure of symptoms. This could be done through

either a composite or a co-primary outcome. Assuming that cranberry extract has more of an effect on women's symptoms compared with placebo, one might expect women in the cranberry group to consume fewer antibiotics. Conversely, one might expect women in the placebo group to consume more antibiotics. The results would therefore be difficult to interpret; the group with women that consume more antibiotics would be likely to have a lower symptom burden, and vice versa. This would not provide meaningful information about the potential efficacy of cranberry extract. Furthermore, UTI patients that I interviewed often found the idea of taking immediate placebo off-putting (see sections 4.4.3.2 and 5.4.4), thus, recruitment to a trial of this design may prove difficult.

I considered adding two further groups to the above trial design and adding an element of participant choice (see Figure 6. 3). As mentioned in section 5.4.4, women would be able to choose whether they would receive immediate or delayed antibiotics. Women generally found this design more acceptable, as they could avoid immediate placebo if they wished. However, this trial design is, again, not without problems. The element of choice means that there are likely to be systematic differences between the women entering the immediate antibiotic groups and the women entering the delayed antibiotic groups. It would not be a true factorial trial (248), as no comparisons could be made between women in the immediate antibiotic groups and the women in the delayed antibiotic groups. It would essentially entail running two separate trials in one, but with no efficiency savings. Furthermore, there would still be the added difficulty of over-coming women's aversion to being assigned to the immediate placebo group.

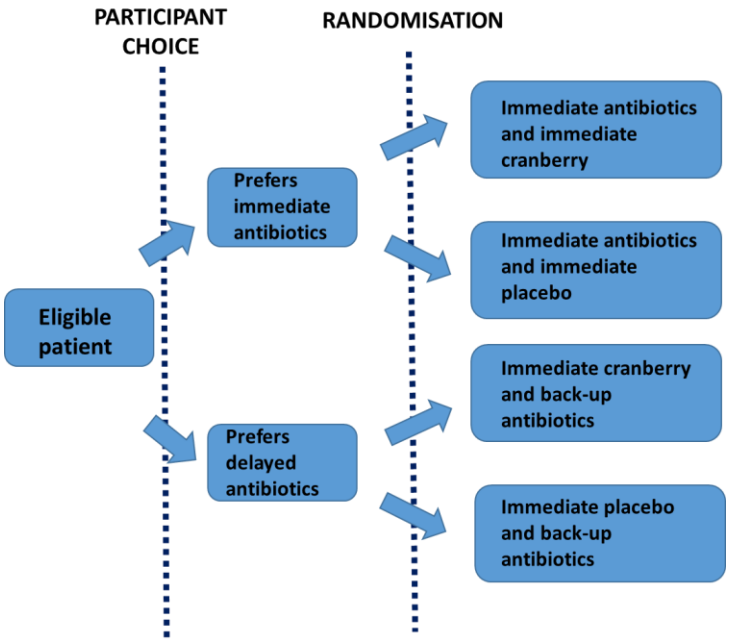


Figure 6. 3 Efficacy trial design 3 – incorporating participant choice

I therefore feel that the most appropriate design to test the efficacy of cranberry extract is a two-armed trial of immediate antibiotics plus immediate cranberry versus immediate antibiotics plus immediate placebo (see Figure 6. 4). As antibiotic consumption is standardised between groups, any difference in symptoms can be attributed to the effect of cranberry or placebo, thereby providing meaningful information about the potential effect of cranberry extract. This design is also likely to be acceptable to women, as they would receive immediate antibiotics in both groups. However, there are drawbacks to this design. Given that antibiotics do help symptoms, a large sample size would be required to establish a potential effect of cranberry over and above the antibiotic effect (see section 6.6.1.3). With this design, a 'negative' trial result would have to be interpreted as a lack of efficacy of immediate cranberry extract in combination with immediate antibiotics, compared with immediate placebo in combination with immediate antibiotics. Furthermore, this design does not have a focus on antibiotic stewardship. However, it does provide a platform for conducting a future

effectiveness trial, which would be targeted primarily at determining whether cranberry extract can be used to reduce antibiotic consumption (see section 6.6.2).

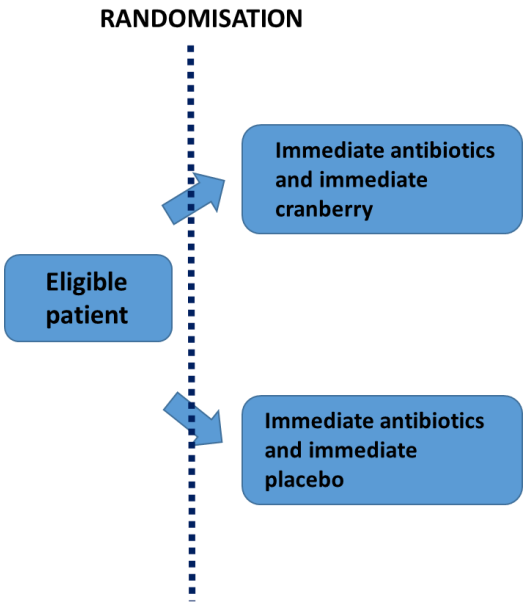


Figure 6. 4 Efficacy trial design 4 – standardising antibiotic consumption

6.6.1.2. Primary Outcome

As the proposed efficacy trial design standardises immediate antibiotic consumption, the primary outcome can be one that focuses solely on a measure of symptoms, and does not incorporate antibiotic consumption. The time to first feeling fully recovered would be an appropriate primary outcome. Women indicated through interviews that this is an important outcome, and discussions with PPI have confirmed this. Furthermore, in the CUTI feasibility trial, time to feeling fully recovered was one of the exploratory outcomes with more complete data (see Table 3. 4), as I was often able to capture this data at two week follow-up call even when the electronic diary was incomplete.

6.6.1.3. Sample size

In the CUTI feasibility trial, women in the immediate antibiotics plus cranberry group felt fully recovered faster than women receiving immediate antibiotics alone, by a median of one day. Discussions with clinician collaborators in the NIHR SPCR and with PPI members suggest that a one day reduction in time to feeling fully recovered would be a clinically meaningful effect. In order to detect a median one day difference between the intervention and comparator groups in the proposed efficacy trial, a sample size of 656 is required (328 per group). This sample size calculation assumes a median survival in the placebo arm of 4 days and a median survival in the cranberry arm of 3 days. Median survival times were converted into a hazard ratio using an online survival converter (249). The resultant hazard ratio of 1.34 was input into Stata version 16.1, and a sample size calculation was performed based on a two-sided alpha of 0.05 and with 90% power. The sample size also takes into account censoring (assuming 6.7% of participants in the control group will not be fully recovered by day 14 - based on estimates from the CUTI feasibility trial) and 20% loss-to-follow.

Further details of the proposed efficacy trial, which will be conducted in collaboration with the Universities of Southampton (Professor Michael Moore) and Bristol (Professor Alastair Hay), are provided in Appendix 6. 2.

6.6.2. An Effectiveness trial, and beyond

If efficacy is established through the above trial design, it would be appropriate to proceed to a pragmatic, open-label effectiveness trial. The outcomes of such a pragmatic trial, being more closely aligned with normal clinical practice than a blinded trial, would be more likely to reflect what would happen if cranberry extract was introduced into routine clinical care. In

order to determine whether cranberry extract can help avert the need for antibiotics altogether, the trial would need to incorporate an immediate cranberry extract with delayed antibiotics arm. An immediate antibiotics alone arm (usual care) would also be required for comparison.

A future effectiveness trial should incorporate a qualitative component. This would build on insights gained from the qualitative research in the present programme of research and the efficacy trial, and would explore the way that UTI patients and clinicians would engage with cranberry extract as a UTI treatment with proven efficacy. In collaboration with a health economist, an economic evaluation to determine the cost-effectiveness of cranberry extract in the context of an acute UTI should be conducted. This would allow the cost-effectiveness of introducing cranberry extract to be compared with usual care, through calculation of an Incremental Cost Effectiveness Ratio (ICER) (250). The ICER takes into account both the costs associated with the intervention, as well as the ability of the intervention to improve quality and quantity of life (QALYs –Quality Adjusted life Years), compared with usual care (251). The National Institute for Health and Care Excellence (NICE) would usually consider an intervention to be cost-effective, and therefore more likely to be introduced into clinical care, if the ICER is under £20,000 per QALY gained (252).

Ultimately, if cranberry extract was found to be effective, it may be helpful to test it as part of a complex intervention. Changing clinicians' approach to acute UTI consultations through a complex intervention has the potential to impact patients' subsequent health-seeking behaviour, as discussed in section 4.5.3. This might include training in how to approach discussions with patients about using cranberry extract in conjunction with a delayed antibiotic prescription. The implementation of a complex intervention has previously led to

changes in clinicians' antibiotic prescribing behaviour for acute UTI (253). Through a cluster randomised trial, Vellinga and colleagues introduced a complex intervention to Irish General Practices, with the aim of improving the proportion of guideline-appropriate prescribing for acute UTIs (253). The intervention included audit reports, training in antibiotic prescribing guidelines, and evidence to support delayed antibiotic prescription. The authors found that there was a significant increase in the odds of prescribing first line antibiotics in the intervention General Practices, compared with control Practices (253).

6.7. Final Conclusions

This programme of research has demonstrated the feasibility of conducting a trial of cranberry extract for acute UTI in primary care, and consequently helps to fill a vital evidence gap, as evidenced by my systematic review. Interviews with UTI patients suggest that further research into non-antibiotic treatment options for acute UTI, such as cranberry extract, is both acceptable and welcome. UTI patient interviews have provided an understanding of how and why UTI patients might engage with cranberry extract for an acute UTI, if found to be effective in future. Interviews with both recruiters and UTI patients have provided insight into the trial processes that did, and did not, work well, which should optimise opportunistic recruitment and participant retention in a future trial. This research programme lays the foundation for a future, adequately powered efficacy trial of cranberry extract for acute UTI. If efficacy is proven, proceeding to an adequately powered effectiveness trial would be appropriate.

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Appendices

Appendix 2. 1 Search strategies for systematic review

Table S1: Search Strategies

Medline

1	urinary tract infections/ or bacteriuria/ or pyuria/	43629
2	("urinary tract infection*" or "urin*" or "urine*" or "UTI*").ti,ab.	1241951
3	Cystitis/	7454
4	Pyelonephritis/	14017
5	cystitis*.ti,ab.	11008
6	pyelonephrit*.ti,ab.	12823
7	Escherichia coli/	263459
8	(bacter* or pyuria or Escherichia*).ti,ab.	996305
9	"E. coli".ti,ab.	131054
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	2274418
11	Vaccinium macrocarpon/	817
12	(cranberr* or vaccinium).ti,ab.	2688
13	("fruit adj5 juice" or "fruit adj5 drink" or "fruit adj5 beverage").ti,ab.	0
14	exp animals/ not humans.sh.	4669577
15	11 or 12 or 13	2744
16	(10 and 15) not 14	820

Embase

1	urinary tract infections/ or bacteriuria/ or pyuria/	47998
2	("urinary tract infection*" or "urin*" or "urine*" or "UTI*").ti,ab.	1653181
3	Cystitis/	14302
4	Pyelonephritis/	15741
5	cystitis*.ti,ab.	15909
6	pyelonephrit*.ti,ab.	14649
7	Escherichia coli/	335259
8	(bacter* or pyuria or Escherichia*).ti,ab.	1107642
9	"E. coli".ti,ab.	150100
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	2795171
11	Vaccinium macrocarpon/	1504
12	(cranberr* or vaccinium).ti,ab.	3271
13	("fruit adj5 juice" or "fruit adj5 drink" or "fruit adj5 beverage").ti,ab.	0
14	(exp animals/ or nonhuman/) not human/	6432532
15	11 or 12 or 13	3604
16	conference*.pt.	4461028
17	(10 and 15) not (14 or 16)	834

Amed

1	urinary tract infections/ or bacteriuria/ or pyuria/	168
2	("urinary tract infection*" or "urin*" or "urine*" or "UTI*").ti,ab.	9588
3	Cystitis/	58
4	Pyelonephritis/	8
5	cystitis*.ti,ab.	80
6	pyelonephrit*.ti,ab.	18
7	(bacter* or pyuria or Escherichia*).ti,ab.	2020
8	"E. coli".ti,ab.	144
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	11637
10	(cranberr* or vaccinium).ti,ab.	113
11	("dietary supplement*" or "herbal adj5 supplement" or "food adj5 supplement" or "fruit adj5 juice" or "fruit adj5 drink" or "fruit adj5 beverage").ti,ab.	541
12	exp animals/ not humans.sh.	12241
13	10 or 11	650
14	(9 and 13) not 12	87

Cinahl

	(MH "Urinary Tract Infections") OR (MH "Bacteriuria") OR (MH "Pyuria") OR (("urinary tract infection*" or "urin*" or "urine*" or "UTI*") OR cystitis OR pyelonephritis OR "Escherichia coli" OR "E.coli"	
AND	("fruit N5 juice" or "fruit N5 drink" or "fruit N5 beverage") OR "Vaccinium macrocarpon" OR cranberr* OR vaccinium	
NOT	(MH "Animals+") NOT (MH Humans)	517

Cochrane

1	(Title/abstract/keyword search)	urinary tract infection OR UTI OR bacteria OR bacteriuria OR pyuria OR urine OR cystitis OR pyelonephritis OR "Escherichia coli" OR "E.coli"
2	(Title/abstract/keyword search)	cranberry OR vaccinium
	1 AND 2	247 trials, 6 reviews

Web of Science

# 5	826	#3 NOT #4
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 4	7,366,900	TS=(animals or animal or mice or mus or mouse or murine or woodmouse or rats or rat or murinae or muridae or cottonrat or cottonrats or hamster or hamsters or cricetinae or rodentia or rodent or rodents or pigs or pig or swine or swines or piglets or piglet or boar or boars or sus scrofa or ferrets or ferret or polecat or polecats or mustela putorius or guinea pigs or guinea pig or cavia or callithrix or marmoset or marmosets or cebuella or hapale or octodon or chinchilla or chinchillas or gerbillinae or gerbil or gerbils or jird or jirds or merione or meriones or rabbits or rabbit or hares or hare or diptera or flies or fly or dipteral or drosphila or drosophilidae or cats or cat or carus or felis or nematoda or nematode or nematoda or nematode or nematodes or sipunculida or dogs or dog or canine or canines or canis or sheep or sheeps or mouflon or mouflons or ovis or goats or goat or capra or capras or rupicapra or chamois or haplorhini or monkey or monkeys or anthropoidea or anthropoids or saguinus or tamarin or tamarins or leontopithecus or hominidae or ape or apes or pan or paniscus or pan paniscus or bonobo or bonobos or troglodytes or pan troglodytes or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or chimpanzee or chimpanzees or prosimians or bush baby or prosimian or bush babies or galagos or galago or pongidae or gorilla or gorillas or pongo or pygmaeus or pongo pygmaeus or orangutans or pygmaeus or lemur or lemurs or lemuridae or horse or horses or pongo or equus or cow or calf or bull or chicken or chickens or gallus or quail or bird or birds or quails or poultry or poultries or fowl or fowls or reptile or reptilia or reptiles or snakes or snake or lizard or lizards or alligator or alligators or crocodile or crocodiles or turtle or turtles or amphibian or amphibians or amphibia or frog or frogs or bombina or salientia or toad or toads or epidalea calamita or salamander or salamanders or eel or eels or fish or fishes or pisces or catfish or catfishes or siluriformes or arius or heteropneustes or sheatfish or perch or perches or percidae or perca or trout or trouts or char or chars or salvelinus or fathead minnow or minnow or cyprinidae or carps or carp or zebrafish or zebrafishes or goldfish or goldfishes or guppy or guppies or chub or chubs or tinca or barbels or barbus or pimephales or promelas or poecilia reticulata or mullet or mullets or seahorse or seahorses or mugil curema or atlantic cod or shark or sharks or catshark or anguilla or salmonid or salmonids or whitefish or whitefishes or salmon or salmons or sole or solea or sea lamprey or lamprey or lampreys or pumpkinseed or sunfish or sunfishes or tilapia or tilapias or turbot or turbots or flatfish or flatfishes or sciuridae or squirrel or squirrels or chipmunk or chipmunks or suslik or susliks or vole or voles or lemming or lemmings or muskrat or muskrats or lemmus or otter or otters or marten or martens or martes or weasel or badger or badgers or ermine or mink or minks or sable or sables or gulo or gulos or wolverine or wolverines or minks or mustela or llama or llamas or alpaca or alpacas or camelid or camelids or

		guanaco or guanacos or chiroptera or chiropteras or bat or bats or fox or foxes or iguana or iguanas or xenopus laevis or parakeet or parakeets or parrot or parrots or donkey or donkeys or mule or mules or zebra or zebras or shrew or shrews or bison or bisons or buffalo or buffaloes or deer or deers or bear or bears or panda or pandas or wild hog or wild boar or fitchew or fitch or beaver or beavers or jerboa or jerboas or capybara or capybaras)
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 3	988	#2 AND #1
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 2	9,076	TS=("fruit near/5 juice" OR "fruit near/5 drink" OR "fruit near/5 beverage" OR "vaccinium macrocarpon" OR cranberr* OR vaccinium)
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 1	954,458	TS=("Urinary Tract Infection" OR urin* OR urine* OR UTI OR cystitis OR pyelonephritis OR "Escherichia coli" OR "E. coli")
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Appendix 3. 1 Recruiter Instructions

RECRUITER INSTRUCTIONS – CUTI trial

Thank you for agreeing to help us with this research study. This leaflet provides some information to support you in the process of recruiting participants.

Please ask us if anything is not clear or you require assistance.

CUTI Trial Office:

Nuffield Department of Primary Care Health Sciences

University of Oxford

Radcliffe Observatory Quarter

Oxford

OX2 6GG

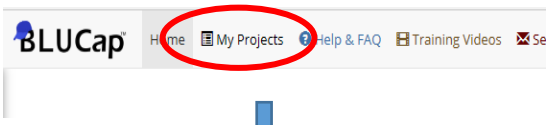
Phone: 01865 289067 **Email:** cuti@phc.ox.ac.uk

Funded by NHS National Institute for Health Research

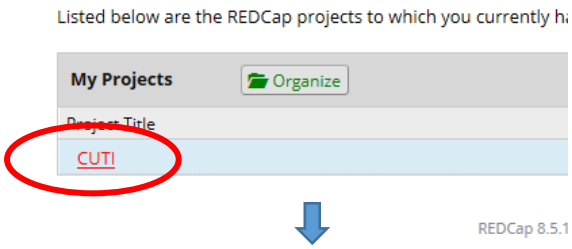
REDCap

After the patient has read the patient information leaflet and signed and dated the consent form, please log in to REDCap using the login credentials that you have been issued.

Select '**My Projects'** at the top of the screen



Click on **'CUTI'**



Click on **'Add/Edit Records'**

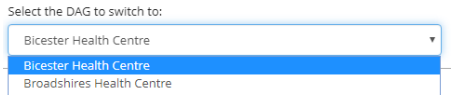


Extra step(s) for CRN nurses

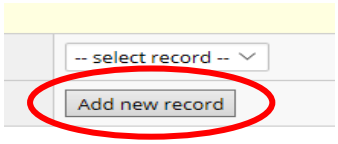
Ensure that you have selected the correct GP practice (called a 'Data Access Group') from which you are recruiting



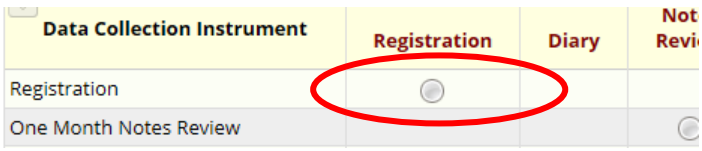
If necessary, change the GP practice by clicking on 'Switch' and then selecting the correct practice using the dropdown button.



Click on **'Add new record'**



Click on the **'Registration'** radio button



Please note, REDCap remembers the page that you were last on when you logged in, so you may find that the starting point when logging in changes to 'Add/Edit Records' after you have recruited your first participant.

1) Participant is assigned an ID number – please add this to the consent form

2) Enter the participant's age

3) Enter the trial registration date (today's date)

4) Go through the eligibility criteria

5) Randomize the participant to one of three treatment groups (See pages 4-7)

6) Ensure that a midstream urine has been sent off (NB If a participant is struggling to produce a urine sample during registration, it can be sent later in the day, but must be on the same day as registration and prior to starting antibiotics/cranberry)

7) Enter the name of the antibiotic prescribed (including the delayed antibiotic for participants in group 3)

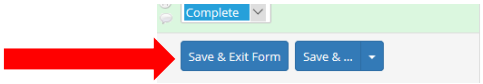
8) Complete the study product accountability log (section 10.4 of site file) if cranberry capsules have been issued - enter the date that you issued the cranberry capsules, the site name, the participant ID and your initials.

9) Select 'complete' from the drop-down box at the bottom of the page.



10) Click on the link to access Sentry

11) Click on 'save and exit form' in REDCap



12) Logout of REDCap

Sentry

Please log in to Sentry with the login credentials that you have been issued. This is a secure database that will be used to store personal data about participants.

Follow the instructions within Sentry to enter:

1) The participant's ID number (which was assigned by REDCap)

2) The participant's name, email address, phone number(s) and whether they consent to be contacted for an interview.

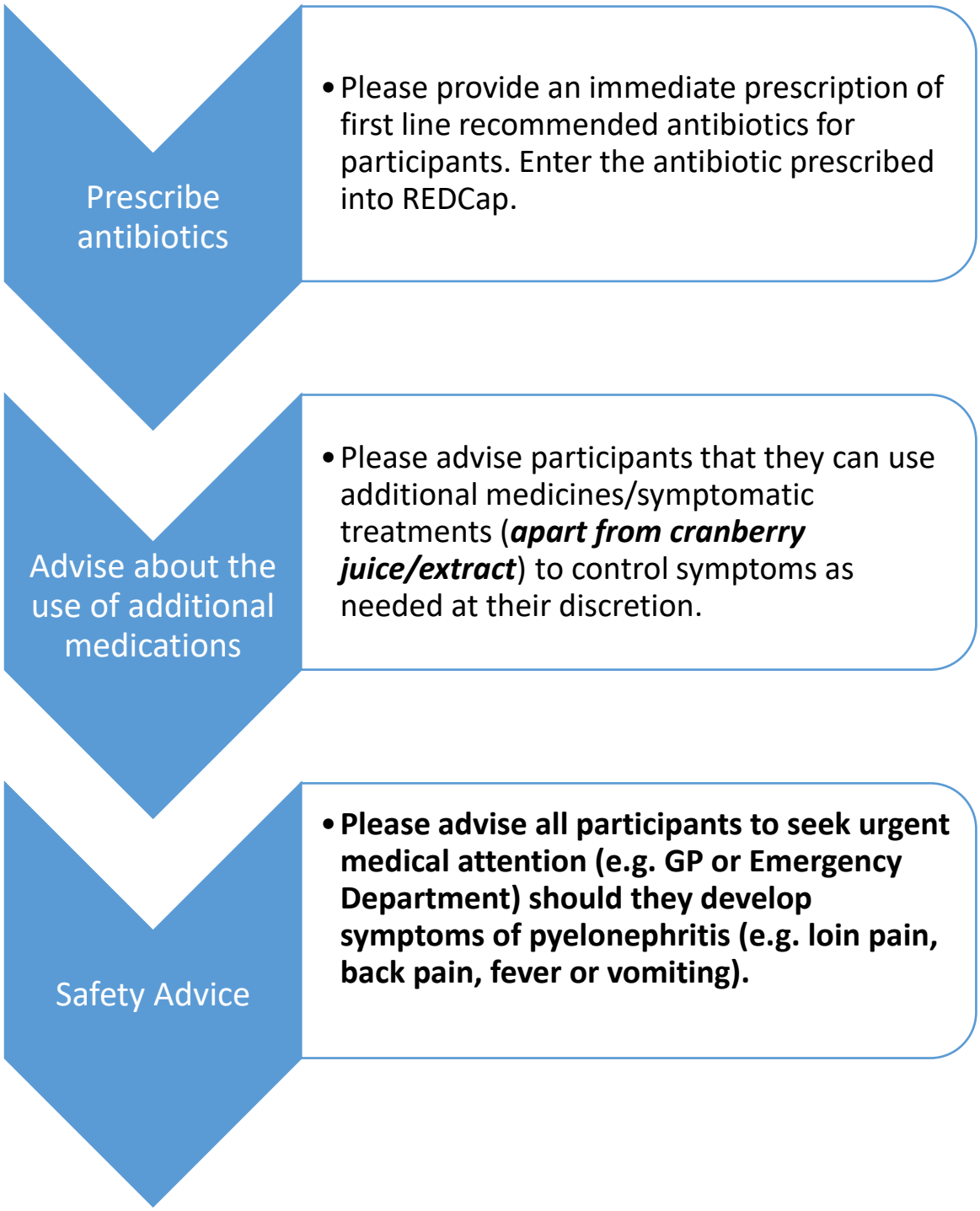
3) Logout

Please note, Sentry will automatically email a link to electronic diary using the email address that you have entered. **Please ensure that the email address entered is correct,** otherwise the participant will not be able to access the diary.

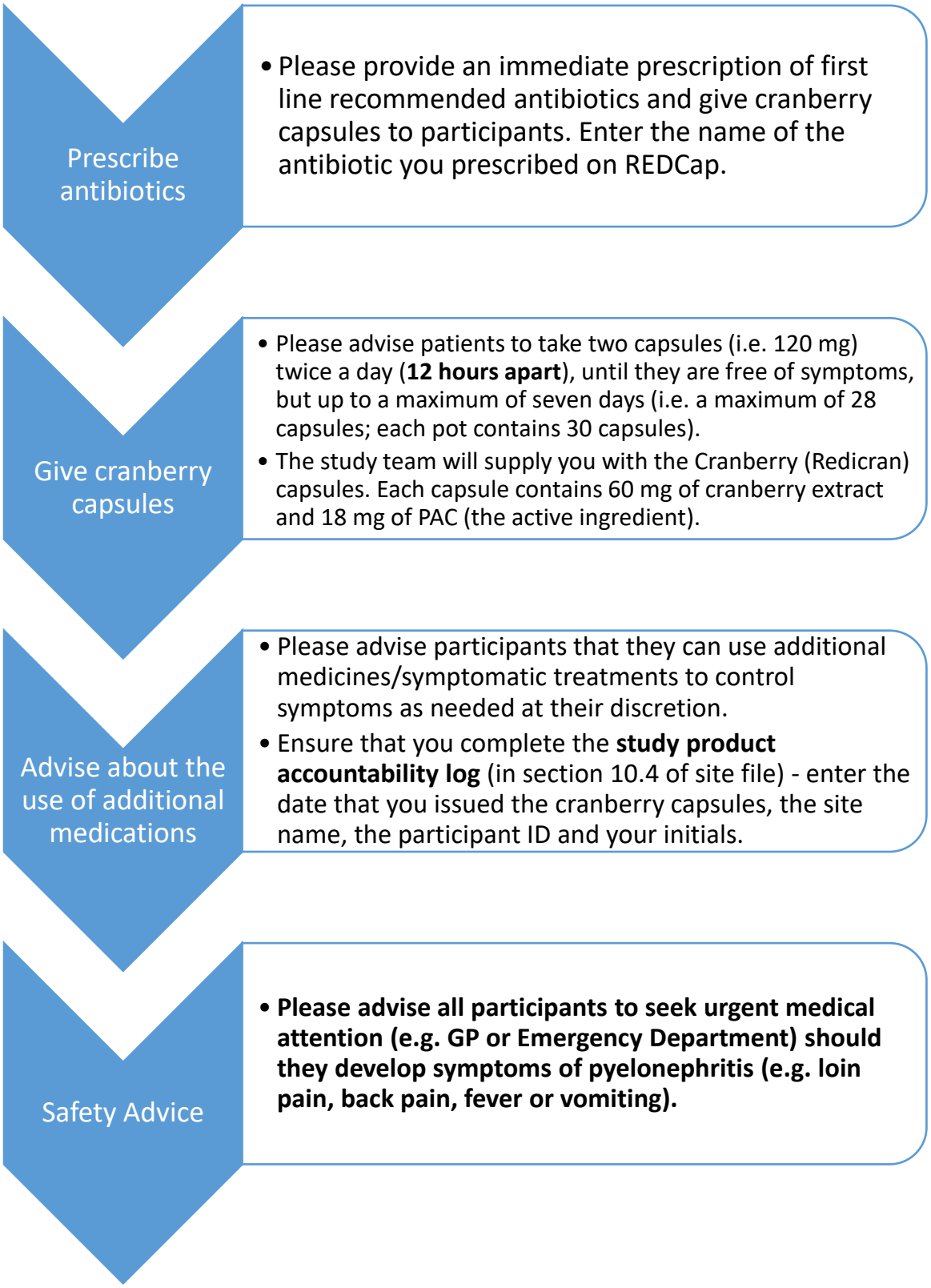
Treatment Groups

REDCap will randomly assign women to one of three groups:

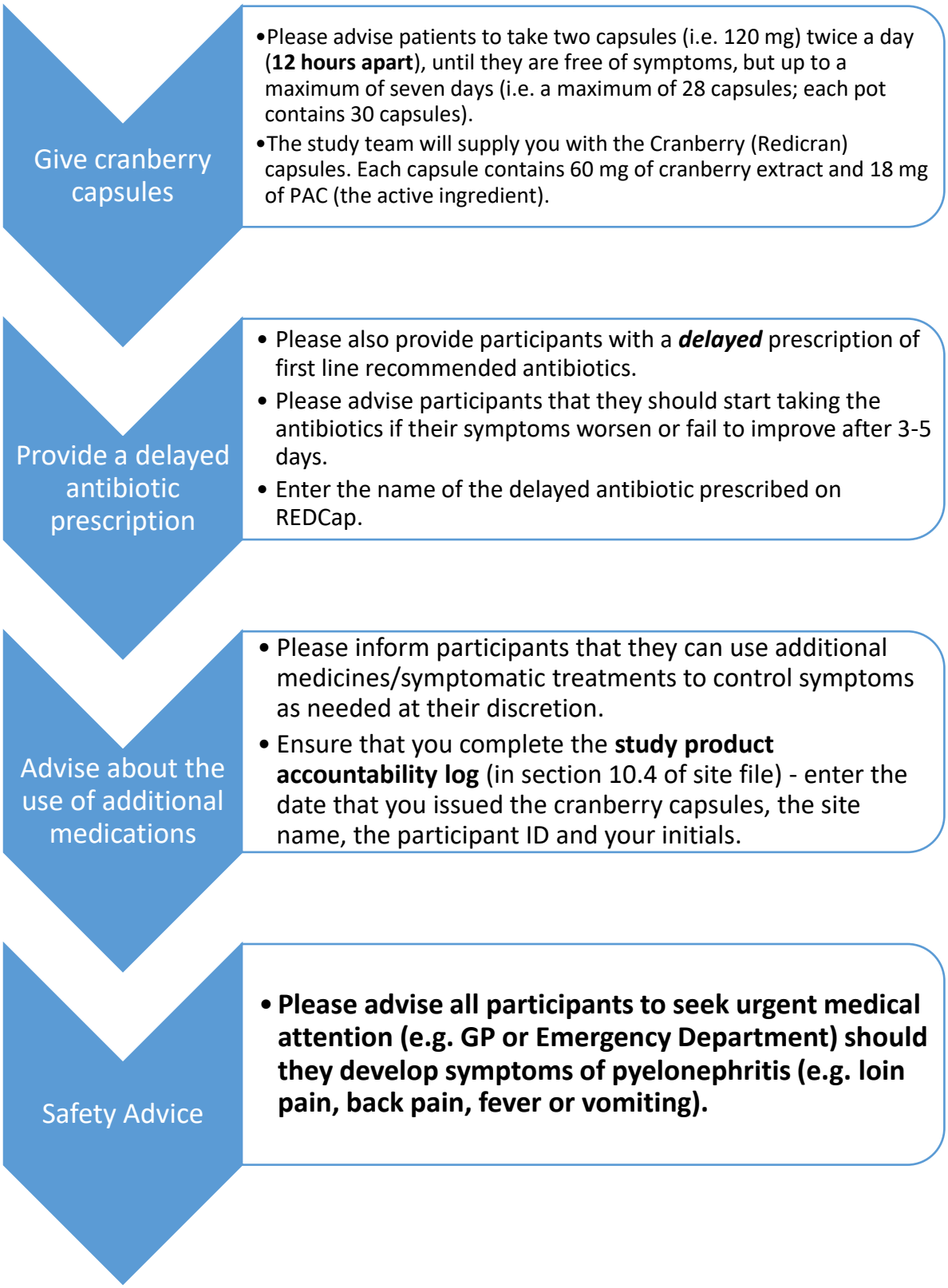
Group 1 - Usual treatment with immediate antibiotics alone (Control group)



Group 2 – Treatment with immediate antibiotics AND cranberry capsules



Group 3 – Treatment with cranberry capsules AND a delayed antibiotic prescription



Safety Information

Pyelonephritis

Please advise all participants to seek urgent medical attention (e.g. GP or Emergency Department) should they develop symptoms of pyelonephritis (e.g. loin pain, back pain, fever or vomiting).

In the event of a participant developing upper urinary tract symptoms, please assess the participant and ensure that first line treatment for pyelonephritis is prescribed. Please note, this is usually a ***seven-day course*** (rather than a three-day course) of antibiotics, and the first line recommended antibiotic may be different to the antibiotic that the participant has been prescribed for the trial.

Discontinuation of cranberry (Redicran) capsules

Discontinuation of Redicran capsules will occur if a participant has an adverse reaction to the capsules, becomes pregnant, or develops a concurrent illness that the PI (Principal Investigator)/CI (Chief Investigator) feels precludes ongoing study involvement.

Screening and Enrolment Log

Please enter a reason for ineligibility, or the reason for an eligible participant declining to take part in the screening and enrolment log (Screening and enrolment log found in section 8.1 of site files).

Thank you for reading this information and helping with this study.

Appendix 3. 2 Recruiter Instructions – one page summary



Appendix 3. 3 CUTI feasibility trial Participant Information Leaflet

CRANBERRIES FOR URINARY TRACT INFECTIONS

PARTICIPANT INFORMATION LEAFLET (CUTI trial)

You are being asked to take part in a research study. Before you decide if you want to participate or not, it is important for you to understand why the research is being done and what it will involve. This leaflet aims to tell you about the purpose of this study and what will happen to you if you decide to take part.

Please ask us if there is anything that is not clear or if you would like more information.

CUTI Study Office:

Nuffield Department of Primary Care Health Sciences

University of Oxford

Radcliffe Observatory Quarter

Oxford

OX2 6GG

Phone: 01865 289067

UNIVERSITY OF OXFORD

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

wellcome

Funded by NHS National Institute for Health Research

1. What is the purpose of the study?

Urinary tract infections (UTIs) are the commonest bacterial infections affecting women, and are usually treated with antibiotics. Because of frequent and sometimes inappropriate use of antibiotics, many bacteria have adapted so that they are no longer killed by antibiotics (antibiotic resistance). As a result, there has been increasing interest in using non-antibiotic treatments, such as cranberry extract. The sugars in cranberries are believed to prevent bacteria from sticking to the wall of the bladder, thus reducing the ability of bacteria to cause a UTI. Cranberries might also make it easier for antibiotics to surround and kill bacteria.

Women with a suspected UTI are being invited to take part in this study and are being randomly assigned to one of three groups:

1) Group 1 - Usual treatment with antibiotics.

2) Group 2 - Treatment with antibiotics AND cranberry capsules.

3) Group 3 - Initial treatment with cranberry capsules. Women in this group will also be given an antibiotic prescription that they can take to the chemist at a later date if they don't get better with cranberry capsules alone ('back-up antibiotics').

The cranberry capsules have been supplied by an Italian company called Indena S.p.A. Each capsule contains 60 mg of cranberry extract and 18 mg of proanthocyanidins ('PAC' for short – this is the active ingredient). We are not aware of any serious or common side effects that are associated with these capsules.

The main aim of this small-scale study is to test whether the study design described works and is acceptable to participants (called a 'feasibility' study). This will help in the planning of a subsequent, similar, but much larger study. By comparing the information from different treatment groups on a larger scale, we will be able to tell whether cranberries actually treat UTIs and help reduce the need for antibiotics. This study is being led by Dr Kome Gbinigie and forms part of her doctoral research.

2. Why have I been invited?

You have contacted a primary care provider with symptoms that suggest you might have a urinary tract infection.

3. Do I have to take part?

No. You are free to decide whether or not to take part. If you decide to take part you are still free to withdraw from the study at any time, without giving a reason. A decision not to take part or to withdraw will not affect the standard of care you receive from the healthcare team.

4. What will happen to me if I agree to take part?

- The clinician/healthcare provider/researcher will check if you are eligible to take part. This **is likely to** involve screening your medical records for relevant information and you will be asked to sign a consent form.
- You will then be randomly assigned (that is, like tossing a coin) to one of three ways of treating your UTI. The random assignment will be done electronically by your clinician/healthcare provider/researcher, by clicking a button. The three different ways are:
  Group 1
  An antibiotic prescription (usual practice)
  Group 2
  An antibiotic prescription AND a course of cranberry capsules to take for up to 7 days.
  Group 3
  An immediate course of cranberry capsules to take for up to 7 days AND a *delayed* prescription for antibiotics. You will be advised to take the antibiotics if your symptoms get worse, or don't get better, within 3-5 days of taking cranberry capsules.

- You will be told which of the three groups you are in, and your clinician/healthcare provider/researcher will provide you with an antibiotic prescription and/or cranberry capsules. If you wish, you can also take pain relief/medicines to help your symptoms (e.g. paracetamol). However, if you are in group 1, we would ask you not to use any cranberry products/cranberry juice. If you are in groups 2 or 3, you will also be provided with a freepost envelope so that you can return any unused cranberry capsules back to the study team. You will be given a participant information pack, which will include a guide on how to complete the electronic symptom diary.

- You will be asked to provide a urine sample (if you have not already provided a sample as part of your routine care). This will be sent to a laboratory for analysis to see whether any bugs grow.

- You will be emailed a link to an electronic questionnaire (a symptom diary). There are three sections to the symptom diary. The first section should be completed on the same day that you agreed to participate in the study (i.e. the day that you saw a healthcare professional/clinician/researcher), and will ask you some background questions (such as whether you have had a urinary tract infection in the past).

- You will be emailed a link to complete the symptom diary on a daily basis for 2 weeks). This part of the questionnaire will allow you to rate how bad your symptoms are and to enter the medications that you are taking.

- If you have not started the electronic diary by day 3, or your diary is incomplete at day 3, you will be telephoned to check whether you are having any problems in accessing the diary.

- Two weeks from now, you will be asked to complete the third section of the electronic symptom diary. In this section you will be asked further questions, including how easy/difficult you found it to use and complete the electronic symptom diary.

- You will also receive an email +/- telephone call two weeks from now from a member of the study team, principally to ensure that you managed to complete the electronic symptom diary.

- Please note that if you are in group 2 or group 3 (i.e. a group that receives cranberry capsules), you will not receive cranberry capsules beyond your period of involvement with the study.

- When you are consented to take part in this study, we will also ask you whether you would be happy to be contacted to take part in an interview to discuss your thoughts on taking part in this study as well as your thoughts on the management of UTIs more generally. There is no obligation for you to take part in the interview study; declining to take part in the interview study will not affect your participation in this study or the level of care provided to you by your healthcare provider. If you decide to also take part in the interview study, you will be provided with more detailed information about what to expect and separate informed consent will be taken. The interview will be arranged at a time to suit you. We anticipate that the interview should take no longer than an hour and can be carried out in person, in your own home or other preferred place, or by telephone, whichever you prefer. The interview will take place between 1 and 6 months from now.

- After one month, your medical notes will be reviewed by a member of the study team (possibly your GP) to find out the results of your urine culture that was sent to the laboratory and also to see whether there have been any side effects/problems related to your participation in the study.

5. What will happen to my urine sample?

Your urine sample will be sent to a laboratory for analysis as per the usual practice of your GP surgery/primary care provider. The urine sample will be destroyed in accordance with usual laboratory procedures.

At a later stage, a member of the study team who is authorised to do so will access your medical notes to determine whether or not your urine grew a bug. This may be a GP at your surgery.

6. What are the possible disadvantages and risks of taking part?

There are no known serious or common side effects associated with taking cranberry capsules.

If you are randomly assigned to group three, you will not receive immediate antibiotics. This may mean that you are at higher risk of developing an upper UTI. ***Irrespective of the group to which you are assigned, if you develop any symptoms that suggest that you have an upper UTI (pain in your back, pain in your side, fever and/or vomiting), you must seek urgent medical attention.*** It is likely that you will require a 7 day course of antibiotics. If you decide to take part in this study, this information will also be in your participant information pack.

7. What are the possible benefits of taking part?

If you complete the electronic symptom diary, you will receive a £10 voucher as a thank you for taking part, after you have finished taking part in the study. If you also take part in the interview, you will receive a further £10 voucher after the interview has been completed.

Taking part in this study will help us to design a similar study to this but on a much larger scale (with more participants and in different parts of the country). The results of the larger study may help us to safely reduce antibiotic use in women with simple urinary tract infections.

8. Will my taking part in this study be kept confidential?

Yes. The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 and all information collected about you during the research will be kept strictly confidential. Only the relevant sections of your medical notes will be reviewed. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. You will be assigned a participant ID number and identified by this on study documents and electronic databases.

9. What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

We will be using information from your medical records and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 6-12 months after the study has finished. We will store the de-identified research data and any research documents with personal information, such as consent forms, securely at the University of Oxford for 5 years after the end of the study. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your

rights with respect to your personal data is available at:
https://compliance.web.ox.ac.uk/individual-rights

Data which does not identify you will be stored by the study team and may be used in future research projects.

You can find out more about how we use your information by contacting the Chief Investigator using the details at the end of this sheet.

10. What if I do not want to take part and/or do not want to carry on with the study once I have started?

If you do not want to take part in the research you can withdraw at any time without affecting your care. Information collected up to your withdrawal will be kept. Withdrawing from the study will not affect the standard of care you receive from the healthcare team. If you would like to withdraw at any time we would ask you to let one of the research team know. If you lose the ability to confirm that you are happy to proceed with the study (i.e. if you lose the capacity to consent to ongoing participation), information collected up until this point will be kept.

11. What if there is a problem?

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Dr Kome Gbinigie (Chief Investigator) on 01865 289067 or cuti@phc.ox.ac.uk, or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrg@admin.ox.ac.uk. The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

12. What will happen to the results of the research study?

We aim to publish the results so that scientists and doctors are aware of the findings. We will also provide your GP practice a copy of our findings for them to display. You will not be personally identifiable in any publication.

13. Who is organizing and funding the research?

This study is sponsored by the University of Oxford and the funding for this research comes from the NIHR School for Primary Care (SPCR) and the Wellcome Trust. Indena S.p.A (an Italian company) have supplied the cranberry capsules (Redicran capsules) for this study; they have no other involvement with the study.

14. Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by South Central Research Ethics Committee.

15. Do you have any further questions or concerns?

If you want to discuss the study please contact Dr Kome Gbinigie, Chief Investigator, by email (cuti@phc.ox.ac.uk) or telephone (01865 289067).

Thank you for taking the time to read this information leaflet

Appendix 3. 4 CUTI feasibility trial participant instructions

CRANBERRIES FOR URINARY TRACT INFECTIONS

PARTICIPANT INSTRUCTIONS (CUTI trial)

Thank you for agreeing to take part in this research study. This leaflet provides some information to support you in completing the symptom diary.

Please ask us if anything is not clear or you require assistance.

CUTI Trial Office:

Nuffield Department of Primary Care Health Sciences

University of Oxford

Radcliffe Observatory Quarter

Oxford

OX2 6GG

Phone: 01865 289067

UNIVERSITY OF OXFORD

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

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Funded by NHS National Institute for Health Research

Electronic symptom diary

An email has been sent to you, which contains a link to access an electronic symptom diary. If you have any difficulty accessing the diary, or have not received a link to the diary, please contact the CUTI trial office (See details on the title page of this information sheet). You will receive daily emails containing a link to the electronic diary.

Section one of the electronic diary should be completed on the day that you saw your GP/healthcare practitioner/researcher. Please follow the prompts to complete the background questions in this section.

Section two of the electronic diary should be completed each evening for *up to two weeks.* Please start this on the evening of the day that you saw your GP/healthcare practitioner/researcher, and continue each evening for 2 weeks, or until your symptoms have completely gone and no treatments are being taken. Please note, if your symptom score is '0' for each of your symptoms for two days in a row, you will no longer need to fill in daily information about your symptoms.

Please enter the medications/treatments that you are taking for your urine infection in the diary. Please indicate how many times you have taken it each day. If you make a mistake when entering the medications/treatments, you can press the 'reset' button.

Please select 'yes' or 'no' in response to the question at the bottom of the treatment/medication section that asks whether you feel completely recovered each day.

If you accidentally forget to complete the diary on one or more days, you can still fill it in later on when you remember.

Section three of the electronic diary should be completed two weeks (14 days) after you saw your GP/healthcare practitioner/researcher. You will receive a reminder about this.

Cranberry Capsules

If you are in groups 2 and 3, you will have received cranberry capsules. Please take two capsules, twice a day up until your symptoms are better, but for a maximum of 7 days (in total, up to 28 capsules). These capsules have been supplied to the CUTI trial by an Italian company called Indena S.p.A. Indena S.p.A have no other involvement with this study.

As there are 30 cranberry capsules in the pot you have been given, you will have at least 2 capsules left over. Please return the pot and any remaining cranberry capsules to the research study team using the freepost envelope that has been provided.

Participant safety

Women taking part in this study have been randomly placed in different groups and are receiving different treatments. **Irrespective of the group to which you are assigned, if you develop any symptoms that suggest that you have an upper UTI (pain in your back/side, fever and/or vomiting), you must seek urgent medical attention.** It is likely that you will require a 7 day course of antibiotics.

Thank you for taking the time to read this information leaflet.

Appendix 3. 5 CUTI feasibility trial Informed Consent Form

INFORMED CONSENT FORM – CUTI Trial

CRANBERRIES FOR URINARY TRACT INFECTIONS

Chief Investigator: Dr Kome Gbinigie. **Address:** Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG. **Email:** cuti@phc.ox.ac.uk **Telephone:** 01865 289067

Study Title: CUTI trial **Participant ID number:** _____

If you are happy to take part in this research then please read each of the statements below and initial the boxes if you agree with them.

Please initial each box

1. I confirm that I have read and understood the information sheet version [number], dated [date month year] for the CUTI trial and have had the opportunity to ask questions and had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	☐
3. I understand that the study team will have access to the results of the urine culture test performed for my UTI episode.	☐
4. I understand that relevant sections of my medical notes will be reviewed after 28 days.	☐
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Oxford or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
6. I understand that the information that I have given to researchers will be transferred to Oxford University and stored securely. I give permission for the research team to use de-identified data collected as part of this study for future research.	☐
7. I give permission for de-identified quotes from the patient symptom diary to be included in reports of the findings from the research.	☐
8. By signing this consent form, I agree to participate in the CUTI trial and follow all trial procedures.	☐

ADDITIONAL STUDY – Please initial either the yes (Y) or no (N) box:

8. I am happy to be contacted regarding an interview study (CUTI Interview study) aiming to find out what patients think about the management of UTIs, their experience of having a UTI and their experience of the CUTI trial.	Y ☐ N ☐

Participant name:…….. Name of person taking consent:……

Date:……..
Date:……

Signature:……..
Signature:……

When completed, one copy should be given to the participant, one copy should stay at the study site and one copy should go in the participant's medical notes

Funded by NHS National Institute for Health Research

Appendix 3. 6 CUTI trial Symptom Diary



Patient ID:

Age: _____ Years

Date of Registration: DD/MM/YYYY

Site ID:

PLEASE COMPLETE THIS TWO WEEK DIARY. IT IS DIVIDED INTO THREE SECTIONS AS EXPLAINED BELOW:

Section 1: Please complete this section **on the day** you saw your health practitioner.

Section 2: Please complete this section **every day over the next two weeks or until symptoms subside and no further treatments are being used.**

Section 3: Please complete this section at the **end of the two weeks.**







SECTION 1: ABOUT YOU. Please complete this section on the day you saw your doctor, nurse, healthcare practitioner or researcher.

PART A – Age in years

☐

PART B – History of Urine Infections

1) Have you ever had a urine infection diagnosed by a doctor or nurse at any point in the past (not including the current infection)?

☐ Yes

☐ No

☐ Do not know

*If you answered **no** or **do not know** then go to Part C*

2) Have you had a urine infection in the past year (not including the current infection)?

☐ Yes

☐ No

3) How many times have you been treated for a urine infection in the past year (not including the current infection)?

- [ ] Zero
- [ ] One
- [ ] Two
- [ ] Three or more
- [ ] Unable to remember

How many months has it been since your last urine infection (not including the current infection)?

- [ ] Months
- [ ] Do not remember - *tick this box if you cannot remember how many months it has been.*

4) How was your last urine infection treated (not including the current infection)? *Please tick all relevant boxes*

- [ ] Antibiotics -> Name of antibiotic(s) (if known) [ ]
- [ ] Other -> Please specify [ ]
- [ ] No treatment
- [ ] Do not remember

PART C – Additional Information

1) When you contacted your GP/healthcare practitioner for your current urine infection were you expecting to receive any of the following? *Please tick one box for each option*

Were you expecting antibiotics?

☐ Yes

☐ No

☐ Unsure

Were you expecting tests/investigations?

☐ Yes

☐ No

☐ Unsure

Were you expecting advice?

☐ Yes

☐ No

☐ Unsure

Were you expecting anything else?

☐ Yes -> Please specify ☐

☐ No

☐ Unsure

2) Before you went to see your doctor/healthcare practitioner did you try and manage your urine infection with any of the following? *Please tick all that apply.*

- ☐ Cranberry juice/cranberry products
- ☐ Other fruit juice
- ☐ Bicarbonate solution
- ☐ Sodium/Potassium citrate (cystitis sachets)
- ☐ Uvacin/Uva ursi (bearberry)
- ☐ Pain relief (e.g. paracetamol/Ibuprofen)
- ☐ Other If other, please specify ☐
- ☐ None

3) Before contacting your GP practice/healthcare provider today, for how many days have you felt that you had symptoms of a urinary infection? *Do not include today.*

- ☐ 0 days (that is, your symptoms started today)
- ☐ 1 day
- ☐ 2 days
- ☐ 3 days
- ☐ More than 3 days

4) Do you believe that cranberry juice/cranberry products might help your symptoms?

☐ Yes

☐ No

☐ Unsure

5) Do you believe that your symptoms can get better without antibiotics?

☐ Yes

☐ No

☐ Unsure

SECTION 2: TWO WEEK DIARY OF URINE INFECTION SYMPTOMS/PROBLEMS/TREATMENTS

Please fill in the diary on the next page and record your symptoms and any treatments (study medication, antibiotics, other medications or products) used. Please start **THIS EVENING** (the evening of the day on which you saw your GP/nurse/healthcare practitioner/researcher) and continue to fill this in each evening for 2 weeks or until all symptoms have completely gone and no treatments are being taken.

If all of your symptoms are rated as 0 for two days in a row you no longer need to complete the symptom scoring chart; please enter the date in the relevant box. However, please continue to record the medication that you have taken and complete Section 3, 2 weeks after you first saw the doctor/nurse.

For each symptom/problem, rate how bad it has been using the scale on the following page. The rating that you give should reflect how you have felt over the past 24 hours.

WEEK 1 SYMPTOMS

For each symptom/problem, please rate how bad it has been using the scale below. If you have no symptoms or problems, please enter 0 (to indicate normal/not affected.) The shaded column is completed as an example – please fill in your own numbers:

0 – Normal/not affected
1-9 – Very little problem
10-19 – Slight problem
20-29 – Moderately bad
30-39 – Bad
40-49 – Very Bad
50 – As bad as it could be

DAY	E.g.	1 (The day you were seen by your GP/nurse/ Healthcare practitioner)	2	3	4	5	6	7
DAY OF WEEK	Mon							
SYMPTOM/PROBLEM								
Fever	0							
Pain in the side of tummy	35							
Blood in urine	0							
Smelly urine	20							
Burning or pain when passing urine	46							
Having to pass urine in a hurry (urgency)	15							
Passing urine *more often than usual* during the day (Day time frequency)	18							
Getting up at night *more than usual* to pass urine (Night time frequency)	12							
Lower tummy pain (When not passing urine)	0							
Restricted activities	0							
Feeling generally unwell	6							

WEEK 1 TREATMENTS

Please also enter any medication that you are taking for your urine infection each day. Please indicate:

- The **medications/treatments** you are taking for your urine infection**.** This includes prescribed medications (such as antibiotics and cranberry capsules) and any medications that you have purchased over the counter. If a medication that you are taking is not listed in the table below, please add at the bottom in one of the empty rows.
- The **number of times** that you have taken the **medication/treatment each day** (Please note that you only need to record the number of times in the day that you have taken the medication, not the number of capsules/tablets/sachets taken each day).
- The shaded row is completed as an example – please fill in your own answers.

Medication	**Day 1**		**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 6**		**Day 7**	
	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?
e.g. Paracetamol	Y	4	Y	4	N		Y	2	Y	3	N		N	
Nitrofurantoin														
Trimethoprim														
Amoxicillin														
Pivmecillinam														
Fosfomycin														
Co-amoxiclav														
Ciprofloxacin														
Cranberry capsules														
Paracetamol														
Ibuprofen														
Cystitis sachets														

WEEK 2 SYMPTOMS

For each symptom/problem, please rate how bad it has been using the scale below. If you have no symptoms or problems, please enter 0 (to indicate normal/not affected.) The shaded column is completed as an example – please fill in your own numbers:

0 – Normal/not affected

1-9 – Very little problem

10-19 – Slight problem

20-29 – Moderately bad

30-39 – Bad

40-49 – Very Bad

50 – As bad as it could be

DAY	E.g.	8	9	10	11	12	13	14
DAY OF WEEK	Mon							
SYMPTOM/PROBLEM								
Fever	0							
Pain in the side of tummy	35							
Blood in urine	0							
Smelly urine	20							
Burning or pain when passing urine	46							
Having to pass urine in a hurry (urgency)	15							
Passing urine *more often than usual* during the day (Day time frequency)	18							
Getting up at night *more than usual* to pass urine (Night time frequency)	12							
Lower tummy pain (When not passing urine)	0							
Restricted activities	0							
Feeling generally unwell	6							

WEEK 2 TREATMENTS

Please also enter any treatments that you are taking for your urine infection each day. Please indicate:

- The **medications/treatments** you are taking for your urine infection**.** This includes prescribed medications (such as antibiotics and cranberry capsules) and any medications that you have purchased over the counter. If a medication that you are taking is not listed in the table below, please add at the bottom in one of the empty rows.
- The **number of times** that you have taken the **medication/treatment each day** (Please note that you only need to record the number of times in the day that you have taken the medication, not the number of capsules/tablets/sachets taken each day).
- The shaded row is completed as an example – please fill in your own answers.

Medication	**Day 8**		**Day 9**		**Day 10**		**Day 11**		**Day 12**		**Day 13**		**Day 14**	
	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?	Taken today? (Y/N)	How many times?
e.g. Paracetamol	Y	3	N		N		N		N		N		N	
Nitrofurantoin														
Trimethoprim														
Amoxicillin														
Pivmecillinam														
Fosfomycin														
Co-amoxiclav														
Ciprofloxacin														
Cranberry capsules														
Paracetamol														
Ibuprofen														
Cystitis sachets														

Did your symptoms go away completely at some point over the past 2 weeks?

☐ Yes

☐ No

If you answered **no,** please skip to section 3.

What was the date that you felt completely recovered?

☐☐ / ☐☐ / ☐☐☐☐

d d m m y y y y

SECTION 3: Please complete this section two weeks (14 days) after you saw your doctor/nurse/health care practitioner

Since you saw your doctor/nurse/healthcare practitioner:

1) Have you consulted a healthcare professional from your **general practice** or **out of hours' provider** about your urine infection? *(Do not include the original visit)*

☐ Yes

☐ No

If you answered **YES** then who did you see? Please enter the number of times you saw them in the box. If you did not see the person in question then please enter 0.

☐ GP at surgery

☐ Nurse at surgery

☐ GP at home

☐ Out of hours' doctor

☐ Other If other, please specify ☐

2) Have you consulted with a healthcare professional in an **accident and emergency** department about your urine infection?

☐ Yes

☐ No

If you answered **YES**, then how many times? ☐

3) Have you been seen by a specialist (not including an admission to hospital) about your urine infection? This might occur if your GP or another healthcare professional had referred you for an urgent opinion about your urine infection, but you were not admitted to hospital.

☐ Yes

☐ No

If you answered **YES**, then how many times? ☐

4) Have you been admitted to hospital for a problem related to your urine infection?

☐ Yes

☐ No

If you answered **YES**, then how many nights did you spend in hospital? ☐

5) Have you used any of the following to try and manage your urine infection since your original consultation? *Not including study medication that you may or may not have received. Please tick all that apply*

☐ Cranberry juice/cranberry products

☐ Other fruit juice

☐ Bicarbonate solution

☐ Sodium/Potassium citrate (cystitis sachets)

☐ Uvacin/Uva ursi (bearberry)

☐ Pain relief (e.g. paracetamol/ibuprofen)

☐ Other If other, please specify ☐

☐ None

6) Did you take any time off paid work/your usual activities because of your urine infection?

☐ Yes

☐ No

If you answered **YES**, then how many days? *Please round to the nearest day.* ☐☐

7) **If you were prescribed cranberry capsules**, did you experience any side effects or problems related to taking the capsules? *If you were not prescribed cranberry capsules, please skip to question 8.*

☐ Yes

☐ No

If you answered **YES**, please explain the problems that you experienced in the box below.

8) Did you have any problems completing this 2 week diary?

☐ No problems

☐ Some problems

☐ Lots of problems

If you experienced **some problems** or **lots of problems** in completing this diary, please explain the difficulty that you experienced in the box below.

9) Did you have any problems using a scale of 0-50 to rate your symptoms?

☐ No problems

☐ Some problems

☐ Lots of problems

If you experienced **some problems** or **lots of problems** using the scale of 0-50 to rate your symptoms, please explain the difficulty that you experienced in the box below.

That is the end of the questions!

Thank you very much for completing the questions. You have made a valuable contribution to this important medical research. The information that you have provided will remain confidential.

Please add in any comments you have about this study or urine infections.

If you have any problems or queries, please contact:

Dr Kome Gbinigie,
CUTI Trial Manager
Radcliffe Primary Care Building, Radcliffe Observatory Quarter
Woodstock Road
Oxford
OX2 6GG
Phone: 01865 289067

Appendix 3. 7 Composition of the Trial Steering Committee

Dr Kome Gbinigie (CI, DPhil student and GP)

Dr. Akke Vellinga (TSC chair and epidemiologist)

Ms. Julia Hamer-Hunt (PPI representative)

Dr. Bernard Gudgin (PPI representative)

Dr. Merlin Willcox (Academic Clinical Lecturer and GP)

Dr. Emma Thomas-Jones (Research fellow and senior trials manager)

Dr. Kathy Hughes (Clinical lecturer and GP)

Dr Anne-Marie Boylan (Departmental lecturer and senior research fellow)

Professor Christopher Butler (Professor of primary care and GP)

Ms Julie Allen (Senior clinical trial manager)

Ms Nicola Williams (Senior clinical trials statistician)

Appendix 3. 8 Composition of the Trial Management Group

Dr Kome Gbinigie (CI, DPhil student and GP)

Professor Mike Moore (Professor of primary health care research and GP)

Professor Alastair Hay (Professor of primary care and GP)

Ms Julie Allen (Senior clinical trial manager)

Dr Anne-Marie Boylan (Departmental lecturer and senior research fellow)

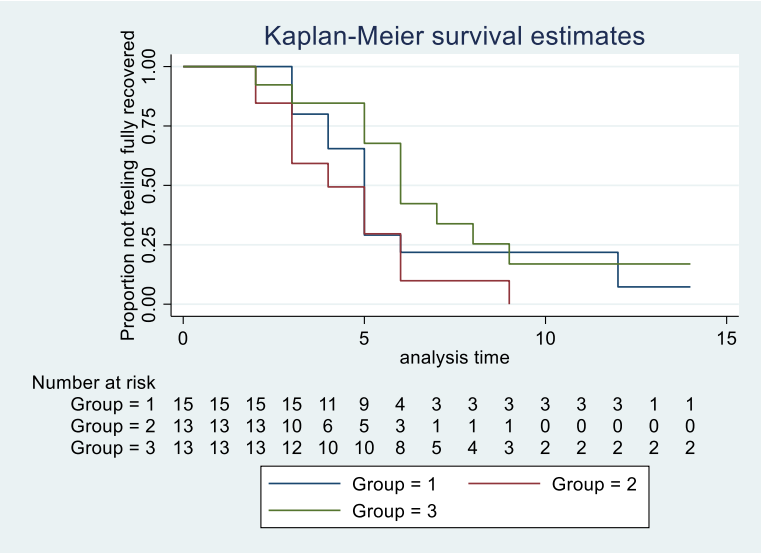
Professor Carl Heneghan (Professor of evidence-based medicine and GP)

Dr Sarah Tonkin-Crine (Senior qualitative researcher)

Professor Christopher Butler (Professor of primary care and GP)

Appendix 3. 9 Kaplan Meier Plot

Kaplan Meier survival plot showing the time to feeling fully recovered by group



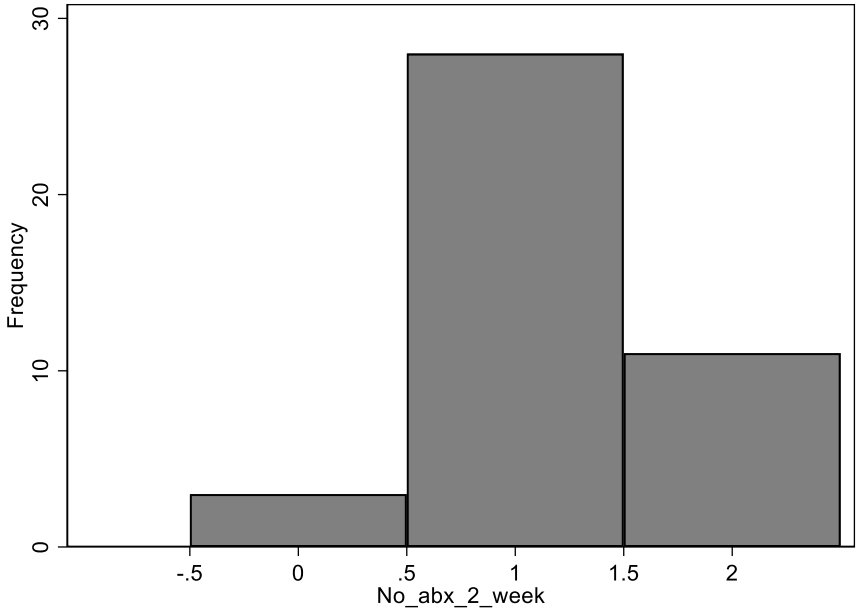
Key: Group 1: Immediate Antibiotics alone; Group 2: Immediate Antibiotics and Immediate Cranberry; Group 3: Immediate Cranberry and Delayed Antibiotics

Appendix 3. 10 Tests of model assumptions

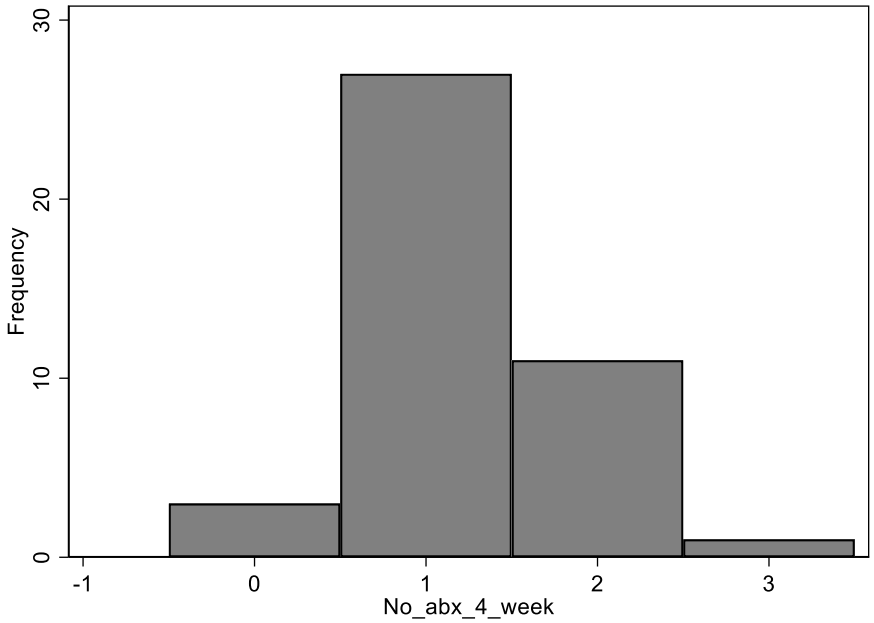
Model assumptions for Poisson regression

Histograms of the number of antibiotics consumed at 2 and 4 weeks were plotted to ensure that there was no over-dispersion of the data. This criterion was met, as evidenced by the short tails of both histograms.

Histogram showing number of antibiotic courses consumed at 2 weeks across all participants



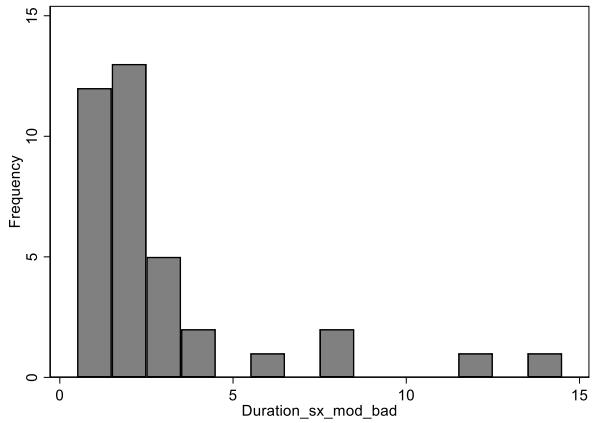
Histogram showing number of antibiotic courses consumed at 4 weeks across all participants



Testing model assumptions of negative binomial regression

I first plotted a histogram was plotted to visually summarize of the data within this variable.

Histogram of the duration of symptoms rated moderately bad or worse across all participants

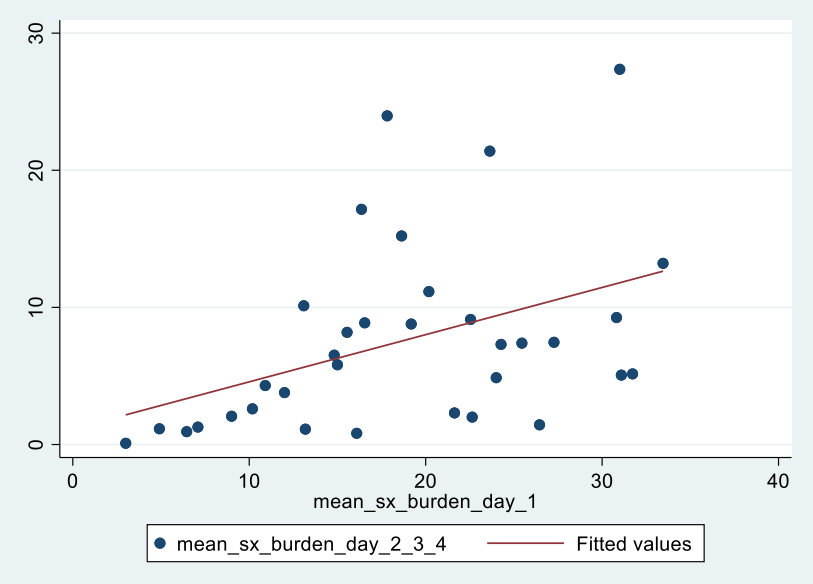


Negative binomial regression does not handle data that is under-dispersed well, that is, when the conditional variance is smaller than the conditional mean. I calculated the conditional variance and conditional mean, and found that the total conditional variance (9.0) was greater than the conditional mean (2.9), confirming that the data was not under-dispersed.

Linear regression model assumptions

1) Linearity of the data was checked by plotting a Scatterplot of the day 2-4 mean symptom burden against the day 1 (baseline) mean symptom burden.

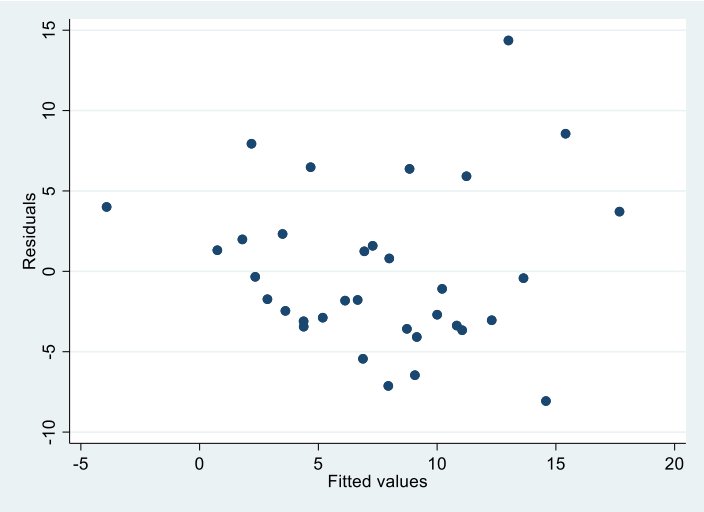
Scatterplot of the mean symptom burden between days 2 and 4 (inclusive) against baseline mean symptom burden, across all participants



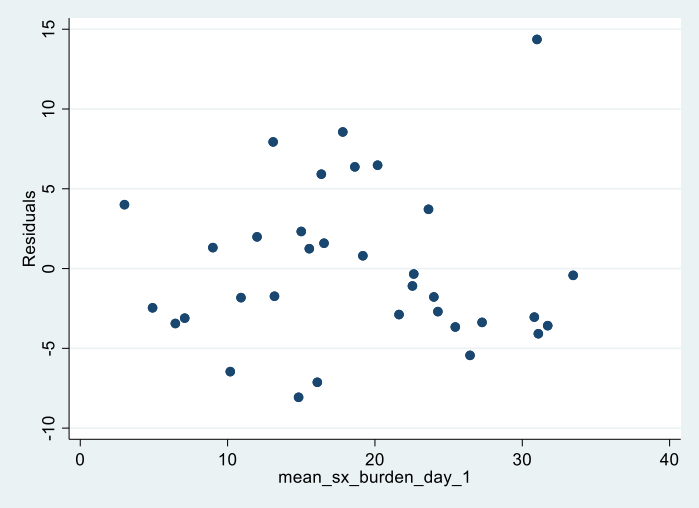
The plot shows a positive correlation, confirming that there is linearity of the data.

2) Homoscedasticity (constant variance) of the errors was checked by plotting the residuals.

Residuals versus fitted values plot



Residual versus predictor plot



These graphs show that there is no pattern to the residuals, thus, the random error is evenly distributed in the data.

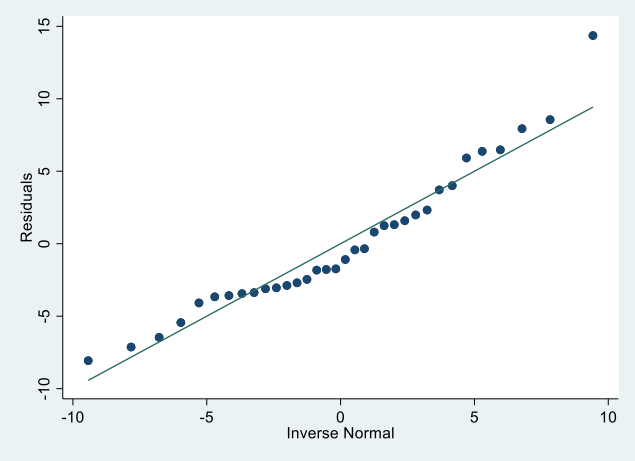
3) Statistical independence of the errors

This was confirmed through the absence of correlation observed in the residuals versus fitted values graph (see above).

4) Normality of the error distribution was checked graphically in the following two ways

a) I plotted a q-q plot of the residuals

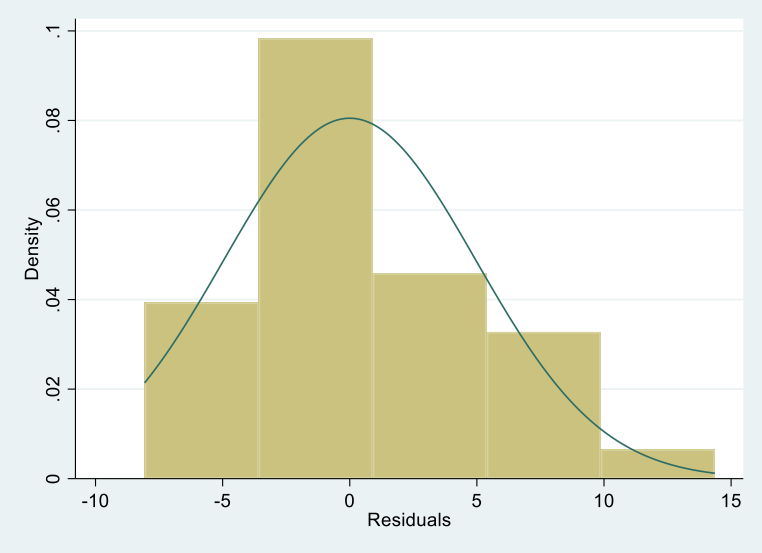
q-q plot of residuals



In the q-q-plot, the plotted residuals do not deviate far from the line of best fit.

b) A histogram of the residuals was plotted

Histogram of residuals



The histogram shows a roughly normal distribution.

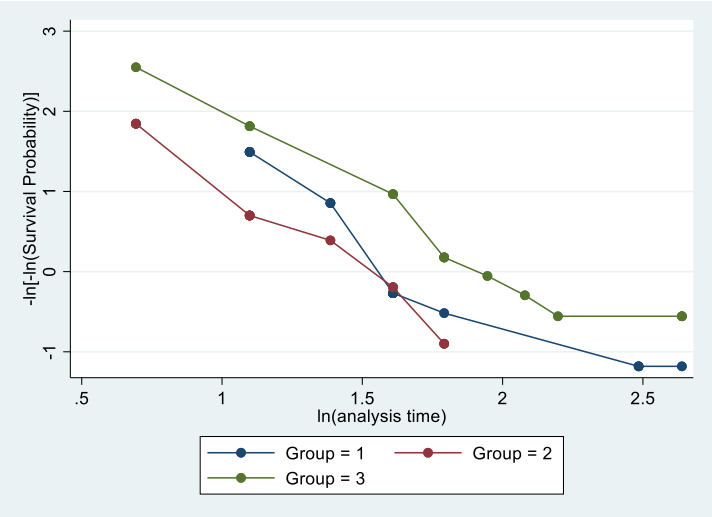
Both of these graphs suggest that the assumption of normality of the residuals is met.

Cox proportional hazard model assumptions

1) Censoring in this analysis is believed to be 'non-informative;' that is, people who dropped out of the study do not appear to be related to study procedures.

2) Two methods were used to check that the hazards for any two groups were proportional over time:
    a) Graphical assessment using a Log-log plot

Figure 1 – Log-log plot



Key: Group 1: Antibiotic alone; Group 2: Antibiotics and cranberry; Group 3: Immediate cranberry and delayed antibiotics

As the lines are roughly parallel and do not cross each other, this model assumption is met by the data.

b) Schoenfeld residuals to check goodness of fit

Test of proportional-hazards assumption

Time: Time

	chi2	df	Prob>chi2
global test	0.31	5	0.9974

The global test for the model has a chi squared value of 0.43 and a p value of 0.9974. Therefore, the null hypothesis that the hazards are proportional for this model is not rejected.

Appendix 4. 1 CUTI Interview study Participant Information Leaflet

CRANBERRIES FOR URINARY TRACT INFECTIONS

PARTICIPANT INFORMATION LEAFLET (CUTI Interview study)

You are being asked to take part in an interview study. Before you decide if you want to take part or not, it is important for you to understand why the research is being done and what it will involve. This leaflet aims to tell you about the purpose of this study and what will happen to you if you decide to take part.

Please ask us if there is anything that is not clear or if you would like more information.

CUTI Study Office:

Nuffield Department of Primary Care Health Sciences

University of Oxford

Radcliffe Observatory Quarter

Oxford

OX2 6GG

Phone: 01865 289067

1. What is the purpose of the study?

We are currently running a trial (called the 'CUTI' trial) in which women are being divided into three treatment groups to test whether cranberry capsules can help treat urinary tract infections (UTIs). Group 1 receive antibiotics to treat their UTI, group 2 receive antibiotics *and* cranberry capsules, and group 3 receive cranberry capsules with a back-up antibiotic prescription in case they don't get better with cranberry capsules alone. The main aim of this trial is to test whether the way we do this research works and is acceptable to the women who take part (called a 'feasibility trial'). This will help us to plan a similar but bigger trial. By comparing the information from different treatment groups in the bigger trial, we will be able to tell whether cranberries actually treat UTIs, reducing the need for antibiotics.

In order to help us understand better how to run the bigger trial successfully, in addition to comparing measurable data from the feasibility trial (e.g. the *number* of people in each group who required antibiotics), we also need to explore data that cannot be measured (e.g. how women *feel* about taking part in the feasibility trial). The best way to do this is through interviews (called 'qualitative research').

We intend to interview some women who take part in the feasibility trial, as well as some women who do not participate in the trial but have experience of UTIs. We want to explore women's experience of having UTIs, what influences the way they seek help for UTIs, their attitudes towards self-care/alternative treatments, their experience (if applicable) of participating in the CUTI trial and what might influence somebody to want, or not want, to take part in the CUTI trial.

This information, combined with measurable data that we obtain from the feasibility trial, will provide deep insights into why our feasibility trial does or doesn't work, and will help us to plan a successful bigger trial. This study is being led by Dr Kome Gbinigie and forms part of her doctoral research.

2. Why have I been invited?

We are inviting two groups of women. You are being invited because either:
1) You are also taking part in the CUTI trial.
2) You are not taking part in the CUTI, but you have experienced at least one UTI in the past year.
We would like to interview you to find out your experience of having had a UTI, what influences the way you seek help for UTIs, your attitude towards self-care/alternative treatments (e.g. cranberry capsules), your experience (if applicable) of participating in the CUTI trial and also what might influence you to want, or not want, to take part in the CUTI trial.

3. Do I have to take part?

No. You are free to decide whether or not to take part. If you decide to take part you are still free to withdraw from the study at any time, without giving a reason. A decision not to take part or to withdraw will not affect the standard of care you receive from the healthcare team.

4. What will happen to me if I agree to take part?

The interview will be arranged at a time to suit you. We anticipate that the interview should take no longer than an hour and can be carried out in person, in your own home or other preferred place, or by telephone, whichever you prefer. The interview will be audio recorded with your consent.

Before starting the interview you will be asked to sign a form (called a 'consent' form) to confirm that you fully understand what taking part in the study will involve and that your questions about the research have been answered. If you decide to be interviewed by telephone, we will ask you to sign a consent form and post it back to the research team before the telephone interview takes place. You will be provided with a freepost envelope.

If you are interested in taking part please contact the research team by returning your reply slip or by contacting the research team using the details provided in Section 14 below. The research team will be able to answer any questions you have and make sure you understand the study information. You will be given as long as you need to decide whether or not to take part.

5. What are the possible disadvantages and risks of taking part?

We do not anticipate that the interview will cause you emotional distress. If at any stage you do not wish to answer a question, that's fine. Just let the researcher know. If you are feeling distressed during the interview, you can take a break, continue on another day, or stop the interview altogether. You may also wish to speak to your GP for support.

6. What are the possible benefits of taking part?

After you have completed the interview, you will receive a £10 voucher as a thank you for taking part in this study.

Taking part in this study will help us to design a large study to test the use of cranberry capsules in treating UTIs in women. The results of the larger study may help us to safely reduce antibiotic use in women with simple UTIs.

7. Will my taking part in this study be kept confidential?

With your permission the interview will be audio-recorded to make an accurate record of what is said and then the recording will be stored on a secure computer on University of

Oxford premises. The recording will be sent securely to an independent transcription company who will type up the recording. This company will hold a confidential agreement with the University of Oxford. This written record will not include the names or other defining details that can identify you, to ensure confidentiality. Once the recording has been transcribed, the recording will be stored securely on University of Oxford premises until the end of the study and then deleted. De-identified transcripts will be stored at the University of Oxford and may be accessed by researchers for future research studies. Other study documents will be stored for 5 years following the end of the study and then destroyed. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. The findings from this study will be used in research reports but no names will be included in the report so any quotes from the interview will be de-identified. The only time that your interview would not remain confidential is if it were possible that you or someone else were at risk, but this would be discussed with you first. You will be assigned a participant ID number and identified by this on study documents and electronic databases.

8. What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

We will be using information from your medical records and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 6-12 months after the study has finished. We will store the de-identified research data and any research documents with personal information, such as consent forms, securely at the University of Oxford for 5 years after the end of the study. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at:
http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/]

Data which does not identify you will be stored by the study team and may be used in future research projects.

You can find out more about how we use your information by contacting the Chief Investigator using the details at the end of this sheet.

9. What happens if I change my mind?

Taking part in this research is voluntary. If you do not want to take part in the research you can withdraw yourself and your data at any time and without giving a reason. If you withdraw from the study your data will be withdrawn from our records. Withdrawing from the study will not affect the standard of care you receive from the healthcare team. If you would like to withdraw at any time we would ask you to let one of the research team know. If you lose the ability to confirm that you are happy to proceed with the study (i.e. if you lose the capacity to consent to ongoing participation), information collected up until this point will be kept.

10. What if there is a problem?

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Dr Kome Gbinigie (Chief Investigator) on 01865 289067 or cuti@phc.ox.ac.uk, or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrg@admin.ox.ac.uk.

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

11. What will happen to the results of the research study?

We aim to publish the results so that scientists and doctors are aware of the findings. With your consent we would like to use anonymous quotes from interviews to be included in the research reports. We will also provide your GP practice a copy of our findings for them to display. You will not be personally identifiable in any publication.

12. Who is organizing and funding the research?

This study is sponsored by the University of Oxford and the funding for this research comes from the NIHR School for Primary Care (SPCR) and the Wellcome Trust.

13. Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by South Central Research Ethics Committee.

14. Do you have any further questions or concerns?

If you want to discuss the study please contact Dr Kome Gbinigie, Chief Investigator, by email (cuti@phc.ox.ac.uk) or telephone (01865 289067).

Thank you for taking the time to read this information leaflet.

Appendix 4. 2 Patient reply slip – CUTI Interview study



Patient reply slip – CUTI Interview study

Name ……

I am willing to be contacted by the research study team for the above interview study.

Email [please print]……

Phone ……

Best day and time to contact……

Signature:…… **Date:**……

Please complete the above information and return in the enclosed FREEPOST envelope







Appendix 4. 3 CUTI Interview Study – Participation Invitation Letter

GP PRACTICE HEADED PAPER

Date:_____

Dear [Patient's name],

Re: Cranberries for Urinary Tract Infections (CUTI): An interview study

We have identified that you have had a urinary tract infection (UTI) in the past 12 months and we would like to invite you to take part in an interview study. The study is being led by researchers at the University of Oxford. During the interviews, the researchers will be asking women about their experiences of having a UTI, their views on self-care and seeking help for treatment, and their views on the use of alternative treatments (like cranberry extract).

Enclosed is a Participation Information Leaflet which gives you more information about the study and what it would involve for you. You will receive a £10 voucher for taking part.

If you are interested in taking part, please complete the reply slip and return it in the enclosed FREEPOST envelope. If you have any questions about taking part, please contact the study team using the details below.

Yours sincerely,

Cowley Road Medical Practice.

Name of lead study investigator: Dr Kome Gbinigie

Lead study investigator's address: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

Lead study investigator's email address: cuti@phc.ox.ac.uk

Lead study investigator's phone number: 01865 289067

Funded by NHS National Institute for Health Research

Appendix 4. 4 Topic Guide for UTI Patient Interviews

Patient Interview Guide

Research Study: Cranberries for Urinary Tract Infections (CUTI): Interview Study

Investigators: Dr Kome Gbinigie, Dr Anne-Marie Boylan, Professor Carl Heneghan, Professor Chris Butler

Topics to be explored: Below is a list of questions to be explored in this study. This is intended to be used as a guide and not as a prescriptive tool. As is good practice in qualitative research, the participants' experiences will be prioritised. This means the same questions may not be asked of all participants in the same order. As new ideas emerge from data collection, new topics and questions may be developed.

Briefing:

CONTACT A-MB

1) Thank participant for agreeing to take part and introduce self.

2) This interview is for the Cranberries for UTI (CUTI) study. The patient information leaflet has hopefully given you some background about why I'm speaking to you today. I'm going to speak to you about your experience of having a UTI and your thoughts on the CUTI trial, in which we are looking at using cranberries to help treat UTIs. I'll be asking you lots of questions, but you're the expert in this and I'll be guided by you. I hope you don't mind; I might jot down some notes as I go along to help remind me of some important points and things to ask you.

3) If at any time during the interview you do not wish to answer a question, that's fine. Just let me know.

4) As you know from the information you were given about the study, I would like to digitally record our conversation. The recording will be typed out, but everything you say will be anonymous. Your name and any names you mention, and any places you mention will be taken out, so that if someone read your interview they would not know who you are.

5) Your interview will remain confidential, unless (as outlined in the information leaflet) it is possible that you or someone else is at risk, but this will be discussed with you first.

6) If at any stage you wish to stop the audio recorder, please let me know.

7) Do you have any questions?

8) Just before I start recording, do you mind if I ask you a few questions about your background? This is just so that we can try to talk to people from a range of backgrounds.

Age in years ☐

18-30 ☐
31-50 ☐
51-64 ☐
65+ ☐

Marital status (Mark with an 'x')**:**
Single, never married ☐
Married or domestic partnership ☐
Widowed ☐
Divorced ☐
Separated ☐

Employment status (Mark with an 'x')**:**
Employed for wages ☐
Self-employed ☐
Out of work and looking for work ☐
Out of work but not currently looking for work ☐ (Please see overleaf)
Homemaker ☐
Student ☐
Retired ☐
Unable to work ☐

What is the highest level of school or degree you have completed (Mark with an 'x')?
No schooling completed ☐
Some secondary school ☐
GCSE level ☐
A-level ☐

☐

College qualification or equivalent
Trade/technical/vocational training ☐
University bachelor's degree ☐
Master's degree ☐
Doctorate degree ☐
Other (Please specify) ☐

Please specify your ethnic group (Mark with an 'x'):

White
English / Welsh / Scottish / Northern Irish / British ☐
Irish ☐
Gypsy or Irish Traveller ☐
Any other White background, please describe ☐

Mixed / Multiple ethnic groups
White and Black Caribbean ☐
White and Black African ☐
White and Asian ☐
Any other Mixed / Multiple ethnic background, please describe ☐

Asian / Asian British
Indian ☐
Pakistani ☐
Bangladeshi ☐
Chinese ☐
Any other Asian background, please describe ☐

Black / African / Caribbean / Black British
African ☐
Caribbean ☐
Any other Black / African / Caribbean background, please describe ☐

Other ethnic group
Arab ☐
Any other ethnic group, please describe ☐

GP practice: _____

For CUTI Trial participants

PART A – Before CUTI trial recruitment

1) I'd like you to tell me all about the last UTI you had. What it felt like, what you thought was wrong, what you did and when you went to see someone about it? Everything about it. So, could you start by telling me what happened from the moment you noticed something was wrong?

Prompts: What was it like? How did you first realise that you were unwell? What sort of symptoms did you have? What do you think caused it?

2) What did you do when you realised that something was wrong?

Prompts: Did you try anything for your symptoms before you contacted your GP/healthcare provider? If so, what did you take? Where did you get it from? Did you ask anyone else for advice? Did you try any over the counter medicines? Did you try any alternative treatments/homeopathy?

3) What made you contact your GP/healthcare provider?

Prompts: How long after your symptoms started did you contact your GP/healthcare provider? Would you normally have gone in to see your healthcare provider/GP, i.e. if you hadn't agreed to take part in the CUTI trial? What were you hoping for or expecting from your GP/healthcare provider? Did you find it difficult deciding when to go/contact them? Why is that? Was there any particular trigger that made you contact your GP/healthcare provider?

PART B – Self-care and alternative treatments for UTIs (e.g. cranberry capsules/extract)

I would now like to ask you a bit about your general thoughts on/experience of managing UTIs, self-help and alternative treatments for UTIs.

1) How do you feel about being prescribed antibiotics for UTIs?

Prompts: What are your thoughts on and experiences of taking antibiotics? Do you feel that antibiotics are always required? Have you had any problems with them (if applicable)? Do they work for you (if applicable)? What are your thoughts on the cost of getting a prescription for an antibiotic? Does this influence whether or not you contact your GP?

2) What do you think about treatments that you can buy over the counter?

Prompts: Have you tried anything other than antibiotics? Do you ever try painkillers? Have you tried/do you know of/what are your thoughts on alternative treatments? Do you have/would you have any concerns about trying these types of treatments? Would you consider them alongside or instead of antibiotics? Where do you go to get non-antibiotic treatments? Do you go to health shops/pharmacy/herbal medicine shops? What are your thoughts on the cost of over the counter treatments? What are your thoughts on the use of cranberry?

3) Have you ever discussed over the counter/non-antibiotic treatments for UTI with your GP/pharmacist/healthcare provider?

Prompts: If yes, what did they say? Were they positive, negative or neutral about them? Does your GP/pharmacist/healthcare provider's thoughts influence how you feel about alternative treatments?

4) What do you do to look after yourself when you have a UTI?

Prompts: Have you ever tried drinking more fluids/water? Do you think that there are any actions that you can take to prevent/treat UTIs?

PART C – CUTI trial recruitment and experience

I would now like to ask you some questions about your experience of being in the CUTI trial.

1) How did you find out about the CUTI trial?

Prompts: Who told you about it?

2) Why did you take part in the trial?

Prompts: What were your thoughts when you were told about the trial?

3) Could you talk me through what happened when you were told about the trial, before deciding to take part?

Prompts: What was the consultation like? What did your GP/healthcare provider/researcher say?

4) What happened during the rest of your consultation with the GP/healthcare provider/researcher?

Prompts: How was the consent process? Which group were you placed into (e.g. antibiotics alone, antibiotics and cranberry capsules, or cranberry capsules and delayed antibiotics? Were the instructions given to you by the person who consented you clear?

5) Could you tell me what it has been like for you to take part in the CUTI trial?

Prompts: Were there any problems? Was there anything that might put people off taking part? What were the worst things about taking part? How did you feel about the group that you were put in? Is there a group that you were hoping to be in? Is there a group that you didn't want to be in? How did you feel about being randomly assigned to a group? What were the best things about taking part?

6) How did you feel about being asked to provide a urine sample?

7) How did you find using the electronic symptom diary? (Can show paper copy)

Prompts: Were there any difficulties? Was it easy to remember to use the diary? What are your thoughts on completing an electronic diary? How did you find rating your symptoms on a scale from 0-50? Did you complete it using a computer/laptop or a mobile phone? What

would be your thoughts on using a mobile phone app? Do you have any thoughts on what the app should look like? What might make it easy for you to use?

8) You should have received daily email reminders for 2 weeks after you were recruited to the trial to remind you to complete the electronic symptom diary – how was that?

Prompt: If received, was this acceptable to you? If not received, would this have been helpful/acceptable to you? What would your thoughts be on receiving text message reminders instead?

9) A member of the research team should have contacted you 2 weeks after you were recruited to the trial – did this happen? If yes, how was that?

Prompts: Was the length of the phone call okay? Were the questions okay? Did you receive a phone call at day 3? If so, how did you find that?

How did you find being asked to be interviewed? Can you think of reasons that people might not like to be interviewed as part of the study?

10) Did you have to see a healthcare professional/GP/out of hours/ED/hospital after you were recruited to this study, due to a complication/problem related to this study? If yes, could you tell me what happened?

Prompts: Who did you see? How did you feel? Did you have to take time off work/your usual activities?

11) Is there anything we could change to make it easier for people to take part in this study?

Prompts: Do you think that there are things that we could make easier? Do you think that there are things that we should/should not do?

12) How would you have felt if you could have been randomised to a group that had a placebo (i.e. sugar pill)? Advice to take a placebo, but with a back-up prescription for antibiotics if needed? You would still be able to take painkillers and other OTC medicines as needed.

Prompts: How would you feel if you were put in this group only if you were happy to try to delay antibiotics? What would your thoughts be on a study in which you receive immediate antibiotics (with PLA or cranberry) if you don't want to delay antibiotics, and in which you receive immediate cranberry or PLA (with back-up antibiotics) if you are willing to delay taking antibiotics? Is there any group that you would not like to be in? Why?

13) How would you feel if we focussed the study only on women with milder symptoms? In this case, we might have two groups to see whether we can help them to delay antibiotics. Either back-up antibiotics, or cranberry+ back-up antibiotics.

Prompts: How would you feel about this design? Would you take part? Do you think that this answers a helpful question?

14) Is there anything else you would like to mention that we haven't talked about?

That is the end of the interview, thank you very much for taking part.

END

Contact A-MB

For non-CUTI Trial participants

PART A – Your UTI experience

1) I'd like you to tell me all about the last UTI you had. What it felt like, what you thought was wrong, what you did and when (or if) you went to see someone about it? Everything about it. So, could you start by telling me what happened from the moment you noticed something was wrong?

Prompts: Prompts: What was it like? How did you first realise that you were unwell? How did you know it was a UTI? What sort of symptoms did you have? How long did it take for you to feel completely better?

2) What did you do when you realised that something was wrong?

Prompts: Did you try anything over the counter for your symptoms (before you contacted your GP/healthcare provider)? Did you ask anyone else for advice?

3) What made you contact your GP/healthcare provider (if applicable)?

Prompts: If yes, was there any particular trigger that made you contact your GP/healthcare provider? How long after your symptoms started did you contact them? What were you hoping for or expecting from your GP/healthcare provider?

4) (If applicable) Did you have any examinations or tests?

Prompts: What sort? How did these go? If none were done, were you expecting any?

5) (If applicable) What did the GP/healthcare provider suggest to improve your symptoms?

Prompts: What advice were you given? Were you advised to use any particular medications?

6) (If applicable) Did your doctor prescribe you antibiotics?

Prompts: How did you feel about this? Did you feel you needed them?

7) (If applicable) How do you feel about the consultation that you had with your GP/healthcare provider?

Did you feel you got the right treatment? Did you feel you got the right information? **8) What happened during the rest of your UTI episode?**

How long did it take for your UTI to get better? Did you have any problems with the treatments that you tried? (If applicable) Did you have to return to see your GP/ a healthcare professional? If so, why?

PART B – Self-care and alternative treatments for UTIs (e.g. cranberry capsules/extract)

I would now like to ask you a bit about your thoughts on/experience of managing UTIs, self-help and alternative treatments for UTIs.

1) How do you feel about being prescribed antibiotics for UTIs?

Prompts: What are your thoughts on and experiences of taking antibiotics? Do you feel that antibiotics are always required? What are your thoughts on the cost of getting a prescription for an antibiotic? Does this influence whether or not you contact your GP?

2) What do you think about treatments that you can buy over the counter?

Prompts: Have you tried anything other than antibiotics? Do you ever try painkillers? Have you tried/do you know of/what are your thoughts on alternative treatments? Do you have/would you have any concerns about trying these types of treatments? Would you consider them alongside or instead of antibiotics? Where do you go to get non-antibiotic treatments? Do you go to health shops/pharmacy/herbal medicine shops? What are your thoughts on the cost of over the counter treatments? What are your thoughts on the use of cranberry?

3) Have you ever discussed over the counter/non-antibiotic treatments for UTI with your GP/pharmacist/healthcare provider?

Prompts: If yes, what did they say? Were they positive, negative or neutral about them? How might their thoughts influence how you feel about non-antibiotic treatments for UTIs?

4) What do you do to look after yourself when you have a UTI?

Prompts: Have you ever tried drinking more fluids/water? Is there anything you feel you can do to prevent you from getting a UTI?

PART C – Your thoughts on the CUTI trial

You will be aware that at the moment we are asking women who have a UTI to take part in a trial (called the 'CUTI' trial) in which they are being randomly assigned to different treatment groups to test whether cranberry capsules can help treat urinary tract infections (UTIs). *The main aim of this trial is to test whether the way we do this research works and is acceptable to the women who take part (called a 'feasibility trial').* This will help us to plan a similar but bigger trial.

I would like to tell you a bit about the trial, and then find out how you might feel if you were asked to take part.

Women with a UTI who agree to take part in the study are randomly divided randomly into three different groups:

1) Advice to take antibiotics

2) Advice to take antibiotics and cranberry capsules

3) Advice to take cranberry capsules alone. Women in this group would be given a delayed prescription for antibiotics, with advice to start taking antibiotics if their symptoms don't get better in the next 3-5 days.

- Women will be advised to seek medical help if they develop any symptoms of an upper UTI (e.g. vomiting, fever, back pain)

1) What are your thoughts on this?

How does this trial sound to you? Is it something you might be interested in taking part in? How important/valuable do you think this research is? How might you feel about being randomly being put into a group? Is there any group that you might like to be put in? Is there any group that you might not wish to be put in? Is there anything that we could do that you feel might make people feel happier to be in group 3 (cranberry+ delayed abx)?

- Women taking part are emailed a link to an electronic symptom diary to complete over a period of up to 2 weeks (until all symptoms have resolved), with daily reminders to complete the diary. The main part of the diary is rating symptoms daily on a scale of 0-50 (Show them the paper version of the scale)

2) What are your thoughts on this?

Prompts: Does it sound difficult? Would you remember to complete the symptom diary daily? How might you find completing an electronic diary? What would your thoughts be on receiving text message reminders instead? What would you think about having the diary as a mobile phone app? Do you have any thoughts on what the app should look like? What might make it easy for you to use?

3) What are your thoughts on the scale?

Prompts: Do you think it's clear? How do you think this compares to a smaller scale (e.g. 0-6)?

- Participants should also receive a call from someone in the research team 2 weeks after they start the trial as a final encouragement to participants to complete the symptom diary? Participants are also asked whether they are happy to receive information about being interviewed as part of the study.

5) What are your thoughts on this?

Prompts: How would you find this? What might be the positives and negatives in your opinion? Can you think of reasons that people might not like to be interviewed as part of the study?

6) What are your thoughts overall on the trial that I've described to you?

Prompts: Do you think that you would take part? Why, or why not? Do you think that there is anything that could/should be changed/adjusted/removed/added in? Do you think that there is anything that might put people off taking part? What do you think might encourage people to take part?

7) How would you have felt if there were an additional group that you could be randomised to, in which you would take a placebo (i.e. sugar pill)? Advice to take a placebo, but with a back-up prescription for antibiotics if needed? You would still be able to take painkillers and other OTC medicines as needed.

Prompts: How would you feel if you were put in this group only if you were happy to try to delay antibiotics? What would your thoughts be on a study in which you receive immediate antibiotics (with PLA or cranberry) if you don't want to delay antibiotics, and in which you receive immediate cranberry or PLA (with back-up antibiotics) if you are willing to delay taking antibiotics? Is there any group that you would not like to be in? Why?

8) **13) How would you feel if we focussed the study only on women with milder symptoms? In this case, we might have two groups to see whether we can help them to delay antibiotics. Either back-up antibiotics, or cranberry+ back-up antibiotics.**

Prompts: How would you feel about this design? Would you take part? Do you think that this answers a helpful question?

9) Do you have any more questions about the CUTI trial?

10) Is there anything else you would like to mention that we haven't talked about?

That is the end of the interview, thank you very much for taking part.

END

Contact A-MB

Appendix 4. 5 UTI Patient Interview study Informed Consent Form

CRANBERRIES FOR URINARY TRACT INFECTIONS

INFORMED CONSENT FORM – CUTI Interview study

Chief Investigator: Dr Kome Gbinigie. **Address:** Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG. **Email:** cuti@phc.ox.ac.uk **Telephone:** 01865 289067

Study Title: CUTI Interview study **Participant ID number: _____**

If you are happy to take part in this research then please read each of the statements below and initial the boxes if you agree with them.

Please initial each box

1. I confirm that I have read and understood the information sheet version [number], dated [date month year] for the CUTI interview study and have had the opportunity to ask questions and had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

3. I understand that my interview will be audio-recorded and that the interview will be transcribed by an independent person who will transcribe the interview verbatim (word for word). ☐

4. I understand that data collected during the study may be looked at by individuals from the University of Oxford or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

5. I understand that the information that I have given to researchers will be transferred to Oxford University and stored securely. I give permission for the research team to use anonymous data collected as part of this study for future research. ☐

6. I give permission for anonymous quotes from interviews to be included in reports of the findings from the research. ☐

7. By signing this consent form, I agree to participate in the CUTI interview study. ☐

Participant name: …… Name of person taking consent:……..

Date:…… Date:……

Signature:…… Signature:…….

When completed, one copy should be given to the participant, one copy should be kept by the research team and one copy should go in the participant's medical notes

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Funded by NHS National Institute for Health Research

Appendix 5. 1 Recruiter Interview invitation letter and reply slip

CUTI
CRANBERRIES FOR URINARY TRACT INFECTIONS

Invitation to be interviewed

Recruiter interview sub-study: Does cranberry extract reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections? A feasibility study (CUTI study).

You are receiving this invitation because you were involved in recruitment to the CUTI study. We would like to interview you to learn more about your experience of recruiting to this study.

CUTI is a research trial in which women with UTI symptoms were treated in one of three different ways; with antibiotics, or with antibiotics and cranberry capsules, or with cranberry capsules and a 'back-up' antibiotic prescription to take if their symptoms didn't get better in 3-5 days, or got worse. We hope to conduct a study of similar design but on a larger scale. Getting information from you about your experience of recruiting to the study will help us to plan for the larger trial.

This interview study is being led by researchers at the University of Oxford. Attached is a Participation Information Leaflet, which gives you more information about the interview and what it would involve for you.

If you are interested in taking part in the interview, please complete the attached reply slip and return it by email to the email address below. If you have any questions about taking part, please contact the study team using the details below.

Name of lead study investigator: Dr Kome Gbinigie

Lead study investigator's address: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

Lead study investigator's email address: cuti@phc.ox.ac.uk

Lead study investigator's phone number: 01865 289067

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Funded by NHS National Institute for Health Research

Participant reply slip – CUTI recruiter interview sub-study

Name ……

I am willing to be contacted by the research study team for the above interview study.

Email ……

Phone ……

Best day and time to contact……

Signature:…… **Date:**……

Please complete the above information and return by email.

Appendix 5. 2 Recruiter Interview Participant Information Leaflet



PARTICIPANT INFORMATION LEAFLET – CUTI recruiter interview sub-study

You are being asked to take part in a research study. Before you decide if you want to participate or not, it is important for you to understand why the research is being done and what it will involve. This leaflet aims to tell you about the purpose of the study and what will happen to you if you decide to take part.

Please ask us if there is anything that is not clear or if you would like more information.

CUTI Study Office:

Nuffield Department of Primary Care Health Sciences

University of Oxford

Radcliffe Observatory Quarter

Oxford

OX2 6GG

Phone: 01865 289067

1. What is the purpose of this study?

You have been involved in recruiting participants to the Cranberries for Urinary Tract (CUTI) feasibility trial. In this feasibility trial, women with a suspected UTI were invited to take part and were randomly assigned to one of three groups:

1) Group 1 - Usual treatment with antibiotics.
2) Group 2 - Treatment with antibiotics AND cranberry capsules.
3) Group 3 - Initial treatment with cranberry capsules. Women in this group were also given a 'back-up' prescription of antibiotics to take in case their symptoms did not get better within 3-5 days, or got worse.

The main aim of this small-scale (feasibility) study is to test whether the study design described works and is acceptable to participants (called a 'feasibility' study). We hope that this will help in the planning of a subsequent, similar, but much larger study. We are interested to know your experience of recruitment to this study as part of a process evaluation. We hope to use this information to help plan for the larger trial.

2. Why have I been invited to take part?

You have been invited to take part because you were involved in recruiting participants to the CUTI feasibility trial.

3. Do I have to take part?

No. You are free to decide whether or not to take part. If you decide to take part you are still free to withdraw from the study at any time, without giving a reason. You have the right to refuse permission for researchers to use your interview responses. Should you wish to request that information is not used in the study, you can speak directly to the chief investigator (Dr Kome Gbinigie, contact details below), who will ensure that your contribution is not used. Choosing not to participate, or withdrawing from the study will not affect your job in any way.

4. What will happen to me if I agree to take part?

You will be emailed by a member of the research team. If you are happy to take part in this study, you will be asked to sign and date an informed consent form. Once you have given informed consent, you will be interviewed at a time to suit you. We anticipate that the interview should take no longer than 25 minutes and can be carried out in person, in your own home, your place of work or other preferred place, or by telephone, whichever you prefer. If you decide to be interviewed by telephone, we will ask you to sign a consent form and post it back to the research team before the telephone interview takes place. You will be provided with a freepost envelope. The interview will be audio recorded with your consent.

If you are interested in taking part please contact the research team using the details provided in Section 15 below. The research team will be able to answer any questions you have and make sure you understand the study information. You will be given as long as you need to decide whether or not to take part.

5. What will happen after I have completed the interview?

The research team will review and analyse the interview responses. All people's names/place names/practice names will be removed from the record, to ensure you cannot be idenitifed.

6. What are the possible disadvantages and risks of taking part?

You will be asked to give up time to complete the interview. We do not anticipate that this should take longer than 25 minutes.

7. What are the possible benefits of taking part?

You will receive a £20 voucher after the interview has been completed.

Taking part in this study will help us to design a similar study to this but on a much larger scale (with more participants and in different parts of the country). The results of the larger study may help us to safely reduce antibiotic use in women with simple urinary tract infections.

8. Will my taking part in this study be kept confidential?

With your permission the interview will be audio-recorded to make an accurate record of what is said and then the recording will be stored on a secure computer on University of Oxford premises. The recording will be sent securely to an independent transcription company who will type up the recording. This company will hold a confidential agreement with the University of Oxford. This written record will not include the names or other defining details that can identify you, to ensure confidentiality. Once the recording has been transcribed, the recording will be stored securely on University of Oxford premises until the end of the study and then deleted. De-identified transcripts will be stored at the University of Oxford and may be accessed by researchers for future research studies. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. The findings from this study will be used in research reports but no names will be included in the report so any quotes from the interview will be de-identified. The only time that your interview would not remain confidential is if it were possible that you or someone else were at risk, but this would be discussed with you first. You will be assigned a participant ID number and identified by this on study documents and electronic databases.

9. What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of

Oxford is the data controller and is responsible for looking after your information and using it properly.

We will be using information from you in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 6-12 months after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for 5 years after the end of the study. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at:
https://compliance.web.ox.ac.uk/individual-rights

Data which does not identify you will be stored by the study team and may be used in future research projects.

You can find out more about how we use your information by contacting the Chief Investigator using the details at the end of this sheet.

10. What if I do not want to take part and/or do not want to carry on with the study once I have started?

If you do not want to take part in the research you can withdraw at any time without affecting your job. If you withdraw from the study your data will be withdrawn from our records. If you would like to withdraw at any time we would ask you to let one of the research team know. If you lose the ability to confirm that you are happy to proceed with the study (i.e. if you lose the capacity to consent to ongoing participation), information collected up until this point will be kept.

11. What if there is a problem?

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Dr Kome Gbinigie (Chief Investigator) on 01865 289067 or email cuti@phc.ox.ac.uk, or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrg@admin.ox.ac.uk. The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

12. What will happen to the results of the research study?

The main aim is to use the information to inform the design and conduct of a subsequent, similar, but much larger study. We may publish the results so that scientists and doctors are aware of the findings. If you would like to receive a copy of the findings, please contact Dr Kome Gbinigie (Chief Investigator) on 01865 289067 or cuti@phc.ox.ac.uk and a copy of the findings can be sent to you directly. You will not be personally identifiable in any publication.

13. Who is organizing and funding the research?

This study is sponsored by the University of Oxford and the funding for this research comes from the NIHR School for Primary Care Research (SPCR) and the Wellcome Trust. Indena S.p.A (an Italian company) supplied the cranberry capsules (Redicran capsules) for this study; they have no other involvement with the study.

14. Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by South Central – Oxford B Research Ethics Committee.

15. Do you have any further questions or concerns?

If you want to discuss the study please contact Dr Kome Gbinigie, Chief Investigator, by email (cuti@phc.ox.ac.uk) or telephone (01865 289067).

Thank you for taking the time to read this information leaflet

Appendix 5. 3 Recruiter Interview Informed Consent Form

INFORMED CONSENT FORM – CUTI recruiter interview sub-study

CUTI
CRANBERRIES FOR URINARY TRACT INFECTIONS

Chief Investigator: Dr Kome Gbinigie. **Address:** Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG. **Email:** cuti@phc.ox.ac.uk **Telephone:** 01865 289067

Study Title: CUTI recruiter interview study **Participant ID number:** _____

If you are happy to take part in this research then please read each of the statements below and initial the boxes if you agree with them.

Please initial each box

1. I confirm that I have read and understood the information sheet version [number], dated [date month year] for the CUTI recruiter interview and have had the opportunity to ask questions and had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my job or legal rights being affected. ☐

3. I understand that my interview will be audio-recorded and that the interview will be transcribed by an independent person who will transcribe the interview verbatim (word for word). ☐

4. I understand that the data collected during the study may be looked at by individuals from the University of Oxford or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐

5. I give permission for de-identified quotes from the interview to be included in reports of the findings from the research. ☐

6. By signing this consent form, I agree to participate in the CUTI recruiter interview sub-study. ☐

Participant name:..... **Name of person taking consent:**.....

Date:..... **Date:**.....

Signature:..... **Signature:**.....

When completed, one copy should be given to the participant and one copy should be kept in the researcher site file.

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UNIVERSITY OF OXFORD

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Appendix 5. 4 Recruiter Interview topic guide

CRANBERRIES FOR URINARY TRACT INFECTIONS

Recruiter Interview Guide

Research Study: Does cranberry extract reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections? A feasibility study (CUTI): recruiter interview sub-study

Investigators: Dr Kome Gbinigie, Dr Anne-Marie Boylan, Professor Michael Moore, Professor Alistair Hay, Professor Carl Heneghan ,Professor Chris Butler.

Topics to be explored: Below is a list of questions to be explored in this study. This is intended to be used as a guide and not as a prescriptive tool. As is good practice in qualitative research, the participants' experiences will be prioritised. This means the same questions may not be asked of all participants in the same order. As new ideas emerge from data collection, new topics and questions may be developed.

Briefing:
1) Thank participant for agreeing to take part and introduce self.

2) This interview is for the Cranberries for UTI (CUTI) study. The participant information leaflet has hopefully given you some background about why I'm speaking to you today. I'm going to speak to you about your experience of recruiting to and your thoughts on the CUTI trial, in which we looked at using cranberries to help treat UTIs. I'll be asking you lots of questions, but you're the expert in this and I'll be guided by you. I hope you don't mind; I might jot down some notes as I go along to help remind me of some important points and things to ask you.

3) If at any time during the interview you do not wish to answer a question, that's fine. Just let me know.

4) As you know from the information you were given about the study, I would like to digitally record our conversation. The recording will be typed out, but everything you say will be anonymous. Your name and any names you mention, and any places you mention will be taken out, so that if someone read your interview they would not know who you are.

5) Your interview will remain confidential, unless (as outlined in the information leaflet) it is possible that you or someone else is at risk, but this will be discussed with you first.

6) If at any stage you wish to stop the audio recorder, please let me know.

7) Do you have any questions?

PART A – Before starting CUTI trial recruitment

1) Could you tell me your initial thoughts on the CUTI trial, before you started recruiting to the study?

Prompts: How did you first hear about the trial? Did you think it sounded interesting? Did you feel it sounded useful? Did you feel that the study seemed achievable? Did you think it would be easy/hard to recruit to? What did you think about treating a UTI with cranberry? How did you think participants might react to the trial? What made you agree to recruit to this trial?

2) Before the trial started, a site initiation visit took place with the Chief Investigator. Could you tell me your thoughts on/experience of this?

Prompts: What did and didn't go well? Was too much/too little information given? What are your thoughts on the powerpoint presentation? Was the presentation clear? How did the recruitment process seem to you from what was presented? What are your thoughts on the way that electronic recruitment using REDCap/Sentry were explained? Had you used REDCap/Sentry before?

PART B – Recruiting to the CUTI trial

I would now like to ask you a bit about your experience of recruiting to the CUTI trial.

1) How did you feel about approaching participants to take part in the trial?

Prompts: What made it easy or difficult? Is there anything that could have improved this?

2) How did patients generally react when approached to take part in the trial?

Prompts: How do you think they felt about it? What kind of things did they say? Was it easy/hard to recruit patients? What were the reasons that patients gave for declining to take part? Did you notice if there were any types/groups of patients that were more or less likely to take part?

3) How did you find the actual process of recruiting participants?

Prompts: How did you find using REDCap and Sentry systems? Did you encounter any technical problems? Did you need to contact the trial team for help? If so, what was your experience like? How did you find the site file? What do you think about the time that it took to recruit to the trial? Was there any difficulty explaining the different treatment groups to participants and/or issuing cranberry capsules? Did you have any concerns about patients being randomised to the delayed antibiotics group? What was your experience of the scripts for group 3 and the desk prompts?

4) At the end of the study, you may have conducted an electronic notes review. If applicable, could you tell me your experience of this?

Prompts: How did you find accessing the electronic notes review form? Was it easy/hard to complete it? Do you think that there are things that we could make easier?

<u>PART C – Post CUTI trial recruitment</u>

I would now like to ask you some questions about your general thoughts on the CUTI trial.

1) What do you feel could be done to improve the experience for participants (i.e. patient participants) of the trial?

Prompts: Do you think that there are things that we could make easier? Do you think that there are things that we should/should not do?

2) **2) At the two week follow-up call, participants who have given consent are given information about potentially being interviewed about their experience of being in the study.**

Can you think of any reasons that people might not like to be interviewed as part of the study?

3) What do you feel could be done to improve the experience for recruiters to the trial?

Prompts: Could we do anything to make it easier? Do you think that there are things that we should/should not do?

4) We hope to conduct a larger scale trial at a later date. How would you feel about recruiting to this larger study?

Prompts: Would you require any incentives? Do you think that it's important to address the questions being asked by the CUTI trial?

5) Is there anything else you would like to mention that we haven't talked about?

This is the end of the interview, thank you very much for taking part.

END

Appendix 5. 5 Script for recruiters to explain the delayed antibiotics group

"If you are randomly placed in the third group, you will receive cranberry capsules and a prescription for antibiotics. We will ask you not to take the antibiotics immediately, but to start the cranberry capsules and see if there is any improvement in your symptoms. There is evidence to suggest that the cranberry will start to enter your urine within 6 hours, so you might get better with the cranberry alone and be able to avoid antibiotics altogether. However, you are in control and can take the antibiotics whenever you feel you need them."

Appendix 5. 6 Desk Prompt



KEY INCLUSION CRITERIA

- Woman aged 18 years and above with symptoms of an uncomplicated UTI
- Symptom duration 6 days or less

KEY EXCLUSION CRITERIIA

- Already taking cranberry on a regular basis (i.e. 5 days or more per week).
- Known urological tract abnormalities
- Immunosuppressed

STUDY DESIGN

Randomly assigned to:

1. Immediate antibiotics
2. Immediate antibiotics and cranberry capsules
3. Immediate cranberry capsules and back-up antibiotics (women in this group might be able to avoid taking antibiotics)

Appendix 6. 1 Publications, grants, conferences, prizes and courses

Peer-reviewed publications

I have been lead author of **ten** peer-reviewed publications, and have co-authored **six** peer-reviewed publications during my DPhil:

Butler CC, Yu LM, Dorward J, **Gbinigie O**, Hayward G, Saville BR, Van Hecke O, Berry N, Detry MA, Saunders C, Fitzgerald M. *Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial.* The Lancet Respiratory Medicine. 2021 Jul 27.

Hayward, G., Butler, C.C., Yu, L.M., Saville, B.R., Berry, N., Dorward, J., **Gbinigie, O.,** van Hecke, O., Ogburn, E., Swayze, H. and Bongard, E., 2021. *Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE): protocol for a randomised, controlled, open-label, adaptive platform, trial of community treatment of COVID-19 syndromic illness in people at higher risk.* BMJ Open, *11*(6), p.e046799.

Butler, C.C., Dorward, J., Yu, L.M., **Gbinigie, O**., Hayward, G., Saville, B.R., Van Hecke, O., Berry, N., Detry, M., Saunders, C. and Fitzgerald, M., 2021. *Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial.* The Lancet.

Dorward, J., **Gbinigie, O**., Cai, T., Roberts, N.W., Garrett, N., Hayward, G. and Butler, C.C., 2021. *The protease inhibitor lopinavir, boosted with ritonavir, as treatment for COVID-19: a rapid review.* Antiviral Therapy.

Gbinigie, O., Allen, J., Williams, N., Moore, M., Hay, A.D., Heneghan, C., Boylan, A.M. and Butler, C.C., 2021. *Does cranberry extract reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections (CUTI)? A feasibility randomised trial.* BMJ Open, *11*(2), p.e046791.

Gbinigie OA, Spencer EA, Heneghan CJ, Lee JJ, Butler CC. *Cranberry Extract for Symptoms of acute, Uncomplicated Urinary Tract Infection: A Systematic Review.* Antibiotics. 2021 Jan;10(1):12.

- Featured as the cover story of Volume 10, Issue 1 of the Antibiotics journal in January 2021.

Gbinigie, K. and Frie, K., 2020. *Should azithromycin be used to treat COVID-19? A rapid review.* BJGP open.

- This was the second most accessed BJGP Open publication of 2020.

Gbinigie, K. and Frie, K., 2020. *Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review*. BJGP open.

- This was the most accessed BJGP Open publication of 2020.

Gbinigie, O., Allen, J., Boylan, A.M., Hay, A., Heneghan, C., Moore, M., Williams, N. and Butler, C., 2019. Does cranberry extract reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections (CUTI)? Protocol for a feasibility study. *Trials*, *20*(1), pp.1-9.

Cacciatore G, Ugolini A, Sforza C, **Gbinigie O**, Plüddemann A. *Long-term effects of functional appliances in treated versus untreated patients with Class II malocclusion: A systematic review and meta-analysis.* PLoS ONE. 2019 Sept 6.14(9): e0221624.

Gbinigie OA, Onakpoya IJ, Richards GC, Spencer EA, Koshiaris C, Bobrovitz N, Heneghan CJ. *Biomarkers for diagnosing serious bacterial infections in older outpatients: a systematic review.* BMC geriatrics. 2019 Dec;19(1):190.

Gbinigie OA, Ordóñez-Mena JM, Fanshawe T, Plüddemann A, Heneghan CJ. *Limited evidence for diagnosing bacterial skin infections in older adults in primary care: systematic review*. BMC Geriatrics. 2019 Dec;19(1):45.

Gbinigie OA, Ordóñez-Mena JM, Fanshawe TR, Plüddemann A, Heneghan C. *Diagnostic value of symptoms and signs for identifying urinary tract infection in older adult outpatients: Systematic review and meta-analysis.* J Infect. 2018 Jun 30. pii: S0163-4453(18)30190-7. doi: 10.1016/j.jinf.2018.06.012.

Gbinigie O. *Trimethoprim is associated with a greater risk of acute kidney injury and hyperkalaemia in older adults compared with other antibiotics used to treat UTIs*. BMJ Evid Based Med. 2018 Jun 29. pii: bmjebm-2018-110991. doi: 10.1136/bmjebm-2018-110991. – Commentary.

Onakpoya IJ, Walker AS, Tan PS, Spencer EA, **Gbinigie OA**, Cook J, Llewelyn MJ, Butler CC. *Overview of systematic reviews assessing the evidence for shorter versus longer duration antibiotic treatment for bacterial infections in secondary care.* PLoS One. 2018 Mar 28;13(3):e0194858.

Gbinigie OA, Onakpoya IJ, Spencer EA. *Evidence for the effectiveness of pomegranate supplementation for blood pressure management is weak: A systematic review of randomized clinical trials.* Nutrition Research. 2017 Oct 1;46:38-48.

Other publications

Gbinigie, O. *Diagnosing Urinary Tract Infections in older adults – Can we take the sting out of it?* 2018, CEBM website blog, University of Oxford. Cross-posted on NIHR SPCR (School for Primary Care) website.

Gbinigie, O. *Bacterial skin infections in older adults – don't make a rash diagnosis…* 2019, CEBM website blog, University of Oxford.

Gbinigie O, Clark M, Gudgin B, Hamer-Hunt J. *Diagnostic tests for bacterial infections in older adults – unexpected results!* 2019, CEBM website blog, University of Oxford. Cross-posted on NIHR SPCR (School for Primary Care) website.

Frie, K. and **Gbinigie, K**., 2020. *Chloroquine and hydroxychloroquine: Current evidence for their effectiveness in treating COVID-19*. Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences University of Oxford–25th March 2020.

Gbinigie, K. and Frie, K., 2020. *What is the evidence for using macrolide antibiotics to treat COVID-19*. Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences University of Oxford–28th April 2020.

Dorward, J. and **Gbinigie, K**., 2020. *Lopinavir/ritonavir: A rapid review of effectiveness in COVID-19*. Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences University of Oxford–14th April 2020.

Gbinigie, K. and Frie, K., 2020. *Should azithromycin be used to treat COVID-19?* Blog, Nuffield Department of Primary Care Health Sciences website, University of Oxford – 29th May 2020.

Gbinigie OA and Akyea RK. *Should zinc be used for COVID-19 prophylaxis or treatment? A rapid review* [version 1; peer review: awaiting peer review]. Wellcome Open Res 2020, 5:188 (https://doi.org/10.12688/wellcomeopenres.16173.1)

Grants

I was **lead applicant** of two successful grant bids:

1)
Funding body: NIHR School for Primary Care Research (SPCR) Funding Round

Grant number: SPCR-2014-10043

Amount awarded: £110,449

Project: Do cranberry capsules reduce the consumption of antibiotics for symptoms of acute uncomplicated urinary tract infections? A feasibility study.

Role: I was lead applicant

Co-applicants: Professor Chris Butler, Professor Michael Moore, Professor Alistair Hay, Professor Carl Heneghan

Date awarded: 15/3/18

2)
Funding body: NIHR School for Primary Care Research (SPCR) Funding Round

Grant number: SPCR-2014-10043

Awarded: £15,000

Project: Patients' attitudes towards and beliefs surrounding the management of urinary tract infections (UTIs) and participant experiences of the Cranberries for UTI (CUTI) feasibility trial: A qualitative study

Role: I was lead applicant

Co-applicants: Dr Anne-Marie Boylan, Professor Chris Butler, Professor Carl Heneghan

Date awarded: 1/11/18

Conferences

ORAL PRESENTATIONS

International:
'*Does cranberry reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections (CUTI)? A feasibility study'*
I was invited to give an oral presentation of this research at a virtual UTI Symposium, hosted by the University of Wurzburg, Germany:
1) UTI Symposium entitled "Management of UTI in clinical practice:
How to achieve the best use of evidence?" This virtual conference took place on Friday 7th May 2021.

'*Does cranberry reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections (CUTI)? A feasibility study'*
Pre-recorded, virtual oral presentation at:
1) North American Primary Care Research Group (NAPCRG), the conference took place virtually between 20th and 24th November 2020.

'Clinical predictors of Pneumonia in older adults in the community: A systematic review'
Presented at:
1) General Practice Research on Infections Network Conference, Utrecht, Netherlands, 5th October 2018.
2) WONCA conference, Seoul, South Korea, 20th October 2018.
3) North American Primary Care Research Group (NAPCRG), Chicago, 10th November 2018

'What is the diagnostic value of symptoms and signs for identifying Urinary Tract Infection in older adult outpatients?'

Presented at:

1) Urinary Tract Infection Symposium, Oslo, Norway, 6th February 2019.

"Biomarkers for diagnosing serious bacterial infections in older adult outpatients: A systematic review"
Presented at:

1) General Practice Research on Infections Network Conference, Leuven, Belgium, 27th September 2019.
2) North American Primary Care Research Group (NAPCRG), Toronto, 20th November 2019

National:
"the Platform Randomised trial of INterventions against COVID-19 In older people (PRINCIPLE) trial"
I co-led (along with Professor Chris Butler, Professor Richard Hobbs and Professor Phil Evans) a virtual, national press briefing on the background to the PRINCIPLE trial on 28th October 2020, hosted by the Science Media Centre. Thirteen national journalists were present, including representation from the BBC News, Reuters and Telegraph. I gave a 5 minute presentation on the treatments being tested in the trial, the rationale for using them, and also the way that the typical community trial paradigm has been adapted to enable all trial procedures to be conducted remotely.

"Biomarkers for diagnosing serious bacterial infections in older adult outpatients: A systematic review"
Presented at:
1) NIHR School for Primary Care Research (SPCR) Annual Trainees' Meeting, Oxford, 9th September 2019.

"Clinical predictors of serious bacterial infections in older adults in the community: A series of systematic reviews"
Presented at:
1) NIHR School for Primary Care Research (SPCR) Annual Trainees' Meeting, Oxford, 25th September 2018.

Local:
Bathurst Memorial Lecture, Trinity college, University of Oxford, 3rd July 2020.
I was invited to present the findings of my COVID-19 related research (including my rapid reviews on hydroxychloroquine and azithromycin, and my involvement with the PRINCIPLE trial). Due to the pandemic, this was a virtual presentation with an international audience of college benefactors and alumni.

ACCEPTED ABSTRACTS:
'*Does cranberry reduce antibiotic use for symptoms of acute uncomplicated urinary tract infections (CUTI)? A feasibility study'*
Abstract accepted and published in the conference meeting book of General Practice Research on Infections Network (GRIN). This was a virtual, international conference that took place on 25th September 2020.

Prize

I was awarded 1st prize and £250 for submission of my blog 'Diagnosing Urinary Tract Infections in older adults – Can we take the sting out of it?' to the NIHR School for Primary Care Research annual trainees' meeting, 25th September 2018.

Courses

Below is a selection of the courses that I have attended during my DPhil:

Statistics: Designing clinical research and biostatistics – University of Oxford, IT Services – 12th and 13th

February 2020

SPSS: Up and running for academic research - University of Oxford, IT Services – 28th and 30th October 2019

Stata: Introduction and data analysis - University of Oxford, IT Services – 23rd July 2019

Statistics for Clinical Trials - University of Oxford, Department for Continuing Education – 9th – 13th December 2019

Clinical Trial Management - University of Oxford, Department for Continuing Education – 3rd -7th June 2019

Qualitative Research Methods Training Day – University of Oxford, Primary Care Department – 24th July 2019

Introduction to NVivo - University of Oxford, Primary Care Department – 7th June 2019

Building long documents – University of Oxford, IT Services – 26th and 27th May 2020

Writing your thesis – University of Oxford, IT Services – 7th May 2020

Managing your thesis in word - University of Oxford, IT Services – 6th November 2019

Appendix 6. 2 Efficacy trial design

Participant eligibility

The inclusion and exclusion criteria will be largely the same as for the feasibility trial; in brief, women aged 18 years and above contacting primary care with symptoms suggestive of an acute, uncomplicated UTI (see section 3.3.8). Key differences will be that participants must be willing to receive immediate antibiotics, and will be excluded if they are allergic to Nitrofurantoin.

Recruitment and participant procedures

Recruitment will take place in Oxfordshire, Southampton and Bristol. I have already established links with Southampton and Bristol; the CUTI feasibility trial was conducted in collaboration with Professors of Primary care (Professors Moore and Hay) based at the Universities of Southampton and Bristol, respectively. Clinical Research Network (CRN) intelligence will be used to target research active General Practices with diverse ethnic patient populations in each region. This should help to increase diversity of trial participants and the external validity of the trial findings.

Women with symptoms of an acute, uncomplicated UTI presenting to or contacting a participating General Practice will be eligible for recruitment. Given the current COVID-19 pandemic, recruitment will be possible in person and virtually. Virtual recruitment should additionally help with recruitment of women who might otherwise have been unable to attend their General Practice for an in-person appointment (e.g. due to work commitments).

After gaining informed consent, women will be randomly assigned to one of two groups. In both groups, women will receive a prescription for immediate antibiotics –a three day course

of Nitrofurantoin 100 mg twice daily. Given that this is an efficacy trial, it is important that there is consistency in the antibiotic used and duration of the antibiotic course. In the intervention group, women will additionally receive an immediate seven day course of cranberry capsules, containing the equivalent of 72 mg of Proanthocyanidin (PAC) daily (51). In the control group, women will receive an immediate seven day course of placebo capsules, in addition to immediate antibiotics. Cranberry capsules and placebo capsules will look, smell and taste identical.

Women will be sent a link to complete an electronic symptom diary. The interviews that I have conducted with UTI patients suggest that using an electronic diary is appropriate for a study in which women of a range of ages (18 years and above) will be recruited (see section 5.4.3.2). Women will be offered a choice of email and/or text message reminders to complete the electronic diary, in line with feedback from UTI patients (see section 5.4.3.2). Whilst the electronic diary will be similar to the one used in the CUTI feasibility trial, in keeping with the views of UTI patients, a smaller rating scale will be used (see section 5.4.3.2). For example, a seven point Likert scale of 0-6 has been used in some analogous trials (33, 39, 158) . Through the participant instructions and the recruiting clinician, the importance of not consuming any cranberry products during the trial will be highlighted.

Follow-up at Day 14 and Day 28

A two week follow-up call will be conducted with participants to obtain a minimum data set and primary outcome data from women with incomplete diaries, as well as adverse event data.

A review of participants' medical records will take place at 28 days. This review will capture midstream urine culture results (including information on antibiotic sensitivity/resistance), data on total antibiotic consumption attributable to UTI, healthcare attendances, and adverse event/serious adverse event data.

Statistical Analyses

The primary outcome of time to feeling fully recovered will be compared between groups using a hazard ratio estimated using the Cox proportional-hazards model. The models will adjust for age and recruitment sites. A Kaplan-Meier plot of the curves for both groups will be plotted, as well as the median, inter-quartile range and range for both groups. Given that PAC-A in cranberry extract is believed to have specific action against *Escherichia. coli* (*E.coli),* an exploratory subgroup analysis, albeit under-powered, will be conducted to determine the effect size in participants based on whether there was *Escherichia. coli (E.coli)* growth in the urine.

Secondary analyses will include between group comparisons of: the number of courses of antibiotics consumed between groups at day 14 and day 28; symptom measures, such as the mean difference in symptom burden and duration of symptoms rated moderately bad or worse; and, the proportion of adverse events, serious adverse events, and episodes of pyelonephritis.

Qualitative work

Interviews with trial participants and recruiters to the trial will be conducted. These interviews will build upon the qualitative work conducted in the present programme of research, facilitating an iterative process of learning from participants' experiences, and using

this knowledge to improve future research. UTI patients will be asked details about, for example, their experience of taking part in a placebo-controlled trial, their experience of trial procedures (including the electronic diary), and perceived facilitators and barriers to them participating in a future effectiveness trial of cranberry extract. Trial decliners will be asked about perceived barriers and facilitators to them taking part in trials of acute UTI, incorporating cranberry extract and/or placebo.

Trial recruiters will be encouraged to share their experience of being involved in the trial, perceived facilitators and barriers to them recruiting opportunistically to the trial, their thoughts on and experience of recruiting to a trial incorporating placebo, and their thoughts on recruiting to a future effectiveness trial of cranberry extract.

Patient and Public Involvement

Each of the four PPI contributors involved with the present feasibility research are keen to continue their involvement with this research programme. PPI contributors will be involved throughout the trial. They have already confirmed that they feel the efficacy work is important, and they believe the trial design would be acceptable to patients. In due course, they will be asked to scrutinise all public-facing documents, to test the electronic symptom diary; to sit on the TSC committee, to inform dissemination plans, and to provide ongoing insight into what it might be like for participants to be involved in the trial, anticipating barriers to participation.