Journal of Ethnopharmacology 243 (2019) 111935

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

The RUTI trial: A feasibility study exploring Chinese herbal medicine for the treatment of recurrent urinary tract infections.

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ARTICLE INFO

Keywords:
Antimicrobial
Clinical trial
Traditional Chinese medicine*Classifications:*
Clinical studies
Infections
Obstetrics
Gynaecology
And urinary-tract disorder

ABSTRACT

Ethnopharmacological relevance: Chinese herbal medicine (CHM) is a widely used traditional intervention that may have a role to play in addressing the global problem of antimicrobial resistance in conditions such as recurrent urinary tract infections (RUTIs).

Aim of the study: To evaluate the feasibility of administering standardised and individualised formulations of CHM for RUTIs as a Clinical Trial of an Investigational Medicinal Product (CTIMP) within primary care of the UKs National Health Service (NHS).

Materials and methods: Regulatory approval was applied for a placebo controlled, double blinded randomised controlled feasibility trial comparing a) standardised CHM vs placebo administered via General practitioners, and b) individualised CHM vs placebo administered by an experienced CHM practitioner. Primary feasibility outcomes included: gaining regulatory approval, recruitment, randomisation, retention, safety and the relevance of outcomes measures.

Results: Regulatory approval for testing CHM as a CTIMP was successfully obtained. Recruitment to the trial was slow and non-NHS self help networks were required to find participants for the individualised arm (n = 31). Retention and data collection in the standardised arm (n-30) were problematic, but these were acceptable in the individualised arm. The use of a daily symptom diary was not a suitable outcome measure for women with continuous infection. Other measures showed promising preliminary data for the individualised arm on improvement in symptoms, and reduction in antibiotic use during and after the trial.

Conclusion: CHM can fulfil the demanding requirements of a CTIMP study but it may not be feasible at this point in time to recruit and treat via NHS primary care. However acceptable rates of recruitment and retention via self-help groups and promising preliminary results in the individualised arm suggest it would be worth testing this approach in a full trial.

1. Introduction

Acute lower urinary tract infection (also known as UTI, or cystitis), is a bacterial infection of the bladder mucosa characterised by symptoms of burning on urination, urinary frequency including nocturia, and urgency. The most common pathogens causing UTIs are *Escherichia coli* (80%–90%) and *Staphylococcus saprophyticus* (5%–10%). (Milo et al., 2005)

UTIs are the most frequent bacterial infection presented by women in the primary care setting (Butler et al., 2006; Foxman, 2010; Little et al., 2010b; Aydin et al., 2015). Up to half of all women experience one UTI during their lives, and at least 11% report UTIs annually (Kunin, 1994, Silverman et al., 2013). UTI treatment has substantial impact on healthcare resources and accounts for 1%–3% of all general practice consultations in the UK. (Stapleton, 1999) In the US, UTIs result in nearly seven million office visits a year and one million emergency department visits, resulting in 100,000 annual hospitalisation (Foxman, 2010).

Recurrent UTIs (RUTIs) are widely defined as three UTIs in the previous twelve months or two episodes in the previous six months (Albert et al., 2004). Between 20% and 30% of women who have had one UTI will have a recurrence (Sanford, 1975), and around 25% of these will develop subsequent recurrent episodes (Hooton et al., 1996). RUTIs can have a significant negative effect on quality of life (Flower et al., 2014; Renard et al., 2014) and a high impact on healthcare costs as a result of outpatient visits, diagnostic tests and prescriptions. The

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https://doi.org/10.1016/j.jep.2019.111935
Received 27 November 2018; Received in revised form 18 April 2019; Accepted 3 May 2019
Available online 10 May 2019
0378-8741/

Abbreviations

CHM	Chinese Herbal Medicine;
CRN	Clinical Research Network
CTIMP	Controlled Trial of an Investigational Medicinal Product
GMP	Good Manufacturing Practice;
GP	General Practitioner
HPGC	High Pressure Gas Chromatography
HRA	Health Research Authority
IMP	Investigational Medicinal Product
MHRA	Medicines Healthcare Regulatory Authority
NIHR CRN	National Institute for Health Research Clinical Research Network
NRES	National Research Ethics Service
RUTI(s)	Recurrent UTI(s)
SmPC	Summary of Product Characteristics (of an IMP)
TCM	Traditional Chinese Medicine
UTI	Urinary Tract Infection

direct and indirect costs of community-acquired UTIs in the US are estimated at around US Dollars 2.3 billion each year (Foxman, 2010).

Antibiotics are the mainstay treatment for acute and recurrent UTIs. Although they can reduce the duration of severe symptoms in acute episodes (Falagas et al., 2008) (Little et al., 2010a), a recent study showed antibiotic resistance rates of *E. coli* isolates for ampicillin, co-trimoxazole, ciprofloxacin, amoxicillin and nitrofurantoin were 59.8%, 31.8%, 23.4%, 1.9% and 0.9% respectively. (Wong et al., 2017, Wong et al., 2018) It is predicted that antibiotic resistance will continue to increase (Kumarasamy et al., 2010).

Antibiotic prophylaxis can be episodic (for example taken post-coitally) or continuous, typically lasting for between six and twelve months, but potentially extended for up to five years (Franco, 2005). A review of antibiotics for prevention of recurrent UTIs in non-pregnant women found that given continuously for six to twelve months, antibiotics were significantly more effective than placebo in preventing recurrent infection (RR 0.15, 95% CI 0.08 to 0.28; number needed to treat = 1.85, 95% CI 1.60 to 2.20) (Albert et al., 2004). However once prophylaxis is discontinued, even after extended periods of therapy, 50%–60% of women become re-infected within three months (Harding et al., 1982; Car and Sheikh, 2003). Side effects such as urticarial, nausea, diarrhoea and candidiasis can cause considerable discomfort requiring treatment to be withdrawn and may contribute to some women's expressed preference to avoid using antibiotics (Leydon et al., 2010).

Chinese herbal medicine (CHM) has been used to treat the symptoms of UTI for over 2000 years (Maciocia, 1994). A Cochrane Review (Flower et al, 2015) of studies conducted in China suggested that CHM used either on its own, or with antibiotic treatment, may be more effective than antibiotics alone for relieving acute UTIs and preventing recurrent episodes. A small prospective case series of fifteen women receiving CHM treatment for RUTIs conducted in the UK showed encouraging results with all fourteen of the women who completed the study reporting an improvement in their condition (Flower, 2012).

The biological plausibility of CHM for recurrent UTI is supported by in vitro research suggesting that some commonly used Chinese herbs may have diuretic, antibiotic, immune enhancing, antipyretic, anti-inflammatory and pain relieving activities for treatment of recurrent UTIs (Zhu, 1998; Huang, 1999, Bensky et al., 2004; Chen and Chen, 2004).

In order to investigate the possible role of CHM in the treatment of RUTIs in the UK, we conducted a feasibility study (the RUTI trial) designed to explore the practicalities of conducting a clinical trial on CHM within a Primary Care setting and to provide preliminary data on the effect size of CHM treatments. This would enable us to identify some of the differences between delivering CHM as a standardised treatment available via a GP practice compared to individualised treatment administered by a CHM practitioner, and indicate how changing the mode of CHM administration to suit the demands of a Primary Care setting affected participant compliance and response to routine herbal treatment.

2. Materials and methods

2.1. Design

The RUTI trial was planned as a multi-centred, double blind, randomised, placebo controlled feasibility study comparing standardised Chinese herbal treatment versus placebo, delivered by GP practice nurses, with individualised herbal treatment versus placebo delivered by CHM practitioners, over 16 weeks. We aimed to recruit 80 women with RUTIs aged between 18-65 years. Full details of the trial protocol, including entry and exclusion criteria, method of randomisation and outcomes measures can be found in Trials. (Flower, 2016a)

As both GP and CHM practitioner options were to provide active and placebo treatments it was intended there would be 4 arms to this trial:

1. Active standardised CHM treatment delivered via GPs (n = 20)
2. Placebo standardised CHM treatment delivered via GPs (n = 20)
3. Active individualised treatment delivered via CHM practitioners (n = 20)
4. Placebo individualised treatment delivered via CHM practitioners (n = 20)

Analysis of data from these 4 groups was intended to provide preliminary data on:

- the feasibility of administering CHM as an Investigational Medicinal Product (IMP) via GP practices and as routine practice via a private CHM practitioner
- the estimated effect size of individualised, standardised and placebo treatments in reducing the frequency and severity of recurrent UTIs.

2.2. Outcomes

The primary outcomes of the trial relate to feasibility and include obtaining regulatory approval, recruitment, retention, the practicality and relevance of different outcomes measures, fidelity of trial procedures, and an account of the experience of those providing and receiving the herbal treatment.

2.3. Secondary outcome measures included

- evaluation of the severity of frequency symptoms of UTIs experienced during the trial, as recorded in symptom diaries
- participants' perceptions of the overall change in the frequency and severity of their urinary symptoms taken at the end of the trial and 6 months post trial (Global Ratings of Change).
- Use of antibiotics for acute UTIs during the trial.
- Economic assessment (EQ5D) to be completed prior to and on completion of the trial.
- Liver (ALT) and renal function tests (serum creatinine)
- Qualitative research: to provide an in depth exploration of participant experience of taking CHM and conventional care during the trial.

2.4. Provision of herbal medicines during the RUTI trial

2.4.1. The standardised arm

The herbs provided in this group were developed from a process of

Table 1
RUTI trial preventative formula (RUTI-p).

Name (Botanical, PinYin, Common names) Traditional daily dose (grams)	Active compounds	Pharmacological effects	Clinical trial data	Adverse effects/Toxicity	Traditional Use
Astragalus membranaceus (Fisch). Bunge (Fabaceae) Huang Qi Milkvetch root 15-30g	The roots of Astragalus membranaceus contain biologically active saponins (including 11 astragalosides and one soyasaponin), flavones including kaempferol, quercetin); and polysaccharides (including Astragalans I,II and III.(Zhu, 1998, Bensky et al., 2004; Chen and Chen, 2004)	Supports immune function by eg a) increasing phagocytic activity of macrophages, (b) increasing proinflammatory cytokines IL1, IL6 and TNF, and (c) increasing levels of lymphocyte stimulatory IL2 and IL2 receptor expression. (Zhu, 1998; Bensky et al., 2004; Chen and Chen, 2004; Cho and Leung, 2007). May enhance TLR4 gene expression in bladder epithelial cells to promote local neutrophil and cytokine anti microbial activity.(Spelman et al., 2006) May enhance physiological metabolism of renal cells (eg increasing glycogen granules, acid phosphatase and succinic dehydrogenase). (Zhu, 1998) Mild diuretic effect (0.2 g/kg increased urine output by 64%)(Zhu, 1998) Anti-inflammatory effect (may reduce histamine induced increase in vascular permeability)(Zhu, 1998) Hepatoprotective effect(Chen and Chen, 2004)	Preliminary data supporting its use for asthma, chemotherapy induced leucopenia and viral myocarditis.(Liu et al., 2010; Zhang et al., 2013) Demonstrated immunomodulatory and anti microbial effects in a number of common infections (Shon et al., 2002; Tan and Vanitha, 2004; Yesilada et al., 2005) including UTIs.(Yin et al., 2010)	No adverse reactions observed in mice with dosages as high as 100 g/kg of the herb. LD_{50} of the decoction of the herb administered by intraperitoneal injection was 39.82 g/kg.(Zhu, 1998)	Invigorates the vital energy, protects against infection, promotes healing and regulates the 'water pathways'.(Bensky et al., 2004; Chen and Chen, 2004)
Sophora flavescens Aiton (Fabaceae) Ku Shen 6-15g	The known chemical components of Sophora flavescens include alkaloids (3.3%) -principally matrine and oxymatrine; flavonoids (1.5%), alkylxanthones, quinones, triterpene glycosides, fatty acids, and essential oils. (Zhu, 1998, Bensky et al., 2004)	In vitro research shows the flavonoid extracted from Ku Shen (Kurarinone) has a strong inhibitory action on the growth of MRSA (Methicillin-Resistant *Staphylococcus aureus*) and VRE (Vancomycin resistant Enterococci) bacteria.(Chen et al., 2005) Sophora flavescens also has an inhibitory in vitro action against E Coli,(Zhu, 1998) and B-haemolytic Streptococcus.(Zhu, 1998)	There is preliminary evidence supporting the use of Sophora flavescens for asthma, psoriasis, eczema, arrhythmia, and to prevent leukopenia during cancer chemotherapy.(Chen and Chen, 2004)	Occasional reports of mild, transient, gastrointestinal disturbances.(Chen and Chen, 2004) The LD_{50} for injection of the herbal extract in mice corresponded to a dose of 15 g of herb per kg (in human terms, this corresponds, roughly, to a single dose of 1 kg of the herb).(Zhu, 1998)	Clears Heat and drains Damp to treat diarrhea, skin diseases, and relieve painful, frequent urination.(Cho and Leung, 2007)
Lindera aggregata (Sims) Kosterm. (Lauracceae) Wu Yao Lindera Root 6-12g	Contains a number of alkaloids, volatile oils and sesquiterpene esters.(Zhu, 1998, Bensky et al., 2004)	In vitro research suggests this herb exhibits inhibitory effects on the production of inflammatory mediators from macrophages via blocking NF-kappaB and MAPKs signaling pathways. (Luo et al., 2009)	In vitro analysis suggests Lindera essential oils have an anti-bacterial action against common bacteria including E Coli.(Yan et al., 2009) Preliminary evidence that this herb might help slow down diabetic nephropathy.(Ohno et al., 2005)	No reported adverse events.	Circulates vital energy and alleviates pain, warms the 'kidney' and regulates urination. (Bensky et al., 2004; Chen and Chen, 2004)

Table 2
RUTI trial acute formula (RUTI-a).

Name (Botanical, PinYin, Common names) Traditional daily dose (grams)	Active compounds	Pharmacological effects	Clinical trial data	Adverse effects/Toxicity	Traditional Use
Oldenlandia diffusa (Willd.) Roxb. (Rubiaceae) Bai Hua She She Cao Oldenlandia 15-60g	Contains Iridoid and Flavonoid glycosides (eg Oldenlandosides A and B), Anthroquinones, Triterpenes, and p-coumaric acid.(Zhu, 1998, Bensky et al., 2004; Chen and Chen, 2004)	Has demonstrated an in vitro anti-bacterial action against Staphylococcus aureus. E coli, Pseudomonas aeruginosa.(Bian, 2005) Has anti-inflammatory effect by inhibiting the production of tumor necrosis factor (TNF)-α, interleukin (IL)-6 and prostaglandin E(2) (PGE(2).(Kim et al., 2011) May increase leukocyte phagocytic activity. (Zhu, 1998) Oldenlandia diffusa extract effectively inhibited the growth of several cancer cell lines.(Gupta et al., 2004)	Commonly used in Chinese clinical trials as part of a formula for the treatment of acute urinary tract infections. Also used in many trials for the treatment of hepatitis and a number of different cancers.(Zhu, 1998, Bensky et al., 2004; Chen and Chen, 2004)	LD_{50} of the extract of the herb by intraperitoneal administration was 104 g/kg^2 (Zhu, 1998)	Clears Heat and eliminates toxins used for skin diseases, for snakebites, urinary tract infections and recently as an anti-cancer herb.(Bensky et al., 2004;Chen and Chen, 2004)
Phellodendron amurense Rupr. (Rutaceae) Huang Bai Amur Cork tree 9-15g	Contains a number of isoquinoline alkaloids (bereberine is the best documented and is present at levels ranging from 0.6-2.5%). Triterpenes, phytosterols, and phenolic compounds have also been isolated.(Zhu, 1998, Bensky et al., 2004)	Anti-inflammatory effects and anti-microbial effects noted in vitro and in vivo-including against MRSA when used singly or in conjunction with ampicillin and oxacillin.(Yu et al., 2005; Park et al., 2007; Chen et al., 2010)	Preliminary evidence of the effectiveness of the herbs in treating acute and chronic bacillary dysentery.(Zhu, 1998)	No side effects reported for oral administration. LD_{50} after intraperitoneal administration was 2.7 g/kg. (Zhu, 1998)	Clears Heat, dries Damp and clears toxins traditionally used for infectious diarrhoea, urinary tract infections, and skin diseases.(Bensky et al., 2004; Chen and Chen, 2004)
Desmodium styracifolium (Osbeck) Merr. (Fabaceae) Jin Qian Cao Gold Coin herb 15-30g	Contains a number of flavonoids and alkaloids, followed by terpenoids, steroids, phenols, phenylpropanoids, glycosides and a number of volatile oils.(Zhu, 1998, Bensky et al., 2004; Chen and Chen, 2004)	Anti-inflammatory action (Ma et al., 2011) Prevents and treats renal stones (Zhu, 1998; Chen and Chen, 2004; Ma et al., 2011)	Commonly used in clinical trials for the treatment of UTIs.(Zhu, 1998, Bensky et al., 2004; Chen and Chen, 2004; Ma et al., 2011, Peng et al., 2011)	No reports of adverse reactions despite large dosages administered.(Zhu, 1998)	Clears Heat, drains Damp and dissolves stones for the treatment of urinary tract infections, kidney, bladder and gall bladder stones. Also used for jaundice, skin diseases.(Bensky et al., 2004; Chen and Chen, 2004)

defining best practice that included reflective practise, a systematic review of clinical trials, a selective review of historical sources, and interviews with professional CHM practitioners. This has been described in detail elsewhere (Flower et al., 2016a). Table 1and Table 2 show the RUTI Trial Preventative Formula (RUTI-p) and RUTI Trial Acute Formula (RUTI-a) with the Herb Name (Botanical, PinYin, Common names), Traditional daily dose (grams), Active compounds, Pharmacological effects, summarise Clinical trial data and Adverse effects/Toxicity with their Traditional Use.

Women enrolled in the standardised arm of the trial received two forms of 400mg herbal capsule (see Table 3). RUTI-a capsule (administered as 4 capsules q.d.s.) was to be used for acute symptoms of cystitis and RUTI-p capsule (4 capsules b.d.) was used in the intervening period between infections, to help prevent acute episodes. This method of herbal administration was selected in order to avoid inappropriate administration of antibacterial herbs, and to approximate the kind of treatment that.

Would be administered in routine Chinese herbal practise, which places an emphasis on providing treatment for both the symptom (the infection) and the underlying causes for these infections. This approach to treating a recurrent infection differs from the conventional medical model that treats infection but does not attempt to change the 'ecology' of the bladder to prevent recurrence.

In terms of modern pharmacology, the constituents of RUTI-a have antibacterial and anti-inflammatory actions and constituents of RUTI-p have immune enhancing, anti-inflammatory, antibacterial, and mildly diuretic actions Tables 1 and 2 summarise the pharmacology and clinical applications and toxicology of RUTI-a and RUTI-p respectively.

Both of these herbal remedies were considered as Investigational Medicinal Products (IMPs) by the Medicines and Healthcare products Regulatory Authority (MHRA) and it was necessary to fulfil the exacting regulatory requirements made of a Clinical Trial of an IMP (CTIMP). These included providing full data on the sourcing, identification, and key marker compounds of each herb used in the formulae and acceptable certification of Good Manufacturing Practice (GMP) used to transform the raw herbs into the herbal granules being encapsulated for the trial. We elected to work with Phoenix Medical Ltd and their Chinese parent company (Tian Jiang Pharmaceuticals Co. Ltd) because, although they did not have EU GMP certification, they had been inspected and certified by the Australian Therapeutic Goods Administration (TGA), which is accepted by the UK's MHRA as a comparable standard to EU GMP. In addition we were also required to provide a full Investigator's Brochure for all products used in the standardised arm of the trial and a detailed rationale to support each herb used in this arm of the trial. Finally in accordance with CTIMP regulations the production of the herbal capsules could only be undertaken by a UK company with MHRA Manufacturing Authorisation for Clinical Trials. For the purposes of this trial, we used Essential Nutrition Ltd (EN) who had this authorisation and also fairly unique experience in working with other herbal medicines at this level of production. EN tested the herbal product using High Pressure Gas Chromatography (HPGC) to identify key active marker compounds, and to check for contamination from heavy metals, pharmaceuticals, and biological contaminants such as bacteria and fungi. They then managed the production of the herbal product and an identical placebo capsules made from sugar beet fibre. This has been described in our Protocol paper and also for another herbal trial. (Flower et al, 2016a; Trill et al., 2017) Both the herbal product and the placebo used during the trial were tested for stability at 3, 6 12 and 15 months post manufacture. The herbs and placebo product used for this arm of the trial successfully passed these tests.

We have already described some of the regulatory challenges of this process in more detail. (Flower et al, 2016b) The end result is that the RUTI trial marked the first time a Chinese herbal product had met the requirements to be tested as a CTIMP within the UK.

2.4.2. The individualised arm

Participants enrolled in the individualised arm of the trial were treated by an experienced Chinese herbal medicine (CHM) practitioner (AF) and received sachets of concentrated herbal granules that were then administered as a strong tasting herbal drink by the addition of hot water. Each participant received a herbal formula specifically designed to meet their particular presentation. The formula typically comprised of between 10-15 herbal ingredients and was also adjusted during the course of the trial in response to the reported experience of the participant (see Table 4). The daily dosage for these granules varied between 6-9g b.d. which corresponded to routine practice of CHM. Most participants were supplied with preventative herbs to be used between infections and an acute prescription to be taken in the event of the development of acute symptoms of infection. Several participants experienced continuous signs of infection and these women were usually treated with a single acute formula until these symptoms resolved. This approach to treatment conforms to the routine practice and administration of CHM and accordingly was not considered by the MHRA as requiring CTIMP approval.

In this arm of the trial, participants were seen at monthly consultations by the CHM practitioner and their herbal prescription was then emailed to the herbal dispensary at Phoenix Medical Ltd. Each participant was randomised at the outset of the trial by a designated individual at the dispensary to receive either active herbs or a strong tasting herbal placebo. The herbal placebo was made up of food flavourings and colourings and produced in an identical form to active herbs by the Chinese manufacturer.

Unfortunately, as the trial neared its completion, an investigation into an adverse event reported by a participant, supposedly on placebo herbs, revealed that the herbal dispensary had failed to understand that all the herbs detailed by the practitioner should be provided completely in placebo form. In practice the dispensary had mixed approximately 20–30% of the placebo herbs with 70–80% of active herbs which thereby rendered the placebo arm invalid. This discovery represented a serious challenge for the trial management team. After discussion the following course of action was proposed:

On discovery of this serious breach of trial Protocol an amendment was submitted to the Research Ethics Committee and to the MHRA to allow us to extend the duration of the trial and to run a second phase of RUTI that would adhere to the intended randomised placebo control described in our Protocol. Discussion and further training was provided to the dispensary at Phoenix medical to ensure that they clearly understood not to contaminate a placebo prescription with any active herbs. Phase 2 of the RUTI trial commenced at the end of January 2017

Table 3
Acute and Preventative standardised CHM formulae used in the RUTI Trial.

Remedy	Plant	Part	Chinese name	Dose (in 400mg capsule)
RUTI-a (Acute)	*Scleromitrion diffusum* (Willd.) R.J.Wang	Aerial parts	Bai Hua She She Cao	160mg
	Phellodendron chinense C.K.Schneid.	Bark	Huang Bai	80mg
	Lysimachia christinae Hance	Aerial parts	Jin Qian Cao	160mg
RUTI-p (preventative)	*Astragalus mongholicus* Bunge	Root	Huang Qi	200mg
	Lindera aggregata (Sims) Kosterm.	Root	Wu Yao	100mg
	Sophora flavescens Aiton	root	Ku Shen	100mg

Table 4
Example of individualised herbal formula used in RUTI Trial.

Plant	Part Used	Chinese name
Scleromitrion diffusum (Willd.) R.J.Wang	Whole plant	Bai Hua She She Cao
Scutellaria barbata D.Don	Whole plant	Ban Zhi Lian
Paris polyphylla Sm.var yunnanensis (Franch.) Hand.-Mazz.	Rhizome	Chong Lou
Patrinia scabiosifolia Link	Whole plant	Bai Jiang Cao
Pyrrosia petiolosa (Christ) Ching	Leaf	Shi Wei
Scutellaria baicalensis Georgi	Root	Huang Qin
Sophora flavescens Aiton	Root	Ku Shen
Lysimachia christinae Hance	Aerial parts	Jin Qian Cao
Dianthus chinensis L	Aerial parts	Qu Mai
Polygonum aviculare L.	Aerial parts	Bian Xu
Lindera aggregata (Sims) Kosterm.	Root tuber	Wu Yao
Leonurus japonicus Houtt.	Aerial parts	Yi Mu Cao
Glycyrrhiza uralensis Fisch. ex DC.	Root and rhizome	Gan Cao

and resulted in the recruitment of a further 11 women. This time randomisation to placebo control was successful and 4 participants received only placebo herbs.

3. Results

MHRA and NRES approval was finally granted for the RUTI trial in Dec 2015. Recruitment commenced in Jan 2016 and ended April 2017. In total 61 women were recruited to the trial with 30 in the standardised arm and 31 in the individualised arm (see CONSORT diagram).

3.1. Recruitment

Recruitment to the RUTI trial from primary care networks proved to be problematic. In the standardised arm of the trial we hoped to recruit 40 participants directly from 8 GP practices in and around Southampton with the help of the Wessex NIHR Clinical Research Network (CRN). However, recruitment rates were slow so 6 months after the start of the trial we broadened our catchment area to include an additional 10 GP practices in the Peninsula and West of England NIHR CRN areas.

In the individualised arm, screening was carried out on 41 women from 513 (8%) letters sent. 34 of the 41 (82%) were eligible. The reasons for exclusion were on anti-hypertensives, (n = 2), known kidney disease (n = 1), starting a new treatment (n = 2) and age > 65 years (n = 2), with 3 declined post screening. Relying on the individual to make an appointment meant that only 22 of the 34 (65%) made appointments.

Eventually 30 participants were recruited but only 15/30 (50%) completed the trial and limited data was provided from these. Thirteen out of this group of 30 (43.3%) were lost to follow up and it was not possible to find out why they withdrew from the trial.

In the individualised arm of the trial, recruitment was initially organised via 46 GP Practices in London and Brighton acting as Patient Identification Centres to identify participants and then refer them to the CHM practitioner. In total only 13 recruits (42%) were enrolled using this approach during the year-long duration of the trial. The trial management team addressed this deficit by applying for permission to recruit via patient self-help networks. Recruitment using this approach rapidly provided a further 18 participants (58%) to the trial. For a summary of recruitment pathways for both arms of the trial please see the CONSORT diagram .

The recruitment of patients from different populations led to some significant baseline differences between the two groups (see Table 5). Self-referrals to the individualised group were significantly more likely to have more frequent rates of infection ($p < 0.01$), suffer from dysuria ($p = 0.013$) and report a lower level of overall health on the EQ5 outcome measure. Those in the individualised arm presented with far more continuous urinary symptoms when compared to the standardised group with none of the 30 recruits in the standardised arm reporting continuous symptoms of UTI infection (and only 4/13 (13.3%) used antibiotic prophylaxis) compared to 17/31 (54%) of the individualised group with continuous symptoms (of whom 14/31 (45%) were using ongoing antibiotic prophylaxis).

3.2. Retention and treatment fidelity

Participant retention in the trial varied significantly between the standardised and individualised groups. In the standardised arm (Group 1) 30 women were recruited to the trial and 15 (50%) were reported as completing the trial, 13/30 (43.3%) were lost to follow up and 2 (6.6%) withdrew.

In the individualised arm 24/31 (77.4%) completed the trial, 4/31 (12.9%) were lost to follow up and a further 3 (9.7%) withdrew from the trial.

3.3. Group 1 (standardised arm)

At the end of the trial 16/30 of Group 1 provided some data on overall change in UTI symptoms and 15/30 (50%) provided data on change in antibiotic use. The trial diary was only returned by 9/30 (30%) participants in this arm with 2 providing some data on continuous UTI symptoms, 4 providing data on episodes of infection and 3 returning their diaries with no entries made because they experienced no infections during the trial.

3.4. Group 2 (individualised arm)

In Group 2 24/31 (77.4%) of participants provided data on overall changes in UTIs and 20/31 (64.5%) provided data on changes in

Table 5
Baseline data.

	Group 1 (standardised) n = 30	Group 2 (individualised) n = 31
Age	48.5 yrs (SD 13)	45.8 (SD 10.5)
Sexually active	14/18 respondents (77.7%)	19/31 respondents (61.3%)
Menopausal	9/17 (53%)	9/29 (31%)
Prev Experience of CHM	2/17 (11.8%)	8/31 (25.8%)
Duration of RUTIs (Median score)	3 (5-9 years	3 (5-9 years)
Number of UTIs in past 12 months	Mean 1.3	2.8
1 = 3-5	Median 1	Median 4
2 = 6-9		
3= > 10		
4 = continuous		
Number of women with continuous infections	0/30 (0%)	17/31 (55%)
Recruitment		
• Via Primary care	30/30 (100%)	13/31 (42%)
• Self referral	0/30	18/31 (58%)
Symptoms of UTIs		
• Frequency	Mean 2.39 (Med 3)	Mean 2.1 (Med 2)
• Urgency	Mean 2.26 (3)	Mean 2 (2)
• Unable to empty Bladder	1.24 (2)	1.52 (2)
• Dysuria	0.83 (2)	1.65 (2)
• Abdominal pain	2.1 (2.5)	2.2 (2)
EQ5 (Baseline)		
• Pain	0.94	1.23
• Depression/anx	0.59	1.03
• Overall Health (0-100)	75.2 (SD22.3)	60.9 (SD 19.6)
Use of antibiotics		
• was last infection treated with a/bs	Yes 17/18 responses (94.4%)	Yes 30/30 responses (100%)
• Continuous a/bs	4/30 (13.3%)	14/31 (45%)

antibiotic use. Twenty participants in this group (64.5%) provided some diary data with 14 continuous diaries and 6 episodic diaries. However only 8/17 (47%) participants in Group 2 with continuous infection provided diary data for the duration of the trial and no participants from Group 1 provided this data.

3.5. Outcome measurements

The relevance and practicality of outcomes measures are important feasibility findings for this study.

In light of the relatively small numbers who provided data in the standardised arm, and the failure of the placebo control in the individualised arm, it has only been possible to provide some simple descriptive statistics of each group. These are effectively small case series and they are presented as overall changes in the individualised and standardised group. No statistical comparison between these groups has been possible.

3.5.1. The CRF 7 global improvement measure

This was a simple end of trials outcomes measure using a 10cm (−5 to +5) Visual Analogue Scale (VAS) scores to record overall change in urinary symptoms, the number of UTIs experienced, and changes in frequency, and severity. Changes in antibiotic use was recorded using categorical data. The same measure was circulated to women in the individualised group 6 months after the cessation of the trial and provided some data on the longer term implications of treatment.

3.5.2. EQ5 D

EQ5D is a standardised instrument used to measure quality of life and provide health economic data. This was one of the secondary outcomes in the RUTI trial. Data was provided by 14/30 (46.6%) in the standardised group and 16/31 (51.6%) in the individualised group. Given the small numbers of the trial it was not considered possible to meaningfully analyse these data.

These data have been summarised in Table 6. A more complete set of data are available in Appendix A.

4. Serum markers of renal and liver function

Serum alanine aminotransferase (ALT) and serum creatinine were measured at weeks 0, 4 & 16 of the trial. No abnormalities were reported during the trial in either the standardised or the individualised arm. Participation in the trial was contingent upon completing these assessments. In the individualised arm tests were conducted at the TCM clinic on all participants, using a desk top Reflotron® blood analyser. Whilst, due to participants re-scheduling appointments, it was not always possible to test precisely at the 4th week, all required assessments were successfully completed in those who completed the trial.

5. Discussion

The RUTI trial was a feasibility study and the primary focus of its findings related to the practicality of investigating CHM as a CTIMP within a primary care setting. These included obtaining regulatory approval, meeting standards required for an IMP, supplying appropriate herbs to trial participants, using primary care research networks to recruit patients, enrolling, randomising and retaining participants for the 16-week duration of the trial, evaluating outcome measures, and

Table 6
Summary of RUTI Trial outcomes.

Treatment group		Standardised		Individualised	
		Active	Placebo	Active	Placebo only
No of patients randomised		13	17	27	4
No patients who completed the trial		7 (53.8%)	9 (52.9%)	22 (81.5%)	2 (50%)
Patient diaries	Number of patients providing data (N, %)	3/13 (23%)	6/17 (35.3%)	18/27 (66.6%)	2/4 (50%)
	Result in those who provided data (n/N, %)	Invalid data	Invalid data	Invalid data	Invalid data
Global outcomes (end of trial)	Number of patients providing data (N, %)	7/13 (53.8%)	9/17 (52.9%)	22/27 (81.5%)	2/4 (50%)
	Result in those who provided data (n/N, %)	Mean overall improvement +32.6% 3/7 reported no change	Mean overall improvement +30% 5/9 reported no change	Mean overall improvement +44.5% 6/27 reported no change	Mean overall improvement +10% 1 reported no change
Global outcomes 6-12 month follow up	Number of patients providing data (N, %)	N/A	N/A	13/22 (59.1%)	1/2 (50%)
	Result in those who provided data (n/N, %)	N/A	N/A	7/13 (53.8%) reported no infection post trial.	
Change in antibiotic use during trial	Number of patients providing data (N, %)	7/13 (53.8%)	9/17 (52.9%)	18/27 (66.6%)	2/4 (50%)
	Result in those who provided data (n/N, %)	3/6 (50%) reported a reduction in use. 1/6 (16.6%) completely stopped	4/9 (44.4%) reported a reduction in use 3/9 (33.3%) completely stopped.	12/18 (66.7%) reported a reduction in use 5/18 (27.7% completely stopped.	0/2 (0%) reported a reduction in use 0 completely stopped
Change in antibiotic use 6-12 month follow up	Number of patients providing data (N, %)	N/A	N/A	13/22 (59.1%)	1/2 (50%)
	Result in those who provided data (n/N, %)	N/A	N/A	11/13 (84.6%) reported a reduction in use. 7/13 (53.8%) completely stopped	No reduction in use.
EQ5D	Number of patients providing data (N, %)	6/13 (46.2%)	8/17 (47.1%)	14/27 (51.9%)	2/4 (50%)
EQ5D	Result in those who provided data (n/N, %)	Mean overall level of health at week 0 = 91.3/100 At end of trial = 83.2/100	Mean overall level of health at week 0 = 67.5/100 At end of trial = 66.25/100	Mean overall level of health at week 0 = 61.6/100 At end of trial = 66.75/100	Mean overall level of health at week 0 = 40/100 At end of trial = 55/100

finally exploring some of the data produced during the study to provide some preliminary findings about the effectiveness of CHM and whether further research is warranted.

5.1. Regulatory approval

The RUTI trial fulfilled the regulatory requirements set by the MHRA and became the first CTIMP trial exploring CHM in the UK. We were able to meet the exacting standards set for product quality assurance, good manufacturing practice, and trial design and management. In addition to the MHRA, regulatory approval was obtained from Southampton University ethics committee, the East Surrey Research Ethics Committee, NRES Committee based in London/Surrey Borders, and NHS Research and Development, plus as a consequence of changes with the HRA process, the recruiting sites themselves. This enabled the clinical trial to recruit NHS patients via Primary care research networks. Fulfilling these requirements was a demanding process that required patience and understanding from both applicants and regulators. In various areas there were no pre-existing guidelines and precedents were set. For example, the decision of the MHRA to consider the administration of individualised CHM within private practice by a trained herbalist as being exempt from CTIMP requirements, was an important principle that may be used to inform subsequent research into CHM.

5.2. Herbal products

Whilst the herbal suppliers for the RUTI trial were able to meet the standards for the herbal product in the standardised CTIMP arm of trial, unfortunately their lack of experience in conducting clinical trials caused serious problems for the non-CTIMP individualised arm. A misunderstanding of the trial Protocol led to the dispensary team mistakenly combining active herbs together with the placebo formula. This totally invalidated the placebo group of the individualised arm and data from these women was instead included as an active treatment.

The inexperience of the herbal dispensary proved to be a major obstacle to the trial. Although Protocol instructions were clearly given by the management team, and apparently understood by the Chinese dispensary team, an important aspect of the design was obviously lost in translation. Once these issues were clarified then the randomisation, blinding, and allocation to placebo proceeded according to the original plan. Unfortunately, data collection for RUTI was compromised but important lessons were learned. In particular, there needs to be clarity about the Protocol at all levels of the company responsible for dispensing the herbs. Initial training needs to be thorough, tested, and, if using a supplier operated by predominately Chinese speakers, then some key documents may need to be translated into Chinese. Checks in the herbal dispensary need to be initiated soon after the onset of the trial. Clear lines of communication need to be opened so that any concerns or confusion felt by the herbal dispensers can be addressed directly by the trial management team.

5.3. Recruitment and randomisation

Recruitment via NHS primary care networks (NIHR CRNs) to the RUTI trial proved to be slow and problematic. For the standardised arm this may have been partly caused by the lack of resources and limited supplies of herbal products that initially restricted recruitment centres to a small number of GP practices. The number of sites estimated to be required was based on predictions of the prevalence of recurrent UTIs, which are not often given a diagnostic read code in GP records. The absence of adequate coding, and consultations often being recorded using free text, may have led to women with recurrent UTIs being overlooked and it is also possible that the prevalence of recurrent UTIs is not as high as the literature suggests.

There was a disparity in recruitment and retention rates between different GP practices: some sites quickly recruited 6 participants in a matter of weeks whilst others recruited no one over the course of a year. This may reflect the greater willingness of some practices to investigate Chinese herbal medicine; the sites that had a more personal approach to patients, and a more research active community also recruited and retained considerably more participants. One site sent 98 letters and found 29 possible recruits. In contrast, many of the searches conducted in poorly recruiting sites may have been suboptimal. Some sites only invited potential recruits known by clinicians, and recruited no one.

Qualitative interviews were undertaken with the practice nurses and GPs who enrolled and managed women in the trial and this will be published subsequently as a separate paper.

Recruitment via Primary Care was therefore was a significant challenge for this trial. This is an important feasibility finding. It suggests that for any subsequent trial using CHM for RUTIs greater clarity needs to be provided in eligibility criteria, and more resources provided for training and ongoing support of NHS researchers asked to dispense and evaluate an unfamiliar therapeutic intervention administered over a protracted period of time. By contrast recruitment via self-referral from support group networks was relatively easy although there were substantial baseline differences in this population as discussed below. Future research in this area should consider using these networks to facilitate recruitment.

The two methods of randomisation post recruitment used for both groups were successfully applied by the suppliers of the herbal capsules and the pharmacy dispensing individualised herbs, although their mistake post-randomisation has been described above.

5.4. Baseline differences

The requirement to broaden recruitment in the individualised arm to include self-referrals from patient support groups led to significant differences with the standardised arms. Previous experience in recruiting via self-help groups (Flower) resulted in the sample being biased to the more severe end of the symptom spectrum and this is borne out by the baseline differences between the two groups in the trial. Those in the individualised arm had more continuous bladder related symptoms, higher levels of pain, greater use of antibiotic prophylaxis, and a lower reported quality of life. Many of the women in this group had long since abandoned seeking help from their GP and were under the care of urologists. This could explain why they were not represented in recruitment from primary care practices. Future research into the treatment of recurrent UTIs should take these potential differences in population into account in the Protocol design and data analysis. Given the difficulties of recruitment and retention via primary care it may be more fruitful for subsequent research to focus on self help groups and to work in conjunction with urologists rather than GPs.

5.5. Participant retention

Retention and data collection in the individualised arm of the trial was considerably more successful than that of the standardised arm. Twenty-four out of the 31 participants (77.4%) completed the trial with 4 losses to follow up and 3 withdrawals (due to the strong taste of the herbs (n = 1), commencement of new treatment options (n = 1), and one adverse digestive reaction). Data was collected from 24/31 participants (77.4%). This may be due to the practitioner effect and the perceived personal interest he had in the recruits, which is clearly lacking in a standardised mixture delivered by a nurse or GP normally perceived as delivering 'Modern Western Medicine'. Women recruited from self help groups with higher symptom burden may be more motivated to complete and return study materials.

5.6. Outcome measures

To our knowledge, at the outset of the trial, there were no validated measures specifically designed to record changes in the experience of

women suffering from recurrent UTIs. This may reflect a lack of awareness about the scale or severity of this condition. We chose to evaluate the potential of patient diaries validated for use in acute UTIs, to act as the primary outcome for recurrent UTIs.

The diary was designed to record symptoms of acute episodic UTIs. However, given the continuous nature of many of the trial participants' symptoms, discrete episodes of infection were not obvious. This also meant that women with ongoing symptoms were required to provide daily data over the 116 day duration of the trial which was a demanding task for many of the trial participants. These two factors meant that data from the patient diaries could not be meaningfully used to evaluate any changes occurring during the trial.

By contrast the CRF 7 end of trial outcome measure that asked women to score changes in symptom severity, numbers and severity of infections, and use of antibiotics during the trial proved easy to complete and provided some interesting data. An adapted version of this outcome measure was used to provide data for the 6-12 month follow up. For future studies in recurrent UTIs it is recommended that this approach is utilised, developed, and validated. Using these measures as a monthly assessment tool would be a practical way of capturing data on symptom change and antibiotic use during the course of a trial.

Data was collected successfully via the EQ5D outcome measure but the sample size was considered too small to undertake a meaningful analysis of these data.

5.7. Safety monitoring

Chinese herbs are strong tasting and it is expected that they will cause mild and transient nausea and loose stools. One participant in the standardised arm withdrew because of persistent nausea and one woman in the individualised arm withdrew because she could not tolerate the taste of the herbs. One woman in the individualised arm of the trial had to withdraw at week 13 after experiencing severe gastric pain that was diagnosed by her GP as acute gastritis. She had a pre-existing intolerance to anti-inflammatory drugs. Her gastritis resolved after a few weeks off the herbs and there was no report of any lasting problems with regular follow-up over the course of a year. Interestingly she has not experienced any bladder symptoms since completing the trial.

Blood tests were successfully collected at weeks 0, 4 & 16 using the Reflotron® desk top blood analyser. There were no abnormal ALT or creatinine levels reported in either group during the trial. One woman who presented with mildly raised ALT found these levels declined during the time she took the CHM.

The RUTI trial was a feasibility study and was not powered to detect efficacy. These limitations are compounded by the poor provision of data from the standardised arm of the trial and the placebo failure in the individualised arm. Data from the global outcomes measure taken at the end of the trial was generally positive for both groups. Antibiotic use during the trial declined in both groups Given the high prevalence of antibiotic use for recurrent UTIs and the importance of preventing antimicrobial resistance this is an interesting finding that is worthy of further investigation.

The 6 month follow up data from 13/22 (59.1%) of women in the active individualised group suggests that women reported persistent benefits in symptom reduction subsequent to the trial.

Antibiotic use also declined markedly in this follow up group with 11/13 (84.6%) of women reporting a reduction, and 7/13 (53.5%) reporting that they completely stopped antibiotics. This should be seen in the context of studies reporting that 60% of women will re-use antibiotics within just 3 months of stopping long term (> 6 month) antibiotic prophylaxis (ref).

These data are obviously limited by small numbers, by the differently sourced populations for individualised and standardised arms, and by the non-validated status of the outcomes measures used to collect them. It is not possible to provide a meaningful comparison of active and placebo interventions.

6. Implications for future research

Although standardised CHM treatment would seem cheaper and easier to scale up in the NHS, this study shows that recruitment of patients by GPs to a trial of TCM and retention of those patients over a prolonged period is actually very challenging, and possibly not feasible. Paradoxically, it was much easier to recruit and retain patients from self-help groups and from private TCM practices, even though these patients were taking a herbal decoction, whose taste is unpleasant (compared to standardised capsules). The patients under the care of a TCM practitioner, receiving a herbal decoction, seemed to experience benefits from this treatment, although most of them had already been under the care of a specialist for some time. Individualised CHM treatment is dependent upon the availability of trained herbal practitioners and is considerably more expensive to deploy than standardised herbal capsules which can be prescribed by GPs, practice nurses, or in time, made available as over the counter remedies. In a future trial, it will be important to include an economic analysis, to evaluate the cost-effectiveness of this approach. Although the cost is greater than the standardised treatment delivered by GPs, it is possible that this is still cost-effective for patients with severe and recurrent urinary tract infections, who experience severe symptoms and consume large quantities of antibiotics and of specialist time.

7. Conclusion

The RUTI trial has demonstrated that it is feasible, but challenging, to conduct a CTIMP trial on Chinese herbal medicine. It has established regulatory pathways that can be followed by subsequent research, and highlighted difficulties when dealing with herbal suppliers who are trial-naïve, and with recruiters and participants who are unfamiliar with herbal products. It was not possible to recruit or retain sufficient numbers of patients through GPs to receive a standardised preparation of TCM. However, it was feasible to recruit patients through self-help networks and private TCM clinics, to be seen by a TCM practitioner. There were acceptable rates of retention and preliminary results suggest that it would be worth testing this approach in a full trial.

Data sharing statement

Any request for data should be made in writing to the corresponding author Dr Andrew Flower.

Declarations of interest

None.

Funding

Andrew Flower was funded as a National Institute of Health Research (NIHR) post doctoral Research Fellow (PDF-2011-04-027).

Additional funding for the trial was received from the Department of Primary Care and Population Sciences, University of Southampton. The funder and Sponsor had no input into the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Acknowledgements

Andrew Flower (senior Research Fellow) as Principal Investigator was responsible for the overall design of the trial, and the writing of the background, methods, results and discussion sections of the report.

Kim Harman (research Trial Manager) was the lead for trial management and co-ordination of trial implementation and regional recruitment, co-writing the statistical analysis plan, compilation and formatting the manuscript.

Merlin Willcox (GP and Academic Clinical Lecturer) contributed to the writing of the methods and results sections of the report. He was the Chief Investigator in the last stages of the trial.

Michael Moore (GP and Professor in Primary Health Care Research) provided expert advice on running the trial and contributed to the writing of the methods and results sections of the report.

Beth Stuart (senior Research Fellow) was responsible for co-writing the statistical analysis plan and providing statistical support.

Sadly, just before the completion of this trial, the Chief Investigator, Professor George Lewith died unexpectedly. Professor Lewith was integral to this and many other research projects and his death was a personal tragedy for his friends and colleagues, and an irreplaceable loss to research into Complementary Therapies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2019.111935.

Appendix A

Table A1
End of trial global outcomes score.

	Overall change in symptoms	Number of UTIs during the trial	Change in frequency of UTIs	Change in severity of UTIs
Group 1 (Active + Placebo Standardised)	n = 16 +16.3 (SD 18.6) (32.6% improvement)	n = 15 O.3 (SD 0.82)	n = 4 +25 (50% improvement)	n = 3 +8.3 (16.6% improvement)
Group 1 (Placebo only)	n = 9 (+15) SD18.4) (30% improvement)	n = 9 0.22 (SD 0.44)	n/a	n/a
Group 2 (Individualised)	n = 24 +21.2 (SD17.3) (+42.4% improvement)	n = 18 2.3 (SD 1.7)	n = 20 +20.5(SD19.4)(+41% improvement)	n = 21 +14 (SD 21.2) (+28% improvement)

Table A2
Reported use of antibiotics during the trial.

Use of antibiotics during trial	Standardised active (n = 6)	Standardised placebo (n = 9)	Individualised active (n = 18)
Increased a lot	0	0	0
Slightly increased	0	0	3
No Change	3	5	3
Slight decrease	1	0	3
Decreased a lot	1	1	4
Completely stopped	1	3	5

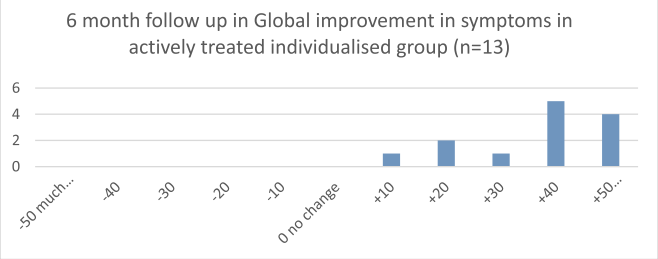
Table A3
Data from the EQ5D measure.

	Pre-Trial Standardised group (n = 17) Mean (SD)	Pre-trial Individualised group (n = 31) Mean (SD)	End of Trial Standardised group (n = 14) Mean (SD)	End of Trial Individualised group (n = 16) Mean (SD)
Mobility	0.47 (1.00)	0.39 (0.71)	0.46 (1.27)	0.38 (0.20)
Pain	0.94 (1.20)	1.23 (1.06)	0.46 (0.78)	1 (0.73)
Anxiety/depression	0.59 (0.94)	1.03 (0.98)	0.38 (0.51)	1 (0.82)
Able to carry out usual activities	0.59 (1.06)	0.58 (0.99)	0.31 (0.86)	0.63 (1.15)
Self care	0.24 (0.56	0.16 (0.52)	0.32 (0.86)	0.13 (0.5)
Overall level of Health (0-100)	75.18 (22.3)	60.9 (19.56)	76.08 (14.75)	66.75 (17.35)

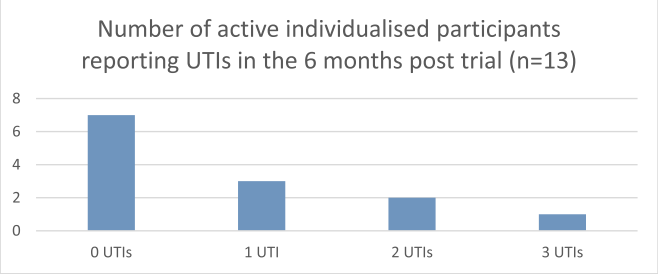
Six-twelve month follow up data:

Six month follow up data was only provided by women in the individualised arm of the trial. Limited resources combined with bureaucratic complexity meant it was not possible to contact patients in the standardised arm to obtain this data. In total 13/22 (59.1%) of participants who underwent active treatment provided follow up data.

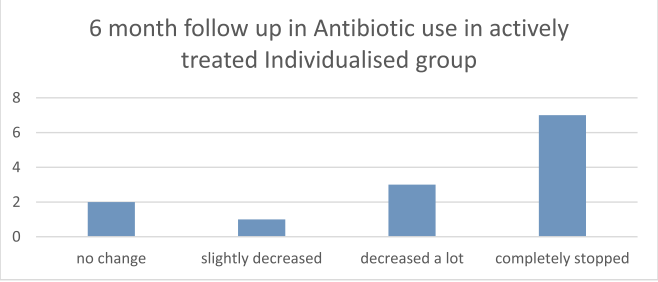
All respondents reported an improvement in their symptoms 6 months post trial. The average improvement was +36.9 (73.8%).

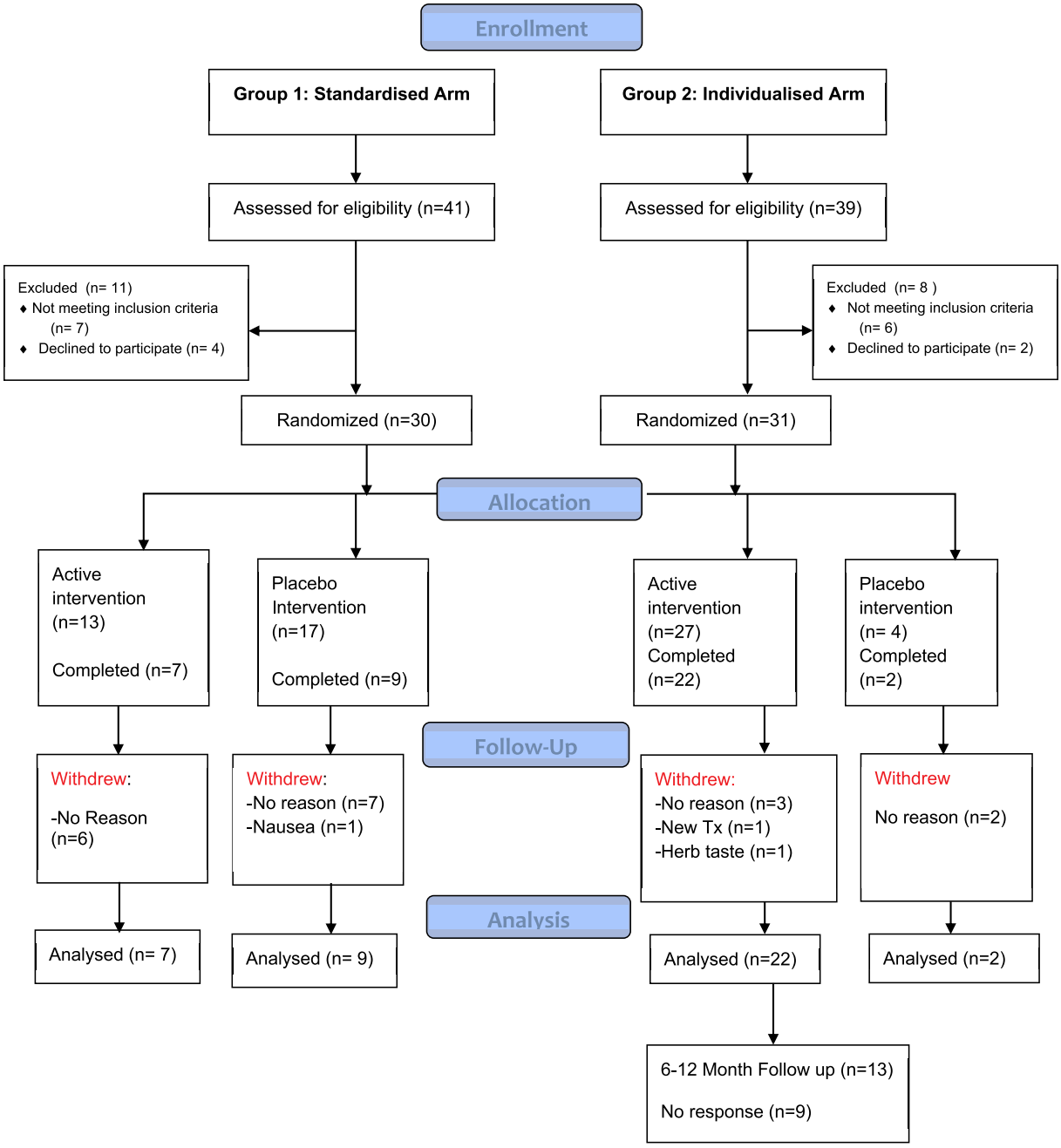


Seven out of thirteen participants (53.8%) reported having no UTIs in the 6-12 months post trial. Overall there was an average frequency of infection per participant of 0.46.



Use of antibiotics showed a marked decline 6 months post trial. Two participants (15.4%) reported no change and 84.6% reported a decrease in usage. Seven participants (53.5%) reported completely stopping antibiotics.





References

Albert, X., Huertas, I., Pereiró, I., Sanfélix, J., Gosalbes, V., Perrota, C., 2004. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst. Rev. 3.

Aydin, A., Ahmed, K., Zaman, I., Khan, M.S., Dasgupta, P., 2015. Recurrent urinary tract infections in women. Int. Urogynecol. J. 26 (6), 795–804.

Bensky, D., Clavey, S., Stoger, E., 2004. Chinese Herbal Medicine: Materia Medica, third ed. .

Bian, C.-M., 2005. Study on the Anti-microbial Effect of the Extraction Oldenlandia diffusa(Willd) Roxb, vol. 10. LiShiZhen Medicine and Materia Medica Research Ethics, pp. 2.

Butler, C.C., Hillier, S., Roberts, Z., Dunstan, F., Howard, A., Palmer, S., 2006. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with E. coli UTIs. Br. J. Gen. Pract. 56 (530), 686–692.

Car, J., Sheikh, A., 2003. Recurrent urinary tract infection in women. Br. Med. J. 327.

Chen, J.K., Chen, T.T., 2004. Chinese Medical Herbology & Pharmacology. Art of Medicine Press.

Chen, L., Cheng, X., Shi, W., Lu, Q., Go, V.L., Heber, D., Ma, L., 2005. Inhibition of growth of Streptococcus mutans, methicillin-resistant Staphylococcus aureus, and vancomycin-resistant enterococci by kurarinone, a bioactive flavonoid isolated from Sophora flavescens. J. Clin. Microbiol. 43 (7), 3574–3575.

Chen, M.L., Xian, Y.F., Ip, S.P., Tsai, S.H., Yang, J.Y., Che, C.T., 2010. Chemical and biological differentiation of cortex phellodendri chinensis and cortex phellodendri amurensis. Planta Med. 76 (14), 1530–1535.

Cho, W.C., Leung, K.N., 2007. In vitro and in vivo immunomodulating and immunorestorative effects of Astragalus membranaceus. J. Ethnopharmacol. 113 (1), 132–141.

Falagas, M.E., Athanasiou, S., Iavazzo, C., Tokas, T., Antsaklis, A., 2008. Urinary tract infections after pelvic floor gynecological surgery: prevalence and effect of antimicrobial prophylaxis. A systematic review. Int. Urogynecol. J. 19 (8), 1165–1172.

Flower, A., Bishop, F.L., Lewith, G., 2014. How women manage recurrent urinary tract infections: an analysis of postings on a popular web forum. BMC Fam. Pract. 15 (1), 1–8.

Flower, A., Lewith, G., 2012. A prospective case series exploring the role of Chinese herbal medicine in the treatment of recurrent urinary tract infections. Eur.. J. of Integr. Med 4 (4), 421–428.

Flower, A., Lewith, G., Liu, J.P., Gibbs, R., Hicks, J., 2016a. Applying the principles of the Five Phase (Wu Xing) model to inform good practice for studies of Chinese herbal medicine. Eur. J. Integr. Med. 8 (3), 191–197.

Flower, A., Wang, L., Lewith, G., Liu, J., Li, Q., 2015. Chinese herbal medicine for treating

recureent urinary tract infections. Cochrane Database Syst. Rev.(6), CD010446. https://doi.org/10.1002/14651858.CD010446.pub2.
Flower, A., Harman, K., Lewith, G., Moore, M., Bishop, F., Stuart, B., Lampard, N., 2016b. Standardised Chinese herbal treatment delivered by GPs compared with individualised treatment administered by practitioners of Chinese herbal medicine for women with recurrent urinary tract infections (RUTI): study protocol for a randomised controlled trial. Trials 17 (358).
Foxman, B., 2010. The epidemiology of urinary tract infection. Nat. Rev. Urol. 7, 653.
Franco, A.V., 2005. Recurrent urinary tract infections. Best Pract. Res. Clin. Obstet. Gynaecol. 19 (6), 861–873.
Gupta, S., Zhang, D., Yi, J., Shao, J., 2004. Anticancer activities of Oldenlandia diffusa. J. Herb. Pharmacother. 4 (1), 21–33.
Harding, G.K., Ronald, A.R., Nicolle, L.E., Thomson, M.J., Gray, G.J., 1982. Long-term antimicrobial prophylaxis for recurrent urinary tract infection in women. Rev. Infect. Dis. 4 (2), 438–443.
Hooton, T.M., Scholes, D., Hughes, J.P., Winter, C., Roberts, P.L., Stapleton, A.E., Stergachis, A., Stamm, W.E., 1996. A prospective study of risk factors for symptomatic urinary tract infection in young women. N. Engl. J. Med. 335 (7), 468–474.
Huang, K.C., 1999. The Pharmacology of Chinese Herbs. CRC Press, London.
Kim, S.J., Chung, W.S., Kim, S.S., Ko, S.G., Um, J.Y., 2011. Antiinflammatory effect of Oldenlandia diffusa and its constituent, hentriacontane, through suppression of caspase-1 activation in mouse peritoneal macrophages. Phytother Res. 25 (10), 1537–1546.
Kumarasamy, K.K., Toleman, M.A., Walsh, T., Bagaria, J., Butt, F., Balakrishnan, R., Chaudhary, U., Doumith, M., Giske, C.G., Irfan, S., 2010. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect. Dis. 10 (9), 597–602.
Kunin, C.M., 1994. Urinary tract infections in females. Clin. Infect. Dis. 18, 10.
Leydon, G., Turner, S., Smith, H., Little, P., 2010. Women's views about management and cause of urinary tract infection: qualitative interview study. BMJ 340.
Little, P., Merriman, R., Turner, S., Rumsby, K., Warner, G., Lowes, J.A., Smith, H., Hawke, C., Leydon, G., Mullee, M., Moore, M.V., 2010a. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. Br. Med. J. 340.
Little, P., Moore, M., Turner, S., Rumsby, K., Warner, G., Lowes, J., Smith, H., Hawke, C., Leydon, G., Arscott, A., 2010b. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ 340, c199.
Liu, Z.L., Liu, Z.J., Liu, J.P., Yang, M., Kwong, J., 2010. Herbal Medicines for Viral Myocarditis, vol. 7 The Cochrane database of systematic reviews CD003711-CD003711.
Luo, Y., Liu, M., Yao, X., Xia, Y., Dai, Y., Chou, G., Wang, Z., 2009. Total alkaloids from Radix Linderae prevent the production of inflammatory mediators in lipopolysaccharide-stimulated RAW 264.7 cells by suppressing NF-kappaB and MAPKs activation. Cytokine 46 (1), 104–110.
Ma, X., Zheng, C., Hu, C., Rahman, K., Qin, L., 2011. The genus Desmodium (Fabaceae)-traditional uses in Chinese medicine, phytochemistry and pharmacology. J. Ethnopharmacol. 138 (2), 314–332.
Maciocia, G., 1994. The Practice of Chinese Medicine. Churchill Livingstone.
Milo, G.K., Eugene, Paul, Mical, Christiaens, Thierry, Baerheim, Anders, Leibovici, Leonard, 2005. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst. Rev.(2).
Ohno, T., Takemura, G., Murata, I., Kagawa, T., Akao, S., Minatoguchi, S., Fujiwara, T., Fujiwara, H., 2005. Water extract of the root of Lindera strychnifolia slows down the progression of diabetic nephropathy in db/db mice. Life Sci. 77 (12), 1391–1403.
Park, E.K., Rhee, H.I., Jung, H.S., Ju, S.M., Lee, Y.A., Lee, S.H., Hong, S.J., Yang, H.I., Yoo, M.C., Kim, K.S., 2007. Antiinflammatory effects of a combined herbal preparation (RAH13) of Phellodendron amurense and Coptis chinensis in animal models of inflammation. Phytother Res. 21 (8), 746–750.
Peng, B.L.Q., Hou, J., Zhou, S.C., 2011. Lysimachia Christinae Hance Tablet in treatment of urinary tract infection:a randomized,multicenter,controlled clinical study. Mod. Med. Health 11.
Renard, J., Ballarini, S., Mascarenhas, T., Zahran, M., Quimper, E., Choucair, J., Iselin, C.E., 2014. Recurrent lower urinary tract infections have a detrimental effect on patient quality of life: a prospective, observational study. Infect. Dis. Ther. (4), 125–135.
Sanford, J.P., 1975. Urinary tract symptoms and infections. Annu. Rev. Med. 26 (1), 485–498.
Shon, Y.H., Kim, J.H., Nam, K.S., 2002. Effect of Astragali radix extract on lipopolysaccharide-induced inflammation in human amnion. Biol. Pharm. Bull. 25 (1), 77–80.
Silverman, J., Schreiber 4th, H.L., Hooton, T.M., Hultgren, S.J., 2013. From physiology to pharmacy: developments in the pathogenesis and treatment of recurrent urinary tract infection. Curr. Urol. Rep. 14 (5), 9 Oct.
Spelman, K., Burns, J., Nichols, D., Winters, N., Ottersberg, S., Tenborg, M., 2006. Modulation of cytokine expression by traditional medicines: a review of herbal immunomodulators. Altern. Med. Rev. 11 (2), 128–150.
Stapleton, A., 1999. Host factors in susceptibility to urinary tract infections. In: Advances in Bladder Research. Springer, pp. 351–358.
Tan, B.K., Vanitha, J., 2004. Immunomodulatory and antimicrobial effects of some traditional Chinese medicinal herbs: a review. Curr. Med. Chem. 11 (11), 1423–1430.
Trill, J., Simpson, C., Webley, F., Radford, M., Stanton, L., Maishman, T., Galanopoulou, A., Flower, A., Eyles, C., Willcox, M., Hay, A., Griffiths, G., Little, P., Lewith, G., Moore, M., 2017. Uva-ursi extract and ibuprofen as alternative treatments of adult female urinary tract infection (ATAFUTI): study protocol for a randomised controlled trial. Trials 18 (421).
Wong, C.K.M., Kung, K., Au-Doung, P.L.W., Ip, M., Lee, N., Fung, N., Wong, S.Y.S., 2017. Antibiotic resistance rates and physician antibiotic prescription patterns of uncomplicated urinary tract infections in southern Chinese primary care. PLoS One 13 (2).
Wong, C.K.M., Kung, K., Au-Doung, P.L.W., Ip, M., Lee, N., Fung, N., Wong, S.Y.S., 2018. Correction: antibiotic resistance rates and physician antibiotic prescription patterns of uncomplicated urinary tract infections in southern Chinese primary care. PLoS One 13 (2).
Yan, R., Yang, Y., Zeng, Y., Zou, G., 2009. Cytotoxicity and antibacterial activity of Lindera strychnifolia essential oils and extracts. J. Ethnopharmacol. 121 (3), 451–455.
Yesilada, E., Bedir, E., Calis, I., Takaishi, Y., Ohmoto, Y., 2005. Effects of triterpene saponins from Astragalus species on in vitro cytokine release. J. Ethnopharmacol. 96 (1–2), 71–77.
Yin, X., Chen, L., Liu, Y., Yang, J., Ma, C., Yao, Z., Yang, L., Wei, L., Li, M., 2010. Enhancement of the innate immune response of bladder epithelial cells by Astragalus polysaccharides through upregulation of TLR4 expression. Biochem. Biophys. Res. Commun. 397 (2), 232–238.
Yu, H.H., Kim, K.J., Cha, J.D., Kim, H.K., Lee, Y.E., Choi, N.Y., You, Y.O., 2005. Antimicrobial activity of berberine alone and in combination with ampicillin or oxacillin against methicillin-resistant Staphylococcus aureus. J. Med. Food 8 (4), 454–461.
Zhang, C., Zhu, C., Ling, Y., Zhou, X., Dong, C., Luo, J., Liu, Y., 2013. The clinical value of Huangqi injection in the treatment of leucopenia: a meta-analysis of clinical controlled trials. PLoS One 8 (12) e83123-e83123.
Zhu, Y.P., 1998. Chinese Materia Medica: Chemistry, Pharmacology and Applications. Harwood Academic Publications.