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The effectiveness and safety of moxibustion as an adjunct or benign prostatic hyperplasia with lower urinary tract symptoms: a protocol for a parallel-group, randomized, controlled pilot trial

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ABSTRACT

Introduction

This study aims to assess the feasibility of moxibustion as a supplementary intervention for patients with benign prostate hyperplasia (BPH) accompanying moderate to severe lower urinary tract symptoms (LUTS).

Methods and analysis

A total of 60 patients diagnosed with benign prostatic hyperplasia by a urologist based on prostate size, prostate-specific antigen (PSA), and clinical symptoms will participate of their own free will, and urologists will monitor patients and evaluate their symptoms. The patients will be randomized into a conventional group or integrative group with a 1:1 allocation according to computer-generated random numbers concealed in opaque, sealed, sequentially numbered envelopes. Watchful waiting or oral medication including alpha-blocker, 5-alpha-reductase inhibitors (5-ARIs) or anti-muscarinic drugs will be offered as a conventional treatment. Integrative treatment will include moxibustion therapy in addition to the conventional treatment. The moxibustion therapy will be conducted twice per week for four weeks on the bilateral acupoints SP6, LR3 and CV4 by a qualified Korean medical doctor (KMD). The primary outcome will be the international prostate symptom score (IPSS) after 8 sessions. The secondary outcomes will be the post-void residual urine volume (PVR), the maximum urinary flow rate (Qmax), IPSS, the results of a short-form 36-question health survey (SF-36) after 12 weeks and the patients' global impression of changes (PGIC) at each visit.

Ethics and dissemination

Written informed consent will be obtained from all participants. This study was approved by the IRBs of both PNUYH and PNUKH.

Trial registration number: clinicaltrials.gov. NCT02051036 (Date: 01/26/2014)

Strengths and limitations of this study

- The design of this clinical trial is based on an experts' conference with KMDs, urologic doctors (UDs), and an Eastern-Western integrative medicine specialist who has both MD and KMD licenses to develop an optimal integrative treatment.

- Optimal conventional oral medications and a customized number of moxibustion layers for each patient are used to reflect the real clinical setting.
- This study's results can serve as a basis for further large studies or studies of intractable urinary disorders.
- The statistical power of the study may be low due to the small sample size.
- Practitioners and patients cannot be blinded.

INTRODUCTION

Korean statistical data show that the prevalence of benign prostatic hyperplasia (BPH) in men over 65 years was 17.9% in 2011[1], and BPH ranked 25th among male outpatient visits by frequency of disease in 2013[2].

BPH causes lower urinary tract symptoms (LUTS) by directly disturbing the bladder outlet or increasing the tension and resistance of smooth muscles[3]. For treatment, watchful waiting at the beginning and behaviour modification with oral medication are recommended[3 4], and these methods have proved effective in improving LUTS, urinary flow rate and post-void residual urine in many previous studies[5-7].

However, this conventional treatment is limited by certain side effects. For alpha-blockers, rhinitis (6.6%), dizziness (4.4%)[5], abnormal ejaculation (2.1-2.8%)[5 8], and faintness (5.4%)[9] as an indicator of cardiovascular side effects of tamsulosin have been observed. Additionally, abnormal ejaculation (14.2%-28.1%) caused by silodosin[8 10]; cardiovascular adverse events (5.7% hypertension, 3.9% non-hypertension)[11] and mild dizziness (13.9%)[9] caused by alfuzosin; severe dizziness leading to drug-suspension (2.0%) caused by terazosin[12]; and erectile dysfunction (3.56%), dizziness (4.41%), postural hypotension (4.03%) and asthenia (4.08%)[13] caused by doxazosin have been verified. In addition, erectile dysfunction (4.53%), dizziness (2.33%), postural hypotension (2.56%), decreased libido (2.36%) and abnormal ejaculation (1.78%)[13] caused by finasteride and dry mouth (24%), dyspepsia (5%), back pain (5%), micturition disorder (5%), constipation (3%), and urinary retention (3%)[14] caused by tolterodine have been shown to occur. In particular, when two or more types of these medications are combined, each side effect is expected; thus, careful use only for patients with moderate to severe BPH is recommended[4].

To overcome this limitation, many studies investigating complementary and alternative medical (CAM) treatment have been conducted, but the 2011 American Urological Association's (AUA) guideline reported that no definite evidence exists to recommend CAM treatment due to the lack of quality and quantity of CAM studies of BPH[3].

In contrast, clinical studies of acupuncture or herbal medication for BPH with LUTS have been consistently performed[15-19] and have demonstrated the effectiveness of these methods. Moxibustion has been shown to be effective in treating urinary disorders[20], but well-designed clinical trials to prove its effectiveness are lacking. Therefore, we designed a clinical trial to evaluate the effectiveness and safety of moxibustion treatment to develop an optimal integrative treatment that can be accepted by both MDs and KMDs in the present medical system. The design of this clinical trial is based on a literature survey and an experts' conference with KMDs,

urologic doctors (UDs), and an Eastern-Western integrative medicine specialist who has both MD and KMD licenses. This study is a randomized controlled trial with a parallel-group, 1:1 allocation, exploratory and pragmatic design.

METHODS AND ANALYSIS

1. Aims

The present study aims to evaluate the feasibility and the effect-size for superiority-verification research on the effectiveness and safety of integrative treatment compared with conventional treatment for patients with BPH accompanying LUTS. This is a single-centre, assessor- and analyser-blinded, parallel-group, 1:1 allocation, pragmatic randomized controlled study.

2. Recruitment

Notices were posted in front of the Pusan National University Yangsan Hospital (PNUYH) urologic office and the Pusan National University Korean Medicine Hospital (PNUKH) genitor-urinary clinic office, and advertising for the study was also placed on the internet homepage of PNUKH. A UD will confirm the diagnosis of benign prostatic hyperplasia and needlessness of surgical treatment for patients who volunteer to participate. A KMD will thoroughly examine all inclusion/exclusion criteria and explain the trial to eligible patients. When the patient decides to participate in the study, the KMD will obtain written informed consent, and a baseline assessment will be performed. The progress of the study will consist of a screening phase, a treatment phase and follow-up. A more detailed description of the study is shown in figure 1. The time schedule for participation is shown in table 1.

3. Study design

Randomization and allocation concealment

A statistician who does not take part in this study will place the computer-generated random list into each double-layered opaque envelope, seal it and write the numbers in sequence. A practitioner will give the envelope to the patient according to the visit order and open it with the patient.

4. Patients

4.1. Sample size

The sample size calculation was not performed based on a power calculation because this is a pilot study. The sample size was determined based on estimates of the number of patients expected to participate and the

minimum number to evaluate the pragmatic purpose of this trial. Thus, a sample size of 30 per group and total number of 60 will be included, which is larger than the minimum number required for pilot studies[21].

4.2. Inclusion criteria

1. Male patients aged 20-80 years diagnosed with BPH with a prostate size over 20 gm
2. IPSS score ≥ eight
3. Written informed consent obtained
4. Patient must understand and answer the IPSS

4.3. Exclusion criteria

1. Prostate or bladder malignancy
2. Received herbal medication for lower urinary tract symptoms within one week
3. History of a brain disease that can cause urinary difficulty
4. Difficulty answering IPSS due to cognitive impairment
5. Signs of acute urinary tract infection
6. Diabetic mellitus
7. Neurogenic bladder

4.4. Drop-out criteria and process of management

4.4.1. Definition of drop-out

Completed cases will be defined as patients who finish the treatment progress and follow-up. Patients who cannot complete the study due to side effects or for other reasons will be considered drop-out cases.

4.4.2. Drop-out criteria

The researcher may stop treatment and observation of a patient according to prescribed criteria, and the patient can drop-out voluntarily at any time. The drop-out criteria are as follows.

1. Violation of inclusion/exclusion criteria
2. Serious adverse events or adverse events making a patient wish to drop out
3. Severe systemic disease that was not recognized at baseline

4. Patients or a legal representative demand cessation of the trial due to unsatisfying effects or withdrawal of consent
5. Trial compliance of less than 80%
6. Protocol violation of patient or researcher
7. Difficulty conducting moxibustion due to newly developed disease or uncooperative manner
8. Patients not replying to outcome measures
9. Patient's desire or UD's recommendation for surgical treatment (including minimally invasive therapies)

4.4.3. Management process

The drop-out date, time and reason will be recorded on the end report. Patients can drop out voluntarily for any reason, at any time, and are not required to submit a reason. The researcher should make every effort to follow up with patients who have dropped out and record the reason for drop-out or the reason for not being able to determine a drop-out cause.

5. Blinding of outcome assessors and data analysers

The practitioner and patients cannot be blinded because this is an open-label study for moxibustion treatment. Assessors and analysers will be blinded. Urodynamic testing will be performed by an assistant who does not take part in the trial, and participants will be asked not to reveal their allotted group to the assistant. Subjective outcomes will be recorded by the patient. The groups will be marked "A" and "B" when the data are sent to the statistician to ensure that the groups are not recognized as the control group and experimental group. Un-blinding of the assessors will be permissible only in the case of a serious adverse event.

6. Interventions

6.1. Conventional treatment protocol

The conventional treatment will be set as the optimum treatment for each patient to develop a reasonable integrative treatment protocol[22].

The optimum treatment for each patient will be based on the UD's opinion. The UD will discuss behavioural modifications, such as water intake, with the patient. Watchful waiting will be used for patients without renal insufficiency, urinary retention, recurring infection or complications of bladder-outlet obstruction (BOO). Oral

medications will be prescribed when no therapeutic effect is observed after watchful waiting, and the medications will be selected in consideration of overactive bladder, prostate size and prostate-specific antigen (PSA). Preferentially, an alpha-blocker, such as alfuzosin, doxazosin, tamsulosin or terazosin, will be used for functional symptom mitigation. 5-ARIs, such as dutasteride and finasteride, will be used when the prostatic volume is > 40 ml or PSA > 1.4 ng/ml. For cases of a high risk of BPH progression, prostate ≥ 30 mg or PSA ≥ 1.5 ng/ml, a combination of an alpha-blocker and a 5-ARI will be used. Anticholinergic agents, such as tolterodine, will be prescribed for patients with overactive bladder but will need to be monitored for patients with ≥ 250 ml post-void residual urine. The conventional treatment components can be changed at the discretion of the UD because this research is a pragmatic study to evaluate the effectiveness and safety of additional moxibustion therapy and the conventional treatment will still be maintained for long-term follow-up[3 4].

6.2. Integrative treatment protocol

Moxibustion therapy will be added to the conventional treatment described in section 6.1 twice per week for four weeks. The moxibustion therapy will be conducted by a skilled KMD who has at least two years' experience in the clinic. The timeframes of the conventional treatment group (CG) and the integrative treatment group (IG) are shown in figure 2. Both the apparatus type and mini-pillar type moxibustion will be used.

The apparatus types are a Hatnim-moxa apparatus (Bosungsa, Incheon, South Korea) and a moxa pillar (Bosungsa, South Korea) that generates 65-70 °C of heat. Moxibustion will be conducted at acupoints CV4 on one layer of gauze (figure 3) for 30 minutes. This acupoint was selected based on the KM theory[20 23] and previous clinical studies[17 24]. Additional gauze will be offered layer by layer when the patient requests it due to intolerable heat. This apparatus-moxibustion will be stopped if the patient complains of intolerable heat even after the additional gauze is offered more than three times. If the patient cannot feel any heat once the moxa pillar is totally burned, the apparatus-moxibustion will be conducted one more time; the procedure can be performed one more time as before, but the number of apparatus-moxibustion applications cannot exceed three. The therapy can be stopped if a second-degree or higher burn occurs even before completing eight treatment sessions.

Kanghwa mini-moxa of "lowest" intensity, which generates heat of approximately 45 °C, will be used for mini-pillar-type indirect moxibustion. Mini-moxa will be conducted at bilateral acupoints SP6[17 20 25] and LR3[20 26 27] (figure 4). The mini-moxa will be removed when totally burned, which takes approximately 5 minutes, but it

may be removed if the patient complains of intolerable heat. The mini-moxa will not be repeated on the acupoint on which moxibustion was stopped per the patient's request. Repetitive mini-moxa will be performed on the acupoints at which the patient did not feel heat and completed prior mini-moxa for the entire burning period, up to a maximum of seven times on each point. Beginning with the second session, the treated region will be checked and further mini-moxa will not be allowed on an acupoint where a second-degree or higher burn occurred. In this case, the mini-moxa will be re-started after the burn is completely healed.

The treatment session of twice per week for 4 weeks was determined based on the studies of Yang T[28], Liu QG[29] and Wang Y[24], which reported the effective results and clinical experiences of two KMDs. The number of performed moxibustion treatments will be recorded in both the electronic medical record (EMR) and case report form (CRF) at every visit in adherence with intervention protocols.

It is reasonable to stop moxibustion therapy if a second-degree or higher burn occurs according to KM theory[30], and in this case, the patient will not be considered a study drop-out. However, if a patient cannot continue the treatment because of discomfort from the moxibustion smoke, allergic response or pigmentation from the moxa-soot, he cannot be regarded as having completed the trial.

6.3. Prohibited or allowed parallel medical treatments

Flexible oral medications according to the discretion of the UD's opinion are allowed to offer the best treatment for each patient; thus, the medications will not be fixed without variation. All types of medication therapy based on AUA guidelines and the Korean prostate society guideline will be allowed.

Surgical treatment, including transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), abdominal prostatectomy, minimally invasive therapy using a laser, transurethral needle ablation of the prostate (TUNA), and transurethral microwave thermotherapy (TUMT), are prohibited; therefore, patients who want or are recommended for such therapies cannot participate in this trial.

6.4. Treatment of adverse events

We will disinfect and dress the wound when a second-degree or higher burn occurs and will refer the patient to dermatology to receive proper treatment when a third-degree or higher burn occurs.

7. Outcome measures

7.1 Primary outcome measure

The IPSS after 8 sessions will be the primary outcome measure. IPSS was developed by the AUA in 1992, and a question regarding quality of life (QoL) was later added[31]. The Korean version was validated in 1996[32]. IPSS consists of seven sub-themes of incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. The severity scoring is as follows: 0-7, mildly symptomatic; 8-19, moderately symptomatic; and 20-35, severely symptomatic BPH. The separate QoL question requires the respondent to select a QoL category ranging from zero (delighted) to six (terrible).

7.2 Secondary outcome measure

7.2.1. Patient's global impression of changes (PGIC)

The PGIC will be recorded for each patient at every visit after the first treatment. PGIC is a scoring system used to evaluate the level of change from the beginning of the treatment, either conventional or integrative, to the time of the PGIC check. This scale considers limitations of physical activity, symptoms, emotions and QoL in general. The scoring is as follows: no change (or condition has become worse), 1; almost the same, hardly any change at all, 2; slightly better, but no noticeable change, 3; somewhat better, but the change has not made any real difference, 4; moderately better and a slight but noticeable change, 5; better and a definite improvement that has made a real and worthwhile difference, 6; a great deal better and a considerable improvement that has made a substantial difference, 7. In a similar way, each patient will be asked to circle one of the numbers 0 (much better) to 10 (much worse) written on a straight line that represents the change from the beginning to the time of evaluation[33].

7.2.2. The short-form 36-question health survey (SF-36)

The SF-36 will be checked at the baseline, after 4 sessions, after 8 sessions and after 12 weeks from the baseline. The SF-36 is a commonly used scale to evaluate health-related quality of life (HRQOL). This scale consists of physical function, physical role capability, bodily pain, general health perceptions, vitality, social role capability, emotional role capability and mental health[34].

7.2.3. The maximum urinary flow rate (Qmax)

Qmax changes from baseline to 12 weeks will be used as an objective outcome measure. Urodynamic study is

an invasive method to obtain objective and quantitative data on bladder-outlet function and storage function. Patients will attend the study when they feel a "normal" desire to urinate. The velocity of the external urine stream will be automatically obtained by a calculation using the voided volume and time[35].

7.2.4. Post-void residual urine volume (PVR)

PVR changes from baseline to 12 weeks will be evaluated because PVR increases when bladder-outlet function is incomplete[35]. PVR will be checked by ultrasonography immediately after the urodynamic study.

7.2.5. Long-term IPSS

The IPSS will be checked 12 weeks after the beginning of the study, after 8 weeks of completed moxibustion therapy, to evaluate the persistency of the effects of moxibustion therapy. This period of 12 weeks was determined based on a previous study[26], the clinical experiences of two KMDs, and the optimum follow-up period recommended in conventional treatment guidelines[60 70-73].

7.3 Adverse events

At every visit, patients will be asked if adverse effects have developed and, if so, what types of adverse effects. In particular, second-degree or higher burns and allergic responses of the skin or whole body will be examined thoroughly, and other types of discomfort will be checked.

8. Data collection

Subjective outcome measurements will be checked for each patient, and objective outcome measurement data will be preserved in both their original form and as an EMR. These data will be written on the CRF by a certificated clinical research coordinator (CRC). To promote patient retention and completion of follow-up, an honorarium will be provided with a differential rate according to the patients' participation.

9. Statistical analysis

9.1. Analysis of efficacy

Both intention-to-treat (ITT) and per-protocol (PP) analyses will be performed. The last observation carried forward (LOCF) method will be used for missing data in ITT analysis. The paired t-test will be used for

intragroup before/after treatment comparisons. The independent t-test will be used for intergroup comparisons. For non-parametric data, the Wilcoxon signed-rank test for intragroup and the Wilcoxon rank-sum test for intergroup test will be used. Categorical data, such as adverse effects, will be investigated by calculating the occurrence rate of adverse events for each group and then performing analysis with the chi-square test or Fisher's exact test. If statistically significant differences between two groups are observed or covariance is expected, analysis of covariance (ANCOVA) will be used. All of the statistical analysis will be done with two-tailed tests, and the significance level will be set as 0.05.

10. Safety

Expected adverse events, such as burns and allergic responses, will be recorded along with their modality, date of occurrence, and duration. Patients will report other unexpected adverse events freely. The severity of the adverse events will be categorized according to the WHO 5-grade performance status classification as follows: 0, able to carry out all normal activity without restriction; 1, restricted in strenuous activity but ambulatory and able to carry out light work; 2, ambulatory and capable of all self-care but unable to carry out any work activities and up and about more than 50% of waking hours; 3, symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden; 4, completely disabled, unable to carry out any self-care; totally confined to bed or chair. The cause-and-effect relation between the intervention and adverse events will be assessed according to the WHO-Uppsala Monitoring Centre (UMC) causality categories of 1, certain; 2, probable/likely; 3, possible; 4, unlikely; 5, conditional/unclassified; 6, unassessable/unclassifiable.

To minimize the expected adverse events, we will describe the risk of adverse events to patients who have prior allergic responses to moxibustion therapy, allergic rhinitis or allergic conjunctivitis. Patients will be informed to notify the practitioner if they experience such symptoms during the treatment to receive proper and prompt treatment. The treatment will be performed in a well-ventilated room, and a mask will be offered to cover the patient's mouth and nose. To prevent burns, patients will be educated about indirect moxibustion therapy and its precautions and informed to notify the practitioner promptly if they feel intolerable heat and wish to stop the treatment. The principal investigator (PI) will describe and assess all of the symptoms that occur during the clinical trial and will report to the institutional review board (IRB) to determine whether to continue or stop the study when serious adverse events occur.

Patients who suffer from adverse events will be treated as described in section 6.4. Additionally, patients who

suffer harm from this trial participation will be cared for through insurance. All patients will be informed of and sign off on the "regulation concerning subject compensation", including detailed descriptions of this regulation.

11. Monitoring

The independent data monitoring committee (DMC), composed of one KMD and one clinical research expert, will examine the process of progress and whether the trial follows the study plan, the standard guidelines, and clinical-trials management criteria and other related standards. Monitoring will be conducted by regular visits and phone calls. The DMC will check the original record and case report forms. If any problem is found, the DMC will discuss this with the PI. If any serious problems that could threaten the security of patients are found, the DMC will discuss this with the IRB and PI. The PI will make the final decision as to whether to continue or to terminate the trial, and the IRB can order the PI to terminate the trial in the case of a serious problem.

12. Ethical considerations and dissemination

12.1. Written informed consent and study approval

This study was approved by the IRBs of both PNUYH and PNUKH. A signed informed consent will be submitted from each patient to the practitioner. If any changes to the inclusion/exclusion criteria, outcome measure methods or data analysis are demanded, the decision will be made through a discussion between the UD and KMD. The changed contents would need to be reapproved by the IRB and reflected in the patient-explanation and study registration (clinicaltrials.gov), and a new consent from the patient would need to be obtained.

12.2. Private information protection

Collected data from patients will be safeguarded with specific serial numbers without any personally identifiable information so that nobody can recognize the patients except a security manager who has a code-table. Computer-stored personal information will be secured using a password, and all matters related to security will be supervised by the PI. Publication will not include any personally identifiable information, and data will be treated anonymously. Strict security is assured even in a case of a patient dropping out mid-study and after the end of the study.

Data used for the study will be disposed of after the collection of materials for a research paper. Computer

storage files will be deleted and documents will be shredded on 31st November, 2017.

The PI, a monitor and an inspector can read the patients' records for the purpose of monitoring and progress oversight in terms of laws and ethics. These data will be stored securely in the National Clinical Research Center for Korean Medicine. This matter will be explained to patients, who will also be provided a written explanation.

12.3. Dissemination

The trial results will be disseminated through open-access journals and conferences.

DISCUSSION

This is the first study protocol of a randomized controlled trial in Korea to evaluate the effectiveness and safety of moxibustion as a complement to conventional therapy for patients with BPH accompanying LUTS.

The medical system of South Korea has been maintained as a dualized system since the revival of KMD by the enactment of the National Medical Insurance Act in 1951. This system has had some negative aspects, such as the incautious use of medicine combinations and distrust between the two medical fields; however, it has had some positive aspects as well, including providing patients with a large variety of treatment choices[36]. Therefore, the necessity of integrative medicine has been propounded steadily to establish a new medical system combining the advantage of Western and Korean medicine[37].

This study was designed as an investigation of add-on treatment without a placebo control because methods of additional alternative treatments in conjunction with the conventional treatment are considered appropriate in light of the medical ethics and medical treatment system[38 39]. Despite relatively acceptable rates of adverse events, increased side effects caused by the combination of different types of oral drug[4] and by patient vulnerability factors, such as ageing and underlying disease, still must be investigated. Therefore, the effectiveness and safety of adjuvant treatments should be evaluated, after which the adjuvant treatment may be considered for intractable urinary disorders including interstitial cystitis and chronic prostatitis. Additionally, a pragmatic design is used to improve applicability to the clinical field and decision making[40 41]. Thus, we set broad inclusion/exclusion criteria and flexible interventions allowing for different treatment regimes according to each patient's medical condition. In addition, conventional oral medication is not restricted to one type considering the pragmatic purpose and the study ethics.

This study has some limitations. The prostate size is not included as an outcome measurement because this study aims to assess the effectiveness of treatment according to the functional improvement of LUTS. Therefore, studies evaluating the effect of the combined treatment on prostate size should be conducted after the LUTS-reduction effect is demonstrated. Future power analysis studies should be performed by determining the effect size based on the results of this study, and cost-effectiveness studies should be performed to provide important details for decision-makers.

TRIAL STATUS

This study is currently in the recruiting phase. The first patient enrolled on March 10th, 2014, and the article including results is expected in approximately 2016.

REFERENCES

1. Statistics Korea. Prevalence of Self-Recognintion On Chronic Disease and Doctor'S Diagnosys Rate by General Feature of The Aged (Over 65 Years Old) Secondary Prevalence of Self-Recognintion On Chronic Disease and Doctor'S Diagnosys Rate by General Feature of The Aged (Over 65 Years Old) 2011. http://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_11771_2011N036&conn_path=I2.
2. Statistics Korea. Outpatient Benefits by Frequency of Disease(Male). Secondary Outpatient Benefits by Frequency of Disease(Male) 2013. http://kosis.kr/statHtml/statHtml.do?orgId=350&tblId=DT_35001_A080011&conn_path=I2.
3. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011;**185**(5):1793-803.
4. Oelke M, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. European urology 2013;**64**(1):118-40.
5. Shim SR, Kim JH, Choi H, et al. General effect of low-dose tamsulosin (0.2 mg) as a first-line treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia: a systematic review and meta-analysis. Curr Med Res Opin 2014:1-36.
6. Cindolo L, Alvarez-Maestro M, Castellucci R, et al. Efficacy and safety of dutasteride for the treatment of symptomatic benign prostatic hyperplasia (BPH): a systematic review and meta-analysis. World J Urol 2014.
7. Guang-Jun D, Feng-Bin G, Xun-Bo J. alpha-Blockers in the management of acute urinary retention secondary to benign prostatic hyperplasia: a systematic review and meta-analysis. Ir J Med Sci 2014.
8. Chapple CR, Montorsi F, Tammela TL, et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. European urology 2011;**59**(3):342-52.
9. Djavan B, Chapple C, Milani S, et al. State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urology 2004;**64**(6):1081-8.
10. Wu YJ, Dong Q, Liu LR, et al. A meta-analysis of efficacy and safety of the new alpha1A-adrenoceptor-selective antagonist silodosin for treating lower urinary tract symptoms associated with BPH. Prostate cancer and prostatic diseases 2013;**16**(1):79-84.
11. van Kerrebroec P, Jardin A, van Cangh P, et al. Long-term safety and efficacy of a once-daily formulation of alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. European urology 2002;**41**(1):54-60; discussion 60-1.

12. Lowe F, Narayan P, Djavan B. Prospective, randomised, multicentre trial to evaluate the rapidity of onset and side effect profile of tamsulosin (TAM) vs terazosin (TER) in men with Benign Prostatic Hyperplasia (BPH). European Urology Supplements 2002;**1**(1):108.
13. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003;**349**(25):2387-98.
14. Abrams P, Kaplan S, De Koning Gans HJ, et al. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol 2006;**175**(3 Pt 1):999-1004; discussion 04.
15. Fu YQ. [Clinical observation on deep-oblique acupuncture with long needle at Guanyuan (CV 4) for urinary retention]. Zhongguo Zhen Jiu 2013;**33**(12):1071-5.
16. Wang Y, Liu B, Yu J, et al. Electroacupuncture for moderate and severe benign prostatic hyperplasia: a randomized controlled trial. PLoS One 2013;**8**(4):e59449.
17. Yu JS, Shen KH, Chen WC, et al. Effects of electroacupuncture on benign prostate hyperplasia patients with lower urinary tract symptoms: a single-blinded, randomized controlled trial. Evid Based Complement Alternat Med 2011;**2011**:303198.
18. Xu ZJ. [Efficacy observation on benign prostatic hyperplasia treated with acupuncture and moxibustion]. Zhongguo Zhen Jiu 2014;**34**(3):241-4.
19. Li S, Lu A, Wang Y. Symptomatic comparison in efficacy on patients with benign prostatic hyperplasia treated with two therapeutic approaches. Complementary therapies in medicine 2010;**18**(1):21-7.
20. Kim KM. A literature study of acupuncture and moxibustion therapy in the [the Urine] section(in the Naegyeong Chapter) of [Dong-Ui-Bo-Gam]. The Journal of Daejeon Oriental Medicine 2010;**19**(1):129-42.
21. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics 2005;**4**(4):287-91.
22. Witt CM, Reinhold T, Jena S, et al. Cost-effectiveness of acupuncture treatment in patients with headache. Cephalalgia 2008;**28**(4):334-45.
23. Li. D. *Perplexities to acupuncture and moxibustion*. Shanghai university of TCM press, 2007.
24. Song FJ, Jiang SH, Zheng SL, et al. [Electroacupuncture for post-stroke urinary incontinence: a multi-center randomized controlled study]. Zhongguo Zhen Jiu 2013;**33**(9):769-73.
25. Huh J. *Donguibogam*. South Korea: Donguibogam publisher, 2005.
26. Korean Acupuncture & Moxibustion Society Textbook Compilation Committee. *The Acupuncture and Moxibustion Medicine*. Paju, Gyeongi, South Korea: Jipmoon, 2008.
27. Kim JWK, T.G.; Lee, J.H.; Baek, J.U. A study on the selecting indications of Five - Viscera Source Point Acupuncture in Suwen. Journal of Korean Medical Classics 2013;**26**(4):23-42.
28. Yang T, Liu Z, Zhang X. Evaluation on therapeutic effects of electro acupuncture for benign prostatic hyperplasia: A prospective randomized controlled study. Chinese Journal of

Rehabilitation Medicine 2008;**23**(11):1028-31.

29. Liu QG, Wang CY, Jiao S, et al. [Electroacupuncture at Zhongji (CV 3) for treatment of benign hyperplasia of prostate: a multi-central randomized controlled study]. Zhongguo Zhen Jiu 2008;**28**(8):555-9.
30. Korean Acupuncture & Moxibustion Society Textbook Compilation Committee. *The Acupuncture and Moxibustion Medicine*. Paju, Gyeongi, South Korea: Jipmoon, 2008.
31. Barry MJ, Fowler FJ, Jr., O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992;**148**(5):1549-57; discussion 64.
32. Choi HR CW, Shim BS, Kwon SW, Hong SJ, Chung BH et al. Translation validity and reliability of I-PSS Korean version. Korean J Urol 1996;**37**:659-65.
33. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;**27**(1):26-35.
34. Han CW, Lee EJ, Iwaya T, et al. Development of the Korean version of Short-Form 36-Item Health Survey: health related QOL of healthy elderly people and elderly patients in Korea. Tohoku J Exp Med 2004;**203**(3):189-94.
35. Schafer W, Abrams P, Liao L, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 2002;**21**(3):261-74.
36. ES L. A study on utilization of oriental medical care. Korea Institute of Oriental Medicine 1999:1-5.
37. Lee SY BY. The present condition and the improvement method for western medicine-Korean medicine cooperative practice system. Korea Institute for Health and Social Affairs, Policy report 1997.
38. Lamb SE, Williamson EM, Heine PJ, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 2014.
39. Kim KH, Ryu JH, Park MR, et al. Acupuncture as analgesia for non-emergent acute non-specific neck pain, ankle sprain and primary headache in an emergency department setting: a protocol for a parallel group, randomised, controlled pilot trial. BMJ Open 2014;**4**(6):e004994.
40. Treweek S, Zwarenstein M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials 2009;**10**:37.
41. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC medical research methodology 2003;**3**:28.

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JNK, SDL and JGN conceived the study. JNK, SDL, JKN, JYH, YJY and HYL initiated the study design, and DHL, SHP, JHL and HLP helped with its implementation. JKN, DHL, JHY and HYL performed the intervention and discussed the optimal complementary medicine. HYL drafted the study protocol manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Competing interests

None

Access to data

The data from this trial will be accessible by contacting the corresponding author.

Ethics approval

The study was approved by IRBs of both Pusan National University Korean Medicine Hospital (IRB approval number 2013021) and Pusan National University Yangsan Hospital (IRB approval number 03-2013-013).

APPENDIX

Table 1. Trial progress

Period	Screening	Active treatment									F/U
Visit	Screening	1	2	3	4	5	6	7	8	9*	10
Week	0	1		2		3		4			12
Consent	●										
Demographic survey	●										
Medical history	●	○	○	○	○	○	○	○	○	●	●
Vital signs	●	○	○	○	○	○	○	○	○		●
Physical examination	●										
Conformity assessment	●										
Check PSA	●										
Check prostate size (TRUS)	●										
Inclusion/exclusion criteria	●										
Inform patient of the visit schedule	●	○	○	○	○	○	○	○	○	○	
Randomization	●										
Moxibustion		○	○	○	○	○	○	○	○		
IPSS	●					○				●	●
SF-36	●					○				●	●
PGIC			○	○	○	○	○	○	○	●	●
Qmax	●										●
PVR	●										●
FVC	●										●
Adverse event monitoring		○	○	○	○	○	○	○	○	○	○
Final compliance assessment											●

○: integrative group

●: both integrative group and conventional group

***visit 9: 1-3 days after visit 8**

PSA: prostate specific antigen; TRUS: transrectalultrasonography; IPSS: international prostate symptom; short-form 36-question health survey; PGIC: patients' global impression of changes; Qmax: maximum urinary flow rate; PVR: post-void residual urine volume; FVC: frequency-volume chart

Table 2. International prostate symptom score

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5

Nocturia	None	1 time	2 times	3 times	4 times	5 times or more
Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7, mildly symptomatic; 8-19, moderately symptomatic; 20-35, severely symptomatic.

Figures

Figure 1. Trial flowchart

Figure 2. Timeframe of the integrative treatment group (IG) and conventional treatment group (TG).

Figure 3. Apparatus-type moxibustion on CV4

Figure 4. Mini-pillar-type moxibustion on bilateral SP6 and LR3

Data Category	Information
Primary Registry and Trial Identifying number	NCT02051036
Date of Registration in Primary Registry	01/26/2014.
Secondary Identifying Numbers	NC1307
Source(s) of Monetary or Material Support	Korea Institute of Oriental Medicine
Primary Sponsor	Korea Institute of Oriental Medicine
Secondary Sponsor(s)	National Clinical Research Center
Contact for Public Queries	Corresponding author
Contact for Scientific Queries	Corresponding author
Public Title	Moxibustion as a complement to benign prostatic hyperplasia accompanying lower urinary tract symptoms
Scientific Title	The effectiveness and safety of moxibustion as a complement for benign prostatic hyperplasia with lower urinary tract symptoms
Countries of Recruitment	Korea, Republic of
Health Condition(s) or Problem(s) Studied	Benign prostatic hyperplasia with lower urinary tract symptoms
Intervention(s)	Treatment: moxibustion plus usual care
	Control: usual care alone
Key Inclusion and Exclusion Criteria	Ages eligible for study: between 20 and 80 years; sexes eligible for study: male; accepts healthy volunteers: no
	Inclusion criteria: 1. Male patients diagnosed benign prostate hyperplasia aged from 20 to 80 years; prostate size over 20 gm 2. Greater than or equal to a score of eight on the IPSS 3. Submit written consent 4. Patients who can understand and answer the IPSS
	Exclusion criteria: 1. Prostate or bladder malignancy 2. Received herbal medication for lower urinary tract symptoms within one week 3. History of brain disease which can cause urinary difficulty 4. Difficulty answering IPSS due to cognitive impairment 5. Signs of acute urinary tract infection 6. Diabetic mellitus 7. Neurogenic bladder
Study Type	Randomized controlled trial, parallel, 1:1 ratio, pilot study
	Allocation: randomized; intervention model: parallel assignment
	Primary purpose: international prostate symptom score
Date of First Enrolment	2014/03/10
Target Sample Size	60
Recruitment Status	recruiting
Primary Outcome(s)	International prostatic symptom score
Key Secondary Outcomes	Maximum uroflow rate, post-void residual urine

Figure 1. Trial flowchart

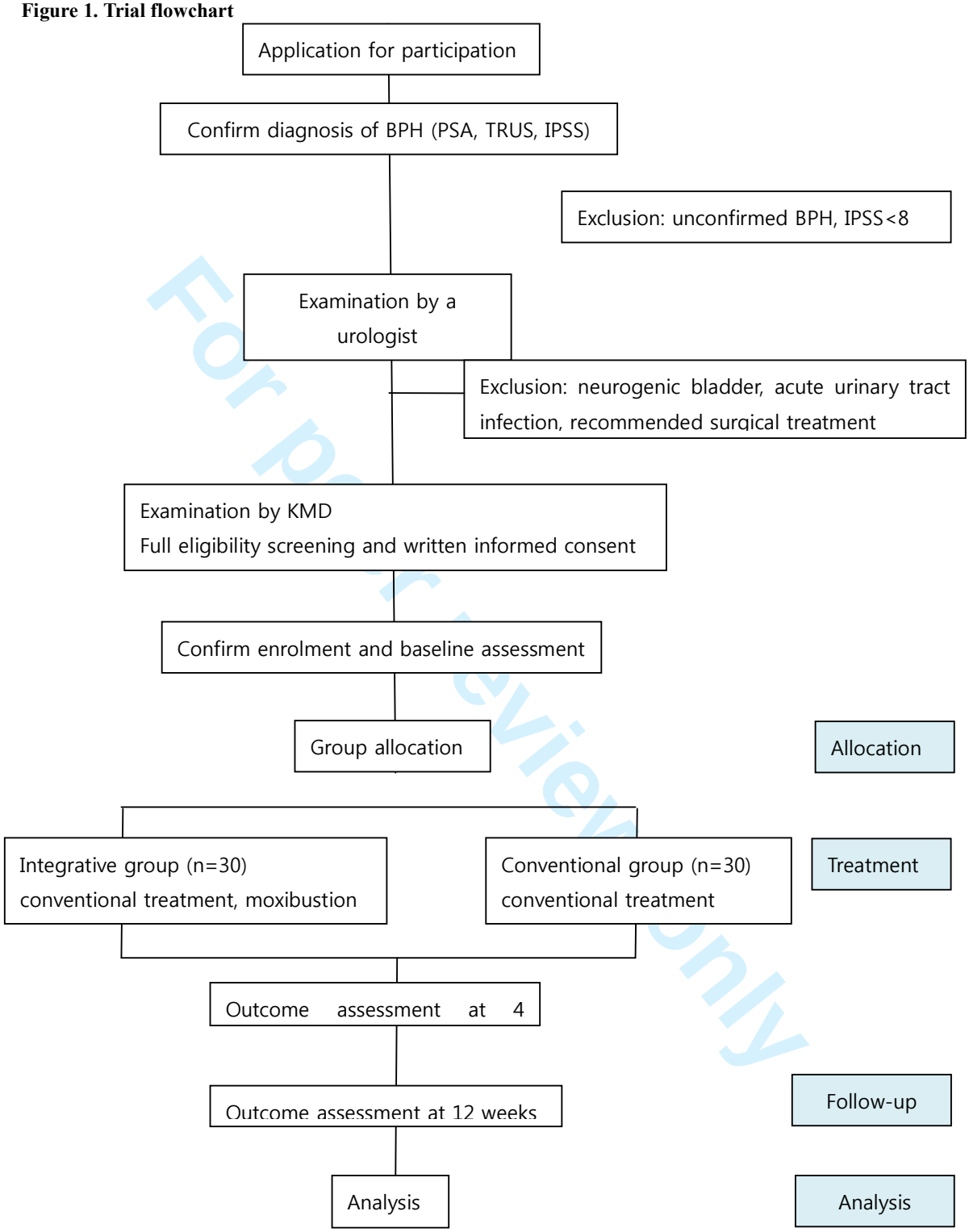


Figure 2. Timeframe of the integrative treatment group (IG) and conventional treatment group (TG).

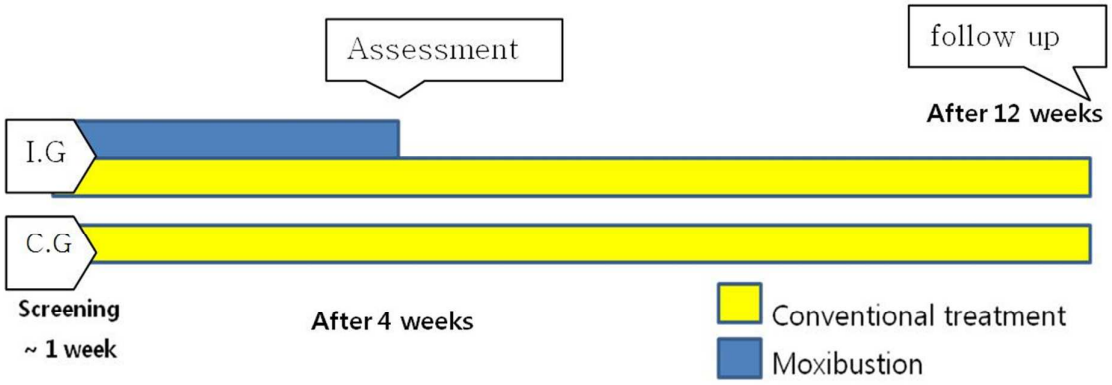


Figure 3. Apparatus-type moxibustion on CV4

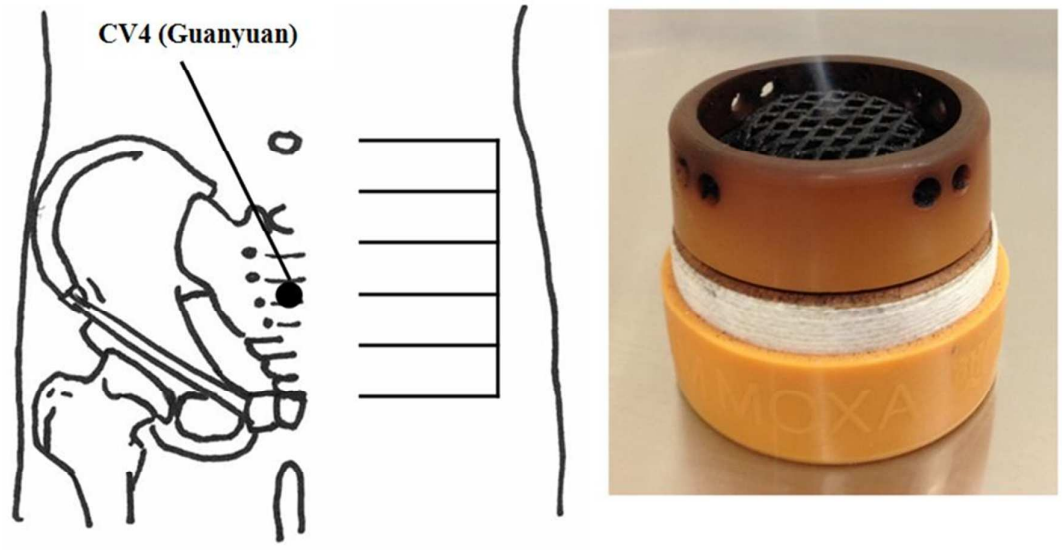
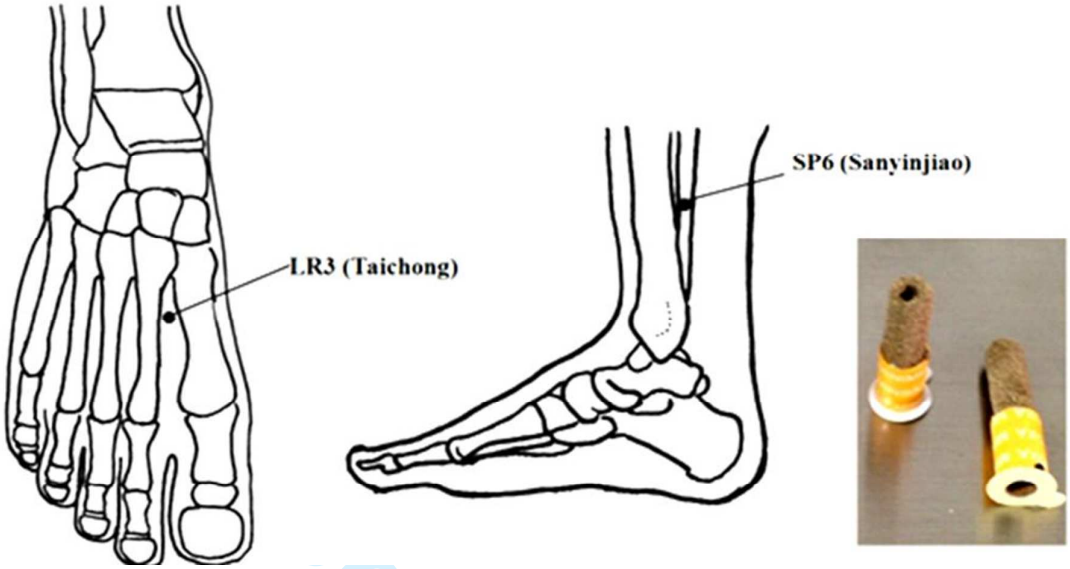


Figure 4. Mini-pillar-type moxibustion on bilateral SP6 and LR3



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	29
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	21

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13, 15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	none
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Moxibustion as an adjuvant for benign prostatic hyperplasia with lower urinary tract symptoms: a protocol for a parallel-group, randomized, controlled pilot trial

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Urology
Keywords:	Prostate disease < UROLOGY, moxibustion, Kidney & urinary tract disorders < UROLOGY, integrative medicine, lower urinary tract symptoms

Moxibustion as an adjuvant for benign prostatic hyperplasia with lower urinary tract symptoms: a protocol for a parallel-group, randomized, controlled pilot trial

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ABSTRACT

Introduction

This study aims to explore the feasibility of moxibustion as a supplementary intervention and to assess the sample size for verifying the effectiveness and safety of integrative treatment involving moxibustion compared with conventional treatment for patients with benign prostate hyperplasia (BPH) accompanying moderate to severe lower urinary tract symptoms (LUTS).

Methods and analysis

A total of 60 patients diagnosed with benign prostatic hyperplasia by a urologist based on prostate size, prostate-specific antigen (PSA), and clinical symptoms will participate of their own free will, and urologists will monitor patients and evaluate their symptoms. The patients will be randomized into a conventional group or integrative group with a 1:1 allocation according to computer-generated random numbers concealed in opaque, sealed, sequentially numbered envelopes. Watchful waiting or oral medication including alpha-blocker, 5-alpha-reductase inhibitors (5-ARIs) or anti-muscarinic drugs will be offered as a conventional treatment. Integrative treatment will include moxibustion therapy in addition to the conventional treatment. The moxibustion therapy will be conducted twice per week for four weeks on the bilateral acupoints SP6, LR3 and CV4 by a qualified Korean medical doctor (KMD). The primary outcome will be the international prostate symptom score (IPSS) after 8 sessions. The secondary outcomes will be the post-void residual urine volume (PVR), the maximum urinary flow rate (Qmax), IPSS, the results of a short-form 36-question health survey (SF-36) after 12 weeks and the patients' global impression of changes (PGIC) at each visit.

Ethics and dissemination

Written informed consent will be obtained from all participants. This study was approved by the IRBs of both PNUYH and PNUKH.

Trial registration number: clinicaltrials.gov. NCT02051036 (Date: 01/26/2014)

Strengths and limitations of this study

- The design of this clinical trial is based on an experts' conference with KMDs, urologic doctors (UDs),

and an Eastern-Western integrative medicine specialist who has both MD and KMD licenses to develop an optimal integrative treatment.

- Optimal conventional oral medications and a customized number of moxibustion layers for each patient are used to reflect the real clinical setting.
- This study's results can serve as a basis for further large studies or studies of intractable urinary disorders.
- The statistical power of the study may be low due to the small sample size.
- Practitioners and patients cannot be blinded.

INTRODUCTION

Korean statistical data show that the prevalence of benign prostatic hyperplasia (BPH) in men over 65 years was 17.9% in 2011[1], and BPH ranked 25th among male outpatient visits by frequency of disease in 2013[2].

BPH causes lower urinary tract symptoms (LUTS) by directly disturbing the bladder outlet or increasing the tension and resistance of smooth muscles[3]. For treatment, watchful waiting at the beginning and behaviour modification with oral medication are recommended[3 4], and these methods have proved effective in improving LUTS, urinary flow rate and post-void residual urine in many previous studies[5-7].

However, this conventional treatment is limited by certain side effects. For alpha-blockers, rhinitis (6.6%), dizziness (4.4%)[5], abnormal ejaculation (2.1-2.8%)[5 8], and faintness (5.4%)[9] as an indicator of cardiovascular side effects of tamsulosin have been observed. Additionally, abnormal ejaculation (14.2%-28.1%) caused by silodosin[8 10]; cardiovascular adverse events (5.7% hypertension, 3.9% non-hypertension)[11] and mild dizziness (13.9%)[9] caused by alfuzosin; severe dizziness leading to drug-suspension (2.0%) caused by terazosin[12]; and erectile dysfunction (3.56%), dizziness (4.41%), postural hypotension (4.03%) and asthenia (4.08%)[13] caused by doxazosin have been verified. In addition, erectile dysfunction (4.53%), dizziness (2.33%), postural hypotension (2.56%), decreased libido (2.36%) and abnormal ejaculation (1.78%)[13] caused by finasteride and dry mouth (24%), dyspepsia (5%), back pain (5%), micturition disorder (5%), constipation (3%), and urinary retention (3%)[14] caused by tolterodine have been shown to occur. In particular, when two or more types of these medications are combined, each side effect is expected; thus, careful use only for patients with moderate to severe BPH is recommended[4].

To overcome this limitation, many studies investigating complementary and alternative medical (CAM) treatment have been conducted, but the 2011 American Urological Association's (AUA) guideline reported that no definite evidence exists to recommend CAM treatment due to the lack of quality and quantity of CAM studies of BPH[3].

In contrast, clinical studies of acupuncture or herbal medication for BPH with LUTS have been consistently performed[15-19] and have demonstrated the effectiveness of these methods. Moxibustion has been shown to be effective in treating urinary disorders[20], but well-designed clinical trials to prove its effectiveness are lacking. Therefore, we designed a pilot trial to explore the feasibility of moxibustion as an adjuvant for BPH with LUTS based on the effectiveness and safety and to estimate the proper sample size for a future, large comparative effectiveness study, with the purpose of developing an optimal integrative treatment that can be accepted by

both MDs and KMDs in the present medical system. The design of this clinical trial is based on a literature survey and an experts' conference with KMDs, urologic doctors (UDs), and an Eastern-Western integrative medicine specialist who has both MD and KMD licenses. This pilot study is a randomized controlled trial with a parallel-group, 1:1 allocation, exploratory and pragmatic design.

METHODS AND ANALYSIS

1. Aims

The present study aims to evaluate the feasibility of moxibustion as an adjuvant for conventional treatment in BPH patients and to assess the proper sample size for verifying, in future studies, the effectiveness and safety of integrative treatment compared with conventional treatment for patients with BPH accompanying LUTS. This is a single-centre, assessor- and analyser-blinded, parallel-group, 1:1 allocation, pragmatic randomized controlled study.

2. Recruitment

Notices were posted in front of the Pusan National University Yangsan Hospital (PNUYH) urologic office and the Pusan National University Korean Medicine Hospital (PNUKH) genitor-urinary clinic office, and advertising for the study was also placed on the internet homepage of PNUKH. A UD will confirm the diagnosis of benign prostatic hyperplasia and needlessness of surgical treatment for patients who volunteer to participate. A KMD will thoroughly examine all inclusion/exclusion criteria and explain the trial to eligible patients. When the patient decides to participate in the study, the KMD will obtain written informed consent, and a baseline assessment will be performed. The progress of the study will consist of a screening phase, a treatment phase and follow-up. A more detailed description of the study is shown in figure 1. The time schedule for participation is shown in table 1.

3. Study design

Randomization and allocation concealment

A statistician who does not take part in this study will place the computer-generated random list into each double-layered opaque envelope, seal it and write the numbers in sequence. A practitioner will give the envelope to the patient according to the visit order and open it with the patient.

4. Patients

4.1. Sample size

The sample size calculation was not performed based on a power calculation because this is a pilot study. The

sample size was determined based on estimates of the number of patients expected to participate and the minimum number to evaluate the pragmatic purpose of this trial. Thus, a sample size of 30 per group and total number of 60 will be included, which is larger than the minimum number required for pilot studies[21].

4.2. Inclusion criteria

1. Male patients aged 20-80 years diagnosed with BPH with a prostate size over 20 gm
2. IPSS score ≥ eight
3. Written informed consent obtained
4. Patient must understand and answer the IPSS

4.3. Exclusion criteria

1. Prostate or bladder malignancy
2. Received herbal medication for lower urinary tract symptoms within one week
3. History of a brain disease that can cause urinary difficulty
4. Difficulty answering IPSS due to cognitive impairment
5. Signs of acute urinary tract infection
6. Diabetic mellitus
7. Neurogenic bladder

4.4. Drop-out criteria and process of management

4.4.1. Definition of drop-out

Completed cases will be defined as patients who finish the treatment progress and follow-up. Patients who cannot complete the study due to side effects or for other reasons will be considered drop-out cases.

4.4.2. Drop-out criteria

The researcher may stop treatment and observation of a patient according to prescribed criteria, and the patient can drop-out voluntarily at any time. The drop-out criteria are as follows.

1. Violation of inclusion/exclusion criteria
2. Serious adverse events or adverse events making a patient wish to drop out

3. Severe systemic disease that was not recognized at baseline

4. Patients or a legal representative demand cessation of the trial due to unsatisfying effects or withdrawal of consent

5. Trial compliance of less than 80%; should attend at least 7 of 8 treatment sessions in the integrative group and all of three major assessments (baseline, visit 9 and visit 10) in both groups

6. Protocol violation of patient or researcher

7. Difficulty conducting moxibustion due to newly developed disease or uncooperative manner

8. Patients not replying to outcome measures

9. Patient's desire or UD's recommendation for surgical treatment (including minimally invasive therapies)

4.4.3. Management process

The drop-out date, time and reason will be recorded on the end report. Patients can drop out voluntarily for any reason, at any time, and are not required to submit a reason. The researcher should make every effort to follow up with patients who have dropped out and record the reason for drop-out or the reason for not being able to determine a drop-out cause.

5. Blinding

5.1. Blinding of outcome assessors and data analysers

The practitioner and patients cannot be blinded because this is an open-label study for moxibustion treatment. Assessors and analysers will be blinded. Urodynamic testing will be performed by an assistant who does not take part in the trial, and participants will be asked not to reveal their allotted group to the assistant. Subjective outcomes will be recorded by the patient. The groups will be marked "A" and "B" when the data are sent to the statistician to ensure that the groups are not recognized as the control group and experimental group. Un-blinding of the assessors will be permissible only in the case of a serious adverse event.

5.2. The rationale for the lack of a sham moxibustion group

For the pragmatic purpose of the future study, we decided to reflect the real clinical situation without omitting the patients' additional time, effort and expectations by comparing patients who receive conventional treatment with patients who receive both conventional treatment and complementary treatment. A sham or placebo

intervention group is the ideal method for efficacy studies with an optimal, strictly restricted design to minimize all influencing factors to prove the efficacy of a specific component of intervention[22 23]. Consequently, a sham moxibustion group will not be included in this study.

6. Interventions

6.1. Conventional treatment protocol

The conventional treatment will be set as the optimum treatment for each patient to develop a reasonable integrative treatment protocol[24].

The optimum treatment for each patient will be based on the UD's opinion. The UD will discuss behavioural modifications, such as water intake, with the patient. Watchful waiting will be used for patients without renal insufficiency, urinary retention, recurring infection or complications of bladder-outlet obstruction (BOO). Oral medications will be prescribed when no therapeutic effect is observed after watchful waiting, and the medications will be selected in consideration of overactive bladder, prostate size and prostate-specific antigen (PSA). Preferentially, an alpha-blocker, such as alfuzosin, doxazosin, tamsulosin or terazosin, will be used for functional symptom mitigation. 5-ARIs, such as dutasteride and finasteride, will be used when the prostatic volume is > 40 ml or PSA > 1.4 ng/ml. For cases of a high risk of BPH progression, prostate ≥ 30 mg or PSA ≥ 1.5 ng/ml, a combination of an alpha-blocker and a 5-ARI will be used. Anticholinergic agents, such as tolterodine, will be prescribed for patients with overactive bladder but will need to be monitored for patients with ≥ 250 ml post-void residual urine. The conventional treatment components can be changed at the discretion of the UD because this research is a pragmatic study to evaluate the effectiveness and safety of additional moxibustion therapy and the conventional treatment will still be maintained for the last follow-up[3 4].

6.2. Integrative treatment protocol

Moxibustion therapy will be added to the conventional treatment described in section 6.1 twice per week for four weeks. The moxibustion therapy will be conducted by a skilled KMD who has at least two years' experience in the clinic. The timeframes of the conventional treatment group (CG) and the integrative treatment group (IG) are shown in figure 2. Both the apparatus type and mini-pillar type moxibustion will be used.

The apparatus types are a Hatnim-moxa apparatus (Bosungsa, Incheon, South Korea) and a moxa pillar (Bosungsa, South Korea) that generates 65-70 °C of heat. Moxibustion will be conducted at acupoints CV4 on

one layer of gauze (figure 3) for 30 minutes. This acupoint was selected based on the KM theory[20 25] and previous clinical studies[17 26]. Additional gauze will be offered layer by layer when the patient requests it due to intolerable heat. This apparatus-moxibustion will be stopped if the patient complains of intolerable heat even after the additional gauze is offered more than three times. If the patient cannot feel any heat once the moxa pillar is totally burned, the apparatus-moxibustion will be conducted one more time; the procedure can be performed one more time as before, but the number of apparatus-moxibustion applications cannot exceed three. The therapy can be stopped if a second-degree or higher burn occurs even before completing eight treatment sessions.

Kanghwa mini-moxa of "lowest" intensity, which generates heat of approximately 45 °C, will be used for mini-pillar-type indirect moxibustion. Mini-moxa will be conducted at bilateral acupoints SP6[17 20 27] and LR3[20 28 29] (figure 4). The mini-moxa will be removed when totally burned, which takes approximately 5 minutes, but it may be removed if the patient complains of intolerable heat. The mini-moxa will not be repeated on the acupoint on which moxibustion was stopped per the patient's request. Repetitive mini-moxa will be performed on the acupoints at which the patient did not feel heat and completed prior mini-moxa for the entire burning period, up to a maximum of seven times on each point. Beginning with the second session, the treated region will be checked and further mini-moxa will not be allowed on an acupoint where a second-degree or higher burn occurred. In this case, the mini-moxa will be re-started after the burn is completely healed.

The treatment session of twice per week for 4 weeks was determined based on the studies of Yang T[30], Liu QG[31] and Wang Y[26], who reported the effective results and clinical experiences of two KMDs considering practicality in terms of the patients' general social environment and the accessibility of the hospital. The number of performed moxibustion treatments will be recorded in both the electronic medical record (EMR) and case report form (CRF) at every visit in adherence with intervention protocols.

It is reasonable to stop moxibustion therapy if a second-degree or higher burn occurs according to KM theory[32], and in this case, the patient will not be considered a study drop-out. However, if a patient cannot continue the treatment because of discomfort from the moxibustion smoke, allergic response or pigmentation from the moxa-soot, he cannot be regarded as having completed the trial.

6.3. Prohibited or allowed parallel medical treatments

Flexible oral medications according to the discretion of the UD's opinion are allowed to offer the best treatment

for each patient; thus, the medications will not be fixed without variation. All types of medication therapy based on AUA guidelines and the Korean prostate society guideline will be allowed.

Surgical treatment, including transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), abdominal prostatectomy, minimally invasive therapy using a laser, transurethral needle ablation of the prostate (TUNA), and transurethral microwave thermotherapy (TUMT), are prohibited; therefore, patients who want or are recommended for such therapies cannot participate in this trial.

6.4. Treatment of adverse events

We will disinfect and dress the wound when a second-degree or higher burn occurs and will refer the patient to dermatology to receive proper treatment when a third-degree or higher burn occurs.

7. Outcome measures

This study aims to 1) obtain information on whether moxibustion can be beneficial to BPH patients accompanying LUTS as an adjuvant treatment based on its effectiveness and safety and 2) determine the effect size to calculate the proper sample size for future research. Thus, outcomes regarding the functional improvement and the adverse events will be measured.

7.1 Primary outcome measure

The IPSS after 8 sessions will be the primary outcome measure. IPSS was developed by the AUA in 1992, and a question regarding quality of life (QoL) was later added[33]. The Korean version was validated in 1996[34]. IPSS consists of seven sub-themes of incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. The severity scoring is as follows: 0-7, mildly symptomatic; 8-19, moderately symptomatic; and 20-35, severely symptomatic BPH. The separate QoL question requires the respondent to select a QoL category ranging from zero (delighted) to six (terrible).

7.2 Secondary outcome measure

7.2.1. Patient's global impression of changes (PGIC)

The PGIC will be recorded for each patient at every visit after the first treatment. PGIC is a scoring system used to evaluate the level of change from the beginning of the treatment, either conventional or integrative, to the

time of the PGIC check. This scale considers limitations of physical activity, symptoms, emotions and QoL in general. The scoring is as follows: no change (or condition has become worse), 1; almost the same, hardly any change at all, 2; slightly better, but no noticeable change, 3; somewhat better, but the change has not made any real difference, 4; moderately better and a slight but noticeable change, 5; better and a definite improvement that has made a real and worthwhile difference, 6; a great deal better and a considerable improvement that has made a substantial difference, 7. In a similar way, each patient will be asked to circle one of the numbers 0 (much better) to 10 (much worse) written on a straight line that represents the change from the beginning to the time of evaluation[35].

7.2.2. The short-form 36-question health survey (SF-36)

The SF-36 will be checked at the baseline, after 4 sessions, after 8 sessions and after 12 weeks from the baseline. The SF-36 is a commonly used scale to evaluate health-related quality of life (HRQOL). This scale consists of physical function, physical role capability, bodily pain, general health perceptions, vitality, social role capability, emotional role capability and mental health[36].

7.2.3. The maximum urinary flow rate (Qmax)

Qmax changes from baseline to 12 weeks will be used as an objective outcome measure. Urodynamic study is an invasive method to obtain objective and quantitative data on bladder-outlet function and storage function. Patients will attend the study when they feel a “normal” desire to urinate. The velocity of the external urine stream will be automatically obtained by a calculation using the voided volume and time[37].

7.2.4. Post-void residual urine volume (PVR)

PVR changes from baseline to 12 weeks will be evaluated because PVR increases when bladder-outlet function is incomplete[37]. PVR will be checked by ultrasonography immediately after the urodynamic study.

7.2.5. Persistency on IPSS

The IPSS will be checked 12 weeks after the beginning of the study, after 8 weeks of completed moxibustion therapy, to evaluate the persistency of the effects of moxibustion therapy. This period of 12 weeks was determined based on a previous study[26], the clinical experiences of two KMDs, and the optimum follow-up

period recommended in conventional treatment guidelines[38-40].

7.3 Adverse events

At every visit, patients will be asked if adverse effects have developed and, if so, what types of adverse effects. In particular, second-degree or higher burns and allergic responses of the skin or whole body will be examined thoroughly, and other types of discomfort will be checked.

8. Data collection

Subjective outcome measurements will be checked for each patient, and objective outcome measurement data will be preserved in both their original form and as an EMR. These data will be written on the CRF by a certificated clinical research coordinator (CRC). To promote patient retention and completion of follow-up, an honorarium will be provided with a differential rate according to the patients' participation.

9. Statistical analysis

9.1. Analysis of efficacy

Both intention-to-treat (ITT) and per-protocol (PP) analyses will be performed. The last observation carried forward (LOCF) method will be used for missing data in ITT analysis. The paired t-test will be used for intragroup before/after treatment comparisons. The independent t-test will be used for intergroup comparisons. For non-parametric data, the Wilcoxon signed-rank test for intragroup and the Wilcoxon rank-sum test for intergroup test will be used. Categorical data, such as adverse effects, will be investigated by calculating the occurrence rate of adverse events for each group and then performing analysis with the chi-square test or Fisher's exact test. If statistically significant differences between two groups are observed or covariance is expected, analysis of covariance (ANCOVA) will be used. All of the statistical analysis will be done with two-tailed tests, and the significance level will be set as 0.05.

10. Safety

Expected adverse events, such as burns and allergic responses, will be recorded along with their modality, date of occurrence, and duration. Patients will report other unexpected adverse events freely. The severity of the adverse events will be categorized according to the WHO 5-grade performance status classification as follows: 0,

able to carry out all normal activity without restriction; 1, restricted in strenuous activity but ambulatory and able to carry out light work; 2, ambulatory and capable of all self-care but unable to carry out any work activities and up and about more than 50% of waking hours; 3, symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden; 4, completely disabled, unable to carry out any self-care; totally confined to bed or chair. The cause-and-effect relation between the intervention and adverse events will be assessed according to the WHO-Uppsala Monitoring Centre (UMC) causality categories of 1, certain; 2, probable/likely; 3, possible; 4, unlikely; 5, conditional/unclassified; 6, unassessable/unclassifiable.

To minimize the expected adverse events, we will describe the risk of adverse events to patients who have prior allergic responses to moxibustion therapy, allergic rhinitis or allergic conjunctivitis. Patients will be informed to notify the practitioner if they experience such symptoms during the treatment to receive proper and prompt treatment. The treatment will be performed in a well-ventilated room, and a mask will be offered to cover the patient's mouth and nose. To prevent burns, patients will be educated about indirect moxibustion therapy and its precautions and informed to notify the practitioner promptly if they feel intolerable heat and wish to stop the treatment. The principal investigator (PI) will describe and assess all of the symptoms that occur during the clinical trial and will report to the institutional review board (IRB) to determine whether to continue or stop the study when serious adverse events occur.

Patients who suffer from adverse events will be treated as described in section 6.4. Additionally, patients who suffer harm from this trial participation will be cared for through insurance. All patients will be informed of and sign off on the "regulation concerning subject compensation", including detailed descriptions of this regulation.

11. Monitoring

The independent data monitoring committee (DMC), composed of one KMD and one clinical research expert, will examine the process of progress and whether the trial follows the study plan, the standard guidelines, and clinical-trials management criteria and other related standards. Monitoring will be conducted by regular visits and phone calls. The DMC will check the original record and case report forms. If any problem is found, the DMC will discuss this with the PI. If any serious problems that could threaten the security of patients are found, the DMC will discuss this with the IRB and PI. The PI will make the final decision as to whether to continue or to terminate the trial, and the IRB can order the PI to terminate the trial in the case of a serious problem.

12. Ethical considerations and dissemination

12.1. Written informed consent and study approval

This study was approved by the IRBs of both PNUYH and PNUKH. A signed informed consent will be submitted from each patient to the practitioner. If any changes to the inclusion/exclusion criteria, outcome measure methods or data analysis are demanded, the decision will be made through a discussion between the UD and KMD. The changed contents would need to be reapproved by the IRB and reflected in the patient-explanation and study registration (clinicaltrials.gov), and a new consent from the patient would need to be obtained.

12.2. Private information protection

Collected data from patients will be safeguarded with specific serial numbers without any personally identifiable information so that nobody can recognize the patients except a security manager who has a code-table. Computer-stored personal information will be secured using a password, and all matters related to security will be supervised by the PI. Publication will not include any personally identifiable information, and data will be treated anonymously. Strict security is assured even in a case of a patient dropping out mid-study and after the end of the study.

Data used for the study will be disposed of after the collection of materials for a research paper. Computer storage files will be deleted and documents will be shredded on 31st November, 2017.

The PI, a monitor and an inspector can read the patients' records for the purpose of monitoring and progress oversight in terms of laws and ethics. These data will be stored securely in the National Clinical Research Center for Korean Medicine. This matter will be explained to patients, who will also be provided a written explanation.

12.3. Dissemination

The trial results will be disseminated through open-access journals and conferences.

DISCUSSION

This study is the first protocol of a randomized controlled pilot trial in Korea to evaluate the feasibility of moxibustion as an adjuvant to conventional therapy in BPH accompanying LUTS by exploring its effectiveness and safety.

The medical system of South Korea has been maintained as a dualized system since the revival of KMD by the enactment of the National Medical Insurance Act in 1951. This system has had some negative aspects, such as the incautious use of medicine combinations and distrust between the two medical fields; however, it has had some positive aspects as well, including providing patients with a large variety of treatment choices[41]. Therefore, the necessity of integrative medicine has been propounded steadily to establish a new medical system combining the advantage of Western and Korean medicine[42].

This study was designed as an investigation of add-on treatment without a placebo control because methods of additional alternative treatments in conjunction with the conventional treatment are considered appropriate in light of the medical ethics and medical treatment system[23 43]. Despite relatively acceptable rates of adverse events, increased side effects caused by the combination of different types of oral drug[4] and by patient vulnerability factors, such as ageing and underlying disease, still must be investigated. Therefore, the effectiveness and safety of adjuvant treatments should be evaluated, after which the adjuvant treatment may be considered for intractable urinary disorders including interstitial cystitis and chronic prostatitis. Additionally, a pragmatic design is used to improve applicability to the clinical field and decision making[44 45]. Thus, we set broad inclusion/exclusion criteria and flexible interventions allowing for different treatment regimes according to each patient's medical condition. In addition, conventional oral medication is not restricted to one type considering the pragmatic purpose and the study ethics. The moxibustion therapy has the limitation of inconvenience because patients must visit the hospital for every treatment, while the conventional oral medication can be provided once for a relatively long period; thus, the experts discussed and decided to perform a relatively short-period treatment and to follow up after 12 weeks, as in conventional treatment[38]

This study has some limitations. The 12-week follow-up was set according to the routine check period of conventional treatment but was not sufficient to evaluate the long-term effects. Furthermore, the development of changes cannot be investigated because frequent and regular IPSS checks were not planned in this trial. Therefore, future trials should include more frequent and regular outcome assessments in both groups and a longer follow-up period of at least one year in order to investigate the development of changes in each group

and the persisting effect so that the treatment sessions, period and interval can be properly modified for the final integrative treatment guideline. Another limitation is that the prostate size is not included as an outcome measurement because the feasibility is the main focus rather than definitive assessment of effectiveness. Therefore, studies evaluating the effect of the combined treatment on prostate size should be conducted after the LUTS-reduction effect is demonstrated. Future power analysis studies should be performed by determining the effect size based on the results of this study, and cost-effectiveness studies should be performed to provide important details for decision-makers.

TRIAL STATUS

This study is currently in the recruiting phase. The first patient was enrolled on March 10, 2014, data collection will be complete in approximately December 2015, and the article including results is expected in approximately 2016.

REFERENCES

1. Statistics Korea. Prevalence of Self-Recognintion On Chronic Disease and Doctor'S Diagnosys Rate by General Feature of The Aged (Over 65 Years Old) Secondary Prevalence of Self-Recognintion On Chronic Disease and Doctor'S Diagnosys Rate by General Feature of The Aged (Over 65 Years Old) 2011. http://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_11771_2011N036&conn_path=I2.
2. Statistics Korea. Outpatient Benefits by Frequency of Disease(Male). Secondary Outpatient Benefits by Frequency of Disease(Male) 2013. http://kosis.kr/statHtml/statHtml.do?orgId=350&tblId=DT_35001_A080011&conn_path=I2.
3. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. The Journal of urology 2011;**185**(5):1793-803.
4. Oelke M, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. European urology 2013;**64**(1):118-40.
5. Shim SR, Kim JH, Choi H, et al. General effect of low-dose tamsulosin (0.2 mg) as a first-line treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia: a systematic review and meta-analysis. Current medical research and opinion 2014:1-36.
6. Cindolo L, Alvarez-Maestro M, Castellucci R, et al. Efficacy and safety of dutasteride for the treatment of symptomatic benign prostatic hyperplasia (BPH): a systematic review and meta-analysis. World journal of urology 2014.
7. Guang-Jun D, Feng-Bin G, Xun-Bo J. alpha-Blockers in the management of acute urinary retention secondary to benign prostatic hyperplasia: a systematic review and meta-analysis. Irish journal of medical science 2014.
8. Chapple CR, Montorsi F, Tammela TL, et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. European urology 2011;**59**(3):342-52.
9. Djavan B, Chapple C, Milani S, et al. State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urology 2004;**64**(6):1081-8.
10. Wu YJ, Dong Q, Liu LR, et al. A meta-analysis of efficacy and safety of the new alpha1A-adrenoceptor-selective antagonist silodosin for treating lower urinary tract symptoms associated with BPH. Prostate cancer and prostatic diseases 2013;**16**(1):79-84.
11. van Kerrebroec P, Jardin A, van Cangh P, et al. Long-term safety and efficacy of a once-daily formulation of alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. European urology 2002;**41**(1):54-60; discussion 60-1.
12. Lowe F, Narayan P, Djavan B. Prospective, randomised, multicentre trial to evaluate the rapidity of onset and side effect profile of tamsulosin (TAM) vs terazosin (TER) in men with Benign Prostatic Hyperplasia (BPH). European Urology Supplements 2002;**1**(1):108.

13. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. The New England journal of medicine 2003;**349**(25):2387-98.
14. Abrams P, Kaplan S, De Koning Gans HJ, et al. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. The Journal of urology 2006;**175**(3 Pt 1):999-1004; discussion 04.
15. Fu YQ. [Clinical observation on deep-oblique acupuncture with long needle at Guanyuan (CV 4) for urinary retention]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2013;**33**(12):1071-5.
16. Wang Y, Liu B, Yu J, et al. Electroacupuncture for moderate and severe benign prostatic hyperplasia: a randomized controlled trial. PloS one 2013;**8**(4):e59449.
17. Yu JS, Shen KH, Chen WC, et al. Effects of electroacupuncture on benign prostate hyperplasia patients with lower urinary tract symptoms: a single-blinded, randomized controlled trial. Evidence-based complementary and alternative medicine : eCAM 2011;**2011**:303198.
18. Xu ZJ. [Efficacy observation on benign prostatic hyperplasia treated with acupuncture and moxibustion]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2014;**34**(3):241-4.
19. Li S, Lu A, Wang Y. Symptomatic comparison in efficacy on patients with benign prostatic hyperplasia treated with two therapeutic approaches. Complementary therapies in medicine 2010;**18**(1):21-7.
20. Kim KM. A literature study of acupuncture and moxibustion therapy in the [the Urine] section(in the Naegyeong Chapter) of [Dong-Ui-Bo-Gam]. The Journal of Daejeon Oriental Medicine 2010;**19**(1):129-42.
21. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics 2005;**4**(4):287-91.
22. Hwang M-S, Heo K-H, Cho H-W, et al. Electroacupuncture as a complement to usual care for patients with non-acute pain after back surgery: a study protocol for a pilot randomised controlled trial. BMJ open 2015;**5**(2):e007031.
23. Kim KH, Ryu JH, Park MR, et al. Acupuncture as analgesia for non-emergent acute non-specific neck pain, ankle sprain and primary headache in an emergency department setting: a protocol for a parallel group, randomised, controlled pilot trial. BMJ open 2014;**4**(6):e004994.
24. Witt CM, Reinhold T, Jena S, et al. Cost-effectiveness of acupuncture treatment in patients with headache. Cephalalgia : an international journal of headache 2008;**28**(4):334-45.
25. Li. D. *Perplexities to acupuncture and moxibustion*: Shanghai university of TCM press, 2007.
26. Song FJ, Jiang SH, Zheng SL, et al. [Electroacupuncture for post-stroke urinary incontinence: a multi-center randomized controlled study]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2013;**33**(9):769-73.
27. Huh J. *Donguibogam*. South Korea: Donguibogam publisher, 2005.
28. Korean Acupuncture & Moxibustion Society Textbook Compilation Committee. *The Acupuncture and Moxibustion Medicine*. Paju, Gyeongi, South Korea: Jipmoon, 2008.
29. Kim JWK, T.G.; Lee, J.H.; Baek, J.U. A study on the selecting indications of Five - Viscera Source Point Acupuncture in Suwen. Journal of Korean Medical Classics 2013;**26**(4):23-42.
30. Yang T, Liu Z, Zhang X. Evaluation on therapeutic effects of electro acupuncture for benign prostatic hyperplasia: A prospective randomized controlled study. Chinese Journal of Rehabilitation Medicine

2008;**23**(11):1028-31.

31. Liu QG, Wang CY, Jiao S, et al. [Electroacupuncture at Zhongji (CV 3) for treatment of benign hyperplasia of prostate: a multi-central randomized controlled study]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2008;**28**(8):555-9.
32. Korean Acupuncture & Moxibustion Society Textbook Compilation Committee. *The Acupuncture and Moxibustion Medicine*. Paju, Gyeongi, South Korea: Jipmoon, 2008.
33. Barry MJ, Fowler FJ, Jr., O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. The Journal of urology 1992;**148**(5):1549-57; discussion 64.
34. Choi HR CW, Shim BS, Kwon SW, Hong SJ, Chung BH et al. Translation validity and reliability of I-PSS Korean version. Korean J Urol 1996;**37**:659-65.
35. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of manipulative and physiological therapeutics 2004;**27**(1):26-35.
36. Han CW, Lee EJ, Iwaya T, et al. Development of the Korean version of Short-Form 36-Item Health Survey: health related QOL of healthy elderly people and elderly patients in Korea. The Tohoku journal of experimental medicine 2004;**203**(3):189-94.
37. Schafer W, Abrams P, Liao L, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourology and urodynamics 2002;**21**(3):261-74.
38. Chung BH. Medical management for benign prostatic hyperplasia. Korean Journal of Urology 2007;**48**(3):233-43.
39. Joung JY, Park JK, Park CH, et al. The role of alpha 1 (A) adrenoceptor antagonist tamsulosin for the treatment of patients with benign prostatic hyperplasia: the effect on lower urinary tract symptoms and nocturia. Korean Journal of Urology 2006;**47**(1):1-6.
40. Jeong DH, Park YI. Clinical experience of symptomatic management of BPH with terazosin, doxazosin or combination of terazosin and finasteride. Korean Journal of Urology 1998;**39**(8):772-76.
41. ES L. A study on utilization of oriental medical care. Korea Institute of Oriental Medicine 1999:1-5.
42. Lee SY BY. The present condition and the improvement method for western medicine-Korean medicine cooperative practice system. Korea Institute for Health and Social Affairs, Policy report 1997.
43. Lamb SE, Williamson EM, Heine PJ, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 2014.
44. Treweek S, Zwarenstein M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials 2009;**10**:37.
45. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC medical research methodology 2003;**3**:28.

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Contributors

JNK, SDL and JGN conceived the study. JNK, SDL, JKN, JYH, YJY and HYL initiated the study design, and DHL, SHP, JHL and HLP helped with its implementation. JKN, DHL, JHY and HYL performed the intervention and discussed the optimal complementary medicine. HYL drafted the study protocol manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Competing interests

None

Access to data

The data from this trial will be accessible by contacting the corresponding author.

Ethics approval

The study was approved by IRBs of both Pusan National University Korean Medicine Hospital (IRB approval number 2013021) and Pusan National University Yangsan Hospital (IRB approval number 03-2013-013).

APPENDIX

Table 1. Trial progress

Period	Screening	Active treatment									F/U
Visit	Screening	1	2	3	4	5	6	7	8	9*	10
Week	0	1		2		3		4			12
Consent	●										
Demographic survey	●										
Medical history	●	○	○	○	○	○	○	○	○	●	●
Vital signs	●	○	○	○	○	○	○	○	○		●
Physical examination	●										
Conformity assessment	●										
Check PSA	●										
Check prostate size (TRUS)	●										
Inclusion/exclusion criteria	●										
Inform patient of the visit schedule	●	○	○	○	○	○	○	○	○	○	
Randomization	●										
Moxibustion		○	○	○	○	○	○	○	○		
IPSS	●					○				●	●
SF-36	●					○				●	●
PGIC			○	○	○	○	○	○	○	●	●
Qmax	●										●
PVR	●										●
FVC	●										●
Adverse event monitoring		○	○	○	○	○	○	○	○	○	○
Final compliance assessment											●

○: integrative group

●: both integrative group and conventional group

***visit 9: 1-3 days after visit 8**

PSA: prostate specific antigen; TRUS: transrectalultrasonography; IPSS: international prostate symptom; short-form 36-question health survey; PGIC: patients' global impression of changes; Qmax: maximum urinary flow rate; PVR: post-void residual urine volume; FVC: frequency-volume chart

Table 2. International prostate symptom score

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5

	None	1 time	2 times	3 times	4 times	5 times or more
Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5

	Delighted	Pleased	Mostly satisfied	Mixed – about equally	Mostly dissatisfied	Unhappy	Terrible
Quality of life due to urinary symptoms If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7, mildly symptomatic; 8-19, moderately symptomatic; 20-35, severely symptomatic.

Figures

Figure 1. Trial flowchart

Figure 2. Timeframe of the integrative treatment group (IG) and conventional treatment group (TG).

Figure 3. Apparatus-type moxibustion on CV4

Figure 4. Mini-pillar-type moxibustion on bilateral SP6 and LR3

Data Category	Information
Primary Registry and Trial Identifying number	NCT02051036
Date of Registration in Primary Registry	01/26/2014.
Secondary Identifying Numbers	NC1307
Source(s) of Monetary or Material Support	Korea Institute of Oriental Medicine
Primary Sponsor	Korea Institute of Oriental Medicine
Secondary Sponsor(s)	National Clinical Research Center
Contact for Public Queries	Corresponding author
Contact for Scientific Queries	Corresponding author
Public Title	Moxibustion as a complement to benign prostatic hyperplasia accompanying lower urinary tract symptoms
Scientific Title	The effectiveness and safety of moxibustion as a complement for benign prostatic hyperplasia with lower urinary tract symptoms
Countries of Recruitment	Korea, Republic of
Health Condition(s) or Problem(s) Studied	Benign prostatic hyperplasia with lower urinary tract symptoms
Intervention(s)	Treatment: moxibustion plus usual care
	Control: usual care alone
Key Inclusion and Exclusion Criteria	Ages eligible for study: between 20 and 80 years; sexes eligible for study: male; accepts healthy volunteers: no
	Inclusion criteria: 1. Male patients diagnosed benign prostate hyperplasia aged from 20 to 80 years; prostate size over 20 gm 2. Greater than or equal to a score of eight on the IPSS 3. Submit written consent 4. Patients who can understand and answer the IPSS
	Exclusion criteria: 1. Prostate or bladder malignancy 2. Received herbal medication for lower urinary tract symptoms within one week 3. History of brain disease which can cause urinary difficulty 4. Difficulty answering IPSS due to cognitive impairment 5. Signs of acute urinary tract infection 6. Diabetic mellitus 7. Neurogenic bladder
Study Type	Randomized controlled trial, parallel, 1:1 ratio, pilot study
	Allocation: randomized; intervention model: parallel assignment
	Primary purpose: international prostate symptom score
Date of First Enrolment	2014/03/10
Target Sample Size	60
Recruitment Status	recruiting
Primary Outcome(s)	International prostatic symptom score
Key Secondary Outcomes	Maximum uroflow rate, post-void residual urine

Figure 1. Trial flowchart

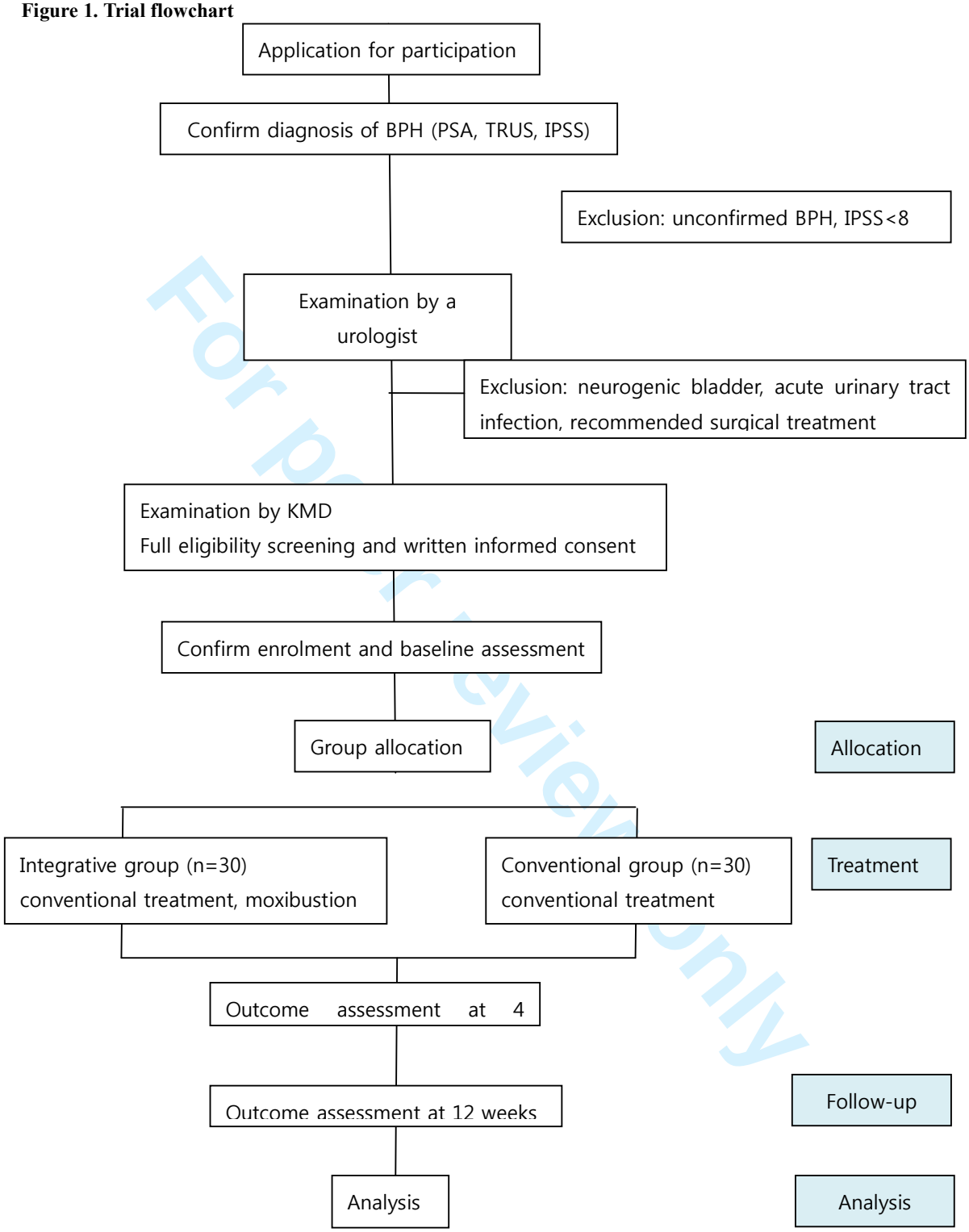


Figure 2. Timeframe of the integrative treatment group (IG) and conventional treatment group (TG).

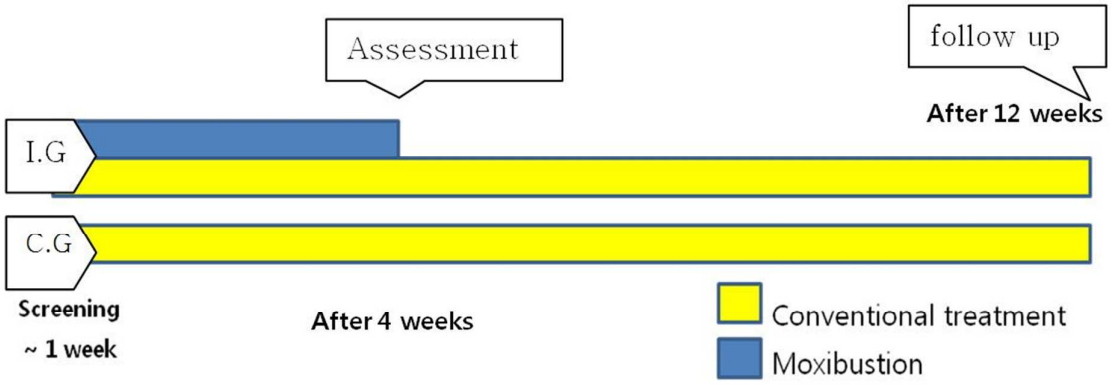


Figure 3. Apparatus-type moxibustion on CV4

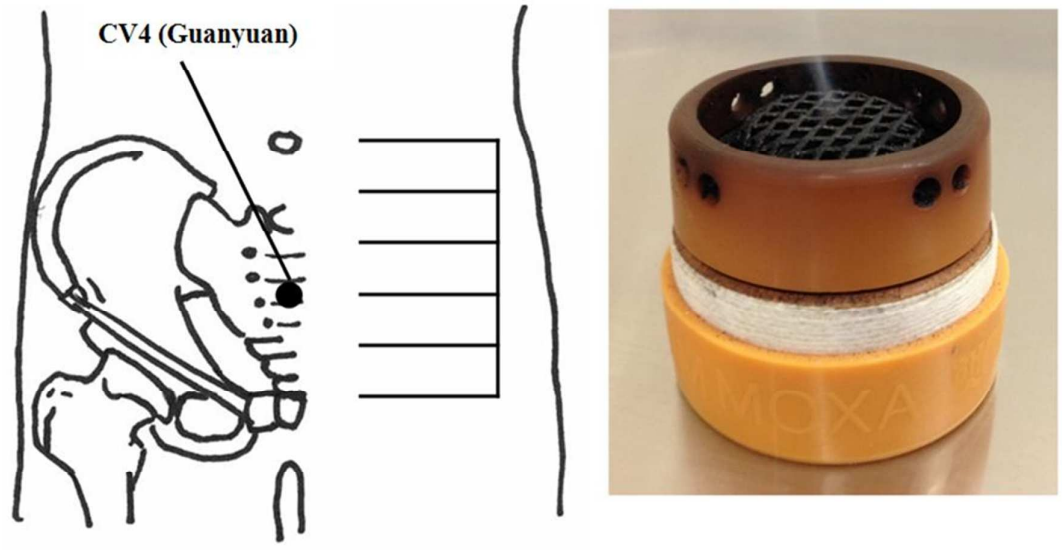
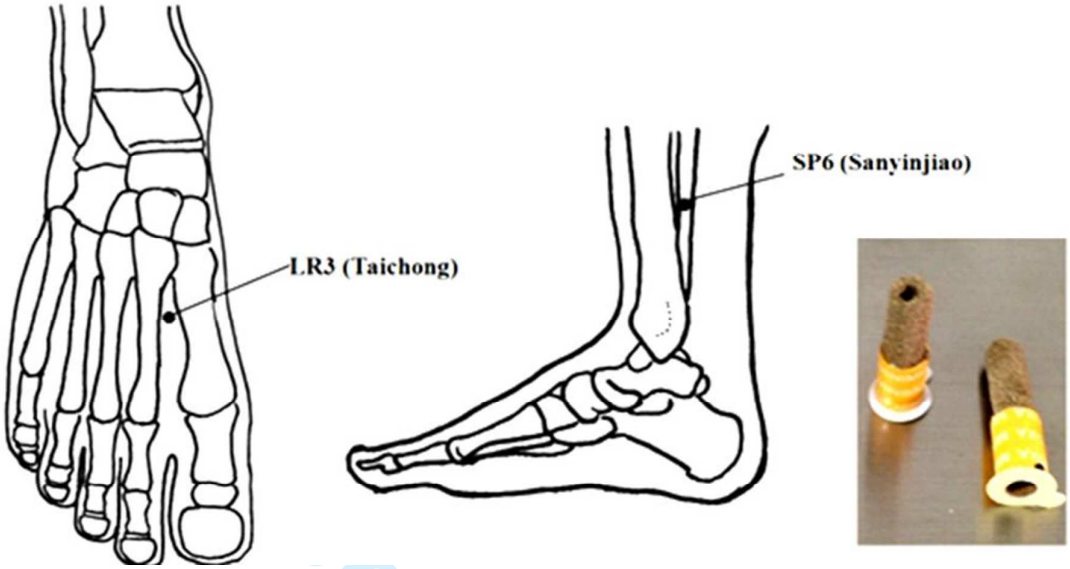


Figure 4. Mini-pillar-type moxibustion on bilateral SP6 and LR3



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	30
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	23
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10,11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13- 15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14,15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	none
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Moxibustion as an adjuvant for benign prostatic hyperplasia with lower urinary tract symptoms: a protocol for a parallel-group, randomized, controlled pilot trial

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Urology
Keywords:	Prostate disease < UROLOGY, moxibustion, Kidney & urinary tract disorders < UROLOGY, integrative medicine, lower urinary tract symptoms

Moxibustion as an adjuvant for benign prostatic hyperplasia with lower urinary tract symptoms: a protocol for a parallel-group, randomized, controlled pilot trial

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ABSTRACT

Introduction

This study aims to explore the feasibility of moxibustion as a supplementary intervention and to assess the sample size for verifying the effectiveness and safety of integrative treatment involving moxibustion compared with conventional treatment for patients with benign prostate hyperplasia (BPH) accompanying moderate to severe lower urinary tract symptoms (LUTS).

Methods and analysis

A total of 60 patients diagnosed with benign prostatic hyperplasia by a urologist based on prostate size, prostate-specific antigen (PSA), and clinical symptoms will participate of their own free will, and urologists will monitor patients and evaluate their symptoms. The patients will be randomized into a conventional group or integrative group with a 1:1 allocation according to computer-generated random numbers concealed in opaque, sealed, sequentially numbered envelopes. Watchful waiting or oral medication including alpha-blocker, 5-alpha-reductase inhibitors (5-ARIs) or anti-muscarinic drugs will be offered as a conventional treatment. Integrative treatment will include moxibustion therapy in addition to the conventional treatment. The moxibustion therapy will be conducted twice per week for four weeks on the bilateral acupoints SP6, LR3 and CV4 by a qualified Korean medical doctor (KMD). The primary outcome will be the international prostate symptom score (IPSS) after 8 sessions. The secondary outcomes will be the post-void residual urine volume (PVR), the maximum urinary flow rate (Qmax), IPSS, the results of a short-form 36-question health survey (SF-36) after 12 weeks and the patients' global impression of changes (PGIC) at each visit.

Ethics and dissemination

Written informed consent will be obtained from all participants. This study was approved by the IRBs of both PNUYH and PNUKH. The trial results will be disseminated through open-access journals and

Trial registration number: clinicaltrials.gov. NCT02051036 (Date: 01/26/2014)

Strengths and limitations of this study

- The design of this clinical trial is based on an experts' conference with KMDs, urologic doctors (UDs),

and an Eastern-Western integrative medicine specialist who has both MD and KMD licenses to develop an optimal integrative treatment.

- Optimal conventional oral medications and a customized number of moxibustion layers for each patient are used to reflect the real clinical setting.
- This study's results can serve as a basis for further large studies or studies of intractable urinary disorders.
- The statistical power of the study may be low due to the small sample size.
- Practitioners and patients will not be blinded.

INTRODUCTION

Korean statistical data show that the prevalence of benign prostatic hyperplasia (BPH) in men over 65 years was 17.9% in 2011[1], and BPH ranked 25th among male outpatient visits by frequency of disease in 2013[2].

BPH causes lower urinary tract symptoms (LUTS) by directly disturbing the bladder outlet or increasing the tension and resistance of smooth muscles[3]. For treatment, watchful waiting at the beginning and behaviour modification with oral medication are recommended[3 4], and these methods have proved effective in improving LUTS, urinary flow rate and post-void residual urine in many previous studies[5-7].

However, this conventional treatment is limited by certain side effects. For alpha-blockers, rhinitis (6.6%), dizziness (4.4%) and abnormal ejaculation (2.8%)[5] caused by tamsulosin have been observed. Moreover, abnormal ejaculation (14.2%-28.1%) caused by silodosin[8 9]; cardiovascular adverse events (5.7% hypertension, 3.9% non-hypertension)[10] and mild dizziness (13.9%)[11] caused by alfuzosin; severe dizziness leading to drug-suspension (2.0%) caused by terazosin[12]; and dizziness (4.41%), postural hypotension (4.03%) and asthenia (4.08%)[13] caused by doxazosin have been verified. In addition, erectile dysfunction (4.53%), decreased libido (2.36%) and abnormal ejaculation (1.78%)[13] caused by finasteride have been identified; and dry mouth (24%), dyspepsia (5%), back pain (5%) and micturition disorder (5%)[14] caused by tolterodine have been shown to occur. In particular, when two or more types of these medications are combined, each side effect is expected; thus, careful use only for patients with moderate to severe BPH is recommended[4].

To overcome this limitation, many studies investigating complementary and alternative medical (CAM) treatment have been conducted, but the 2011 American Urological Association's (AUA) guideline reported that no definite evidence exists to recommend CAM treatment due to the lack of quality and quantity of CAM studies of BPH[3].

In contrast, clinical studies of acupuncture or herbal medication for BPH with LUTS have been consistently performed[15-19] and have demonstrated the effectiveness of these methods. Moxibustion has been shown to be effective in treating urinary disorders[20], but well-designed clinical trials to prove its effectiveness are lacking. Therefore, we designed a pilot trial to explore the feasibility of moxibustion as an adjuvant for BPH with LUTS based on the effectiveness and safety and to estimate the proper sample size for a future, large comparative effectiveness study, with the purpose of developing an optimal integrative treatment that can be accepted by both MDs and KMDs in the present medical system. The design of this clinical trial is based on a literature survey and an experts' conference with KMDs, urologic doctors (UDs), and an Eastern-Western integrative

medicine specialist who has both MD and KMD licenses. This pilot study is a randomized controlled trial with a parallel-group, 1:1 allocation, exploratory and pragmatic design.

METHODS AND ANALYSIS

1. Aims

The present study aims to evaluate the feasibility of moxibustion as an adjuvant for conventional treatment in BPH patients and to assess the proper sample size for verifying, in future studies, the effectiveness and safety of integrative treatment compared with conventional treatment for patients with BPH accompanying LUTS. This is a single-centre, assessor- and analyser-blinded, parallel-group, 1:1 allocation, pragmatic randomized controlled study.

2. Recruitment

Notices were posted in front of the Pusan National University Yangsan Hospital (PNUYH) urologic office and the Pusan National University Korean Medicine Hospital (PNUKH) genito-urinary clinic office, and advertising for the study was also placed on the internet homepage of PNUKH. A UD will confirm the diagnosis of benign prostatic hyperplasia and needlessness of surgical treatment for patients who volunteer to participate. A KMD will thoroughly examine all inclusion/exclusion criteria and explain the trial to eligible patients. When the patient decides to participate in the study, the KMD will obtain written informed consent, and a baseline assessment will be performed. The progress of the study will consist of a screening phase, a treatment phase and follow-up. A more detailed description of the study is shown in figure 1. The time schedule for participation is shown in table 1.

3. Study design

Randomization and allocation concealment

Within 14 days from recruitment, each patient will be allotted to the conventional or integrative group according to the concealed random list. A statistician who does not take part in this study will place the computer-generated random list into each double-layered opaque envelope, seal it and write the numbers in sequence. The KMD will give the envelope to the patient according to the visit order and open it with the patient.

4. Patients

4.1. Sample size

The sample size calculation was not performed based on a power calculation because this is a pilot study. The sample size was determined based on estimates of the number of patients expected to participate and the minimum number to evaluate the pragmatic purpose of this trial. Thus, a sample size of 30 per group and total number of 60 will be included, which is larger than the minimum number recommended for pilot studies[21].

4.2. Inclusion criteria

1. Male patients aged 20-80 years diagnosed with BPH with a prostate size over 20 gm
2. International prostate symptom score (IPSS) ≥ eight
3. Written informed consent obtained
4. Patient must understand and answer the IPSS

4.3. Exclusion criteria

1. Prostate or bladder malignancy
2. Received herbal medication for lower urinary tract symptoms within one week
3. History of a brain disease that can cause urinary difficulty
4. Difficulty answering IPSS due to cognitive impairment
5. Signs of acute urinary tract infection
6. Diabetic mellitus
7. Neurogenic bladder

4.4. Drop-out criteria and process of management

4.4.1. Definition of drop-out

Completed cases will be defined as patients who finish the treatment progress and follow-up. Patients who cannot complete the study due to side effects or for other reasons will be considered drop-out cases.

4.4.2. Drop-out criteria

The researcher may stop treatment and observation of a patient according to prescribed criteria, and the patient can drop-out voluntarily at any time. The drop-out criteria are as follows.

1. Violation of inclusion/exclusion criteria

2. Serious adverse events or adverse events making a patient wish to drop out
3. Severe systemic disease that was not recognized at baseline
4. Patients or a legal representative demand cessation of the trial due to unsatisfying effects or withdrawal of consent
5. Trial compliance of less than 80%; should attend at least 7 of 8 treatment sessions in the integrative group and all of three major assessments (baseline, visit 9 and visit 10) in both groups
6. Protocol violation of patient or researcher
7. Difficulty conducting moxibustion due to newly developed disease or uncooperative manner
8. Patients not replying to outcome measures
9. Patient's desire or UD's recommendation for surgical treatment (including minimally invasive therapies)

4.4.3. Management process

The drop-out date, time and reason will be recorded on the end report. Patients can drop out voluntarily for any reason, at any time, and are not required to submit a reason. The researcher should make every effort to follow up with patients who have dropped out and record the reason for drop-out or the reason for not being able to determine a drop-out cause.

5. Blinding

5.1. Blinding of outcome assessors and data analysers

The practitioner and patients cannot be blinded because this is an open-label study for moxibustion treatment. Assessors and analysers will be blinded. Urodynamic testing will be performed by an assistant who does not take part in the trial, and participants will be asked not to reveal their allotted group to the assistant. Subjective outcomes will be recorded by the patient. The groups will be marked "A" and "B" when the data are sent to the statistician to ensure that the groups are not recognized as the control group and experimental group. Un-blinding of the assessors will be permissible only in the case of a serious adverse event.

5.2. The rationale for the lack of a sham moxibustion group

For the pragmatic purpose of the future study, we decided to reflect the real clinical situation without omitting the patients' additional time, effort and expectations by comparing patients who receive conventional treatment

with patients who receive both conventional treatment and complementary treatment. A sham or placebo intervention group is the ideal method for efficacy studies with an optimal, strictly restricted design to minimize all influencing factors to prove the efficacy of a specific component of intervention[22 23]. Consequently, a sham moxibustion group will not be included in this study.

6. Interventions

6.1. Conventional treatment protocol

The conventional treatment will be set as the optimum treatment for each patient to develop a reasonable integrative treatment protocol[24].

The optimum treatment for each patient will be based on the UD's opinion. The UD will discuss behavioural modifications, such as water intake, with the patient. Watchful waiting will be used for patients without renal insufficiency, urinary retention, recurring infection or complications of bladder-outlet obstruction (BOO). Oral medications will be prescribed when no therapeutic effect is observed after watchful waiting, and the medications will be selected in consideration of overactive bladder, prostate size and prostate-specific antigen (PSA). Preferentially, an alpha-blocker, such as alfuzosin, doxazosin, tamsulosin or terazosin, will be used for functional symptom mitigation. 5-ARIs, such as dutasteride and finasteride, will be used when the prostatic volume is > 40 ml or PSA > 1.4 ng/ml. For cases of a high risk of BPH progression, prostate ≥ 30 mg or PSA ≥ 1.5 ng/ml, a combination of an alpha-blocker and a 5-ARI will be used. Anticholinergic agents, such as tolterodine, will be prescribed for patients with overactive bladder but will need to be monitored for patients with ≥ 250 ml post-void residual urine. The conventional treatment components can be changed at the discretion of the UD because this research is a pragmatic study to evaluate the effectiveness and safety of additional moxibustion therapy and the conventional treatment will still be maintained for the last follow-up[3 4].

6.2. Integrative treatment protocol

Moxibustion therapy will be added to the conventional treatment described in section 6.1 twice per week for four weeks. The moxibustion therapy will be conducted by a skilled KMD who has at least two years' experience in the clinic. The timeframes of the conventional treatment group (CG) and the integrative treatment group (IG) are shown in figure 2. Both the apparatus type and mini-pillar type moxibustion will be used.

The apparatus types are a Hatnim-moxa apparatus (Bosungsa, Incheon, South Korea) and a moxa pillar

(Bosungsa, South Korea) that generates 65-70 °C of heat. Moxibustion will be conducted at acupoints CV4 on one layer of gauze (figure 3) for 30 minutes. This acupoint was selected based on the KM theory[20 25] and previous clinical studies[17 26]. Additional gauze will be offered layer by layer when the patient requests it due to intolerable heat. This apparatus-moxibustion will be stopped if the patient complains of intolerable heat even after the additional gauze is offered more than three times. If the patient cannot feel any heat once the moxa pillar is totally burned, the apparatus-moxibustion will be conducted one more time; the procedure can be performed one more time as before, but the number of apparatus-moxibustion applications cannot exceed three. The therapy can be stopped if a second-degree or higher burn occurs even before completing eight treatment sessions.

Kanghwa mini-moxa of "lowest" intensity, which generates heat of approximately 45 °C, will be used for mini-pillar-type indirect moxibustion. Mini-moxa will be conducted at bilateral acupoints SP6[17 20 27] and LR3[20 28 29] (figure 4). The mini-moxa will be removed when totally burned, which takes approximately 5 minutes, but it may be removed if the patient complains of intolerable heat. The mini-moxa will not be repeated on the acupoint on which moxibustion was stopped per the patient's request. Repetitive mini-moxa will be performed on the acupoints at which the patient did not feel heat and completed prior mini-moxa for the entire burning period, up to a maximum of seven times on each point. Beginning with the second session, the treated region will be checked and further mini-moxa will not be allowed on an acupoint where a second-degree or higher burn occurred. In this case, the mini-moxa will be re-started after the burn is completely healed.

The treatment session of twice per week for 4 weeks was determined based on the studies of Yang T[30], Liu QG[31] and Wang Y[26], who reported the effective results and clinical experiences of two KMDs considering practicality in terms of the patients' general social environment and the accessibility of the hospital. The number of performed moxibustion treatments will be recorded in both the electronic medical record (EMR) and case report form (CRF) at every visit in adherence with intervention protocols.

It is reasonable to stop moxibustion therapy if a second-degree or higher burn occurs according to KM theory[32], and in this case, the patient will not be considered a study drop-out. However, if a patient cannot continue the treatment because of discomfort from the moxibustion smoke, allergic response or pigmentation from the moxa-soot, he cannot be regarded as having completed the trial.

6.3. Prohibited or allowed parallel medical treatments

Flexible oral medications according to the discretion of the UD's opinion are allowed to offer the best treatment for each patient; thus, the medications will not be fixed without variation. All types of medication therapy based on AUA guidelines and the Korean prostate society guideline will be allowed.

Surgical treatment, including transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), abdominal prostatectomy, minimally invasive therapy using a laser, transurethral needle ablation of the prostate (TUNA), and transurethral microwave thermotherapy (TUMT), are prohibited; therefore, patients who want or are recommended for such therapies cannot participate in this trial.

6.4. Treatment of adverse events

We will disinfect and dress the wound when a second-degree or higher burn occurs and will refer the patient to dermatology to receive proper treatment when a third-degree or higher burn occurs.

7. Outcome measures

7.1 Primary outcome measure

The IPSS after 8 sessions will be the primary outcome measure. The results of the IPSS, including the change in IPSS and its standard deviation, will be used to calculate the proper sample size for the future trial by performing a power analysis. IPSS was developed by the AUA in 1992, and a question regarding quality of life (QoL) was later added[33]. The Korean version was validated in 1996[34]. IPSS consists of seven sub-themes of incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. The severity scoring is as follows: 0-7, mildly symptomatic; 8-19, moderately symptomatic; and 20-35, severely symptomatic BPH. The separate QoL question requires the respondent to select a QoL category ranging from zero (delighted) to six (terrible).

7.2 Secondary outcome measure

7.2.1. Patient's global impression of changes (PGIC)

The PGIC will be recorded for each patient at every visit after the first treatment. PGIC is a scoring system used to evaluate the level of change from the beginning of the treatment, either conventional or integrative, to the time of the PGIC check. This scale considers limitations of physical activity, symptoms, emotions and QoL in general. The scoring is as follows: no change (or condition has become worse), 1; almost the same, hardly any

change at all, 2; slightly better, but no noticeable change, 3; somewhat better, but the change has not made any real difference, 4; moderately better and a slight but noticeable change, 5; better and a definite improvement that has made a real and worthwhile difference, 6; a great deal better and a considerable improvement that has made a substantial difference, 7. In a similar way, each patient will be asked to circle one of the numbers 0 (much better) to 10 (much worse) written on a straight line that represents the change from the beginning to the time of evaluation[35].

7.2.2. The short-form 36-question health survey (SF-36)

The SF-36 will be checked at the baseline, after 4 sessions, after 8 sessions and after 12 weeks from the baseline. The SF-36 is a commonly used scale to evaluate health-related quality of life (HRQOL). This scale consists of physical function, physical role capability, bodily pain, general health perceptions, vitality, social role capability, emotional role capability and mental health[36].

7.2.3. The maximum urinary flow rate (Qmax)

An independent tester will measure Qmax at baseline and 12 weeks after baseline. Qmax changes from baseline to 12 weeks will be used as an objective outcome measure. Urodynamic study is an invasive method to obtain objective and quantitative data on bladder-outlet function and storage function. Patients will attend the study when they feel a "normal" desire to urinate. The velocity of the external urine stream will be automatically obtained by a calculation using the voided volume and time[37].

7.2.4. Post-void residual urine volume (PVR)

An independent tester will measure PVR at baseline and 12 weeks after baseline. PVR changes from baseline to 12 weeks will be evaluated because PVR increases when bladder-outlet function is incomplete[37]. PVR will be checked by ultrasonography immediately after the urodynamic study.

7.2.5. Changing progress and persistency on IPSS

The IPSS will be evaluated after 4 sessions in the integrative group to explore the process of change and will be checked 12 weeks after the beginning of the study, after 8 weeks of completed moxibustion therapy, to evaluate the persistency of the effects of moxibustion therapy. This period of 12 weeks was determined based on

a previous study[26], the clinical experiences of two KMDs, and the optimum follow-up period recommended in conventional treatment guidelines[38-40].

7.2.6. Adverse events

To explore safety, adverse events will be recorded. At every visit, patients will be asked whether adverse effects have developed and, if so, what types of adverse effects. In particular, second-degree or higher burns and allergic responses of the skin or whole body will be examined thoroughly, and other types of discomfort will be checked.

7.2.7. The recruitment, compliance and retention rate

For feasibility, the recruitment, compliance and retention rate will be recorded. The recruitment rate will be the ratio of the patients who completely meet the inclusion/exclusion criteria and who register for the trial versus the recruitment goal. The compliance rate will be measured by the attendance rate for the treatment phase in the integrative group and the attendance rate for the three major assessments (baseline, visit 9 and visit 10) in both groups. The retention rate is defined as the ratio of 1) the number of patients who attend the primary outcome assessment after four weeks versus the total number of participants, 2) the number of patients who attend the final assessment after 12 weeks versus the total number of participants and 3) the number of patients who return the frequency-volume chart (FVC) versus the total number of participants.

8. Data collection

Subjective outcome measurements will be checked for each patient, and objective outcome measurement data will be preserved in both their original form and as an EMR. These data will be written on the CRF by a certificated clinical research coordinator (CRC). To promote patient retention and completion of follow-up, an honorarium will be provided with a differential rate according to the patients' participation.

9. Statistical analysis

9.1. Analysis of efficacy

Both intention-to-treat (ITT) and per-protocol (PP) analyses will be performed. The last observation carried forward (LOCF) method will be used for missing data in ITT analysis. The paired t-test will be used for

intragroup before/after treatment comparisons. The independent t-test will be used for intergroup comparisons. For non-parametric data, the Wilcoxon signed-rank test for intragroup and the Wilcoxon rank-sum test for intergroup test will be used. Categorical data, such as adverse effects, will be investigated by calculating the occurrence rate of adverse events for each group and then performing analysis with the chi-square test or Fisher's exact test. If statistically significant differences between two groups are observed or covariance is expected, analysis of covariance (ANCOVA) will be used. All of the statistical analysis will be done with two-tailed tests, and the significance level will be set as 0.05. To explore feasibility, the recruitment, compliance, and retention rates will be calculated, and the percentages will be reported. Furthermore, subgroup analyses will be performed according to the severity in terms of the IPSS or prostate size and the type of conventional treatment.

10. Safety

Expected adverse events, such as burns and allergic responses, will be recorded along with their modality, date of occurrence, and duration. Patients will report other unexpected adverse events freely. The severity of the adverse events will be categorized according to the WHO 5-grade performance status classification as follows: 0, able to carry out all normal activity without restriction; 1, restricted in strenuous activity but ambulatory and able to carry out light work; 2, ambulatory and capable of all self-care but unable to carry out any work activities and up and about more than 50% of waking hours; 3, symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden; 4, completely disabled, unable to carry out any self-care; totally confined to bed or chair. The cause-and-effect relation between the intervention and adverse events will be assessed according to the WHO-Uppsala Monitoring Centre (UMC) causality categories of 1, certain; 2, probable/likely; 3, possible; 4, unlikely; 5, conditional/unclassified; 6, unassessable/unclassifiable.

To minimize the expected adverse events, we will describe the risk of adverse events to patients who have prior allergic responses to moxibustion therapy, allergic rhinitis or allergic conjunctivitis. Patients will be informed to notify the practitioner if they experience such symptoms during the treatment to receive proper and prompt treatment. The treatment will be performed in a well-ventilated room, and a mask will be offered to cover the patient's mouth and nose. To prevent burns, patients will be educated about indirect moxibustion therapy and its precautions and informed to notify the practitioner promptly if they feel intolerable heat and wish to stop the treatment. The principal investigator (PI) will describe and assess all of the symptoms that occur during the clinical trial and will report to the institutional review board (IRB) to determine whether to continue or stop the

study when serious adverse events occur.

Patients who suffer from adverse events will be treated as described in section 6.4. Additionally, patients who suffer harm from this trial participation will be cared for through insurance. All patients will be informed of and sign off on the "regulation concerning subject compensation", including detailed descriptions of this regulation.

11. Monitoring

The independent data monitoring committee (DMC), composed of one KMD and one clinical research expert, will examine the process of progress and whether the trial follows the study plan, the standard guidelines, and clinical-trials management criteria and other related standards. Monitoring will be conducted by regular visits and phone calls. The DMC will check the original record and case report forms. If any problem is found, the DMC will discuss this with the PI. If any serious problems that could threaten the security of patients are found, the DMC will discuss this with the IRB and PI. The PI will make the final decision as to whether to continue or to terminate the trial, and the IRB can order the PI to terminate the trial in the case of a serious problem.

12. Ethical considerations and dissemination

12.1. Written informed consent and study approval

This study was approved by the IRBs of both PNUYH and PNUKH. A signed informed consent will be submitted from each patient to the practitioner. If any changes to the inclusion/exclusion criteria, outcome measure methods or data analysis are demanded, the decision will be made through a discussion between the UD and KMD. The changed contents would need to be reapproved by the IRB and reflected in the patient-explanation and study registration (clinicaltrials.gov), and a new consent from the patient would need to be obtained.

12.2. Private information protection

Collected data from patients will be safeguarded with specific serial numbers without any personally identifiable information so that nobody can recognize the patients except a security manager who has a code-table. Computer-stored personal information will be secured using a password, and all matters related to security will be supervised by the PI. Publication will not include any personally identifiable information, and data will be treated anonymously. Strict security is assured even in a case of a patient dropping out mid-study and after the

end of the study.

Data used for the study will be disposed of after the collection of materials for a research paper. Computer storage files will be deleted and documents will be shredded on 31st November, 2017.

The PI, a monitor and an inspector can read the patients' records for the purpose of monitoring and progress oversight in terms of laws and ethics. These data will be stored securely in the National Clinical Research Center for Korean Medicine. This matter will be explained to patients, who will also be provided a written explanation.

12.3. Dissemination

The trial results will be disseminated through open-access journals and conferences.

DISCUSSION

This study is the first protocol of a randomized controlled pilot trial in Korea to evaluate the feasibility of moxibustion as an adjuvant to conventional therapy in BPH accompanying LUTS by exploring its effectiveness and safety.

The medical system of South Korea has been maintained as a dualized system since the revival of KMD by the enactment of the National Medical Insurance Act in 1951. This system has had some negative aspects, such as the incautious use of medicine combinations and distrust between the two medical fields; however, it has had some positive aspects as well, including providing patients with a large variety of treatment choices[41]. Therefore, the necessity of integrative medicine has been propounded steadily to establish a new medical system combining the advantage of Western and Korean medicine[42].

This study was designed as an investigation of add-on treatment without a placebo control because methods of additional alternative treatments in conjunction with the conventional treatment are considered appropriate in light of the medical ethics and medical treatment system[23 43]. Despite relatively acceptable rates of adverse events, increased side effects caused by the combination of different types of oral drug[4] and by patient vulnerability factors, such as ageing and underlying disease, still must be investigated. Therefore, the effectiveness and safety of adjuvant treatments should be evaluated, after which the adjuvant treatment may be considered for intractable urinary disorders including interstitial cystitis and chronic prostatitis. Additionally, a pragmatic design is used to improve applicability to the clinical field and decision making[44 45]. Thus, we set broad inclusion/exclusion criteria and flexible interventions allowing for different treatment regimes according to each patient's medical condition. In addition, conventional oral medication is not restricted to one type considering the pragmatic purpose and the study ethics. The moxibustion therapy has the limitation of inconvenience because patients must visit the hospital for every treatment, while the conventional oral medication can be provided once for a relatively long period; thus, the experts discussed and decided to perform a relatively short-period treatment and to follow up after 12 weeks, as in conventional treatment[38]

This study has some limitations. The 12-week follow-up was set according to the routine check period of conventional treatment but was not sufficient to evaluate the long-term effects. Furthermore, the development of changes cannot be investigated because frequent and regular IPSS checks were not planned in this trial. Therefore, future trials should include more frequent and regular outcome assessments in both groups and a longer follow-up period of at least one year in order to investigate the development of changes in each group

and the persisting effect so that the treatment sessions, period and interval can be properly modified for the final integrative treatment guideline. Another limitation is that the prostate size is not included as an outcome measurement because the feasibility is the main focus rather than definitive assessment of effectiveness. Therefore, studies evaluating the effect of the combined treatment on prostate size should be conducted after the LUTS-reduction effect is demonstrated. Future power analysis studies should be performed by determining the effect size based on the results of this study, and cost-effectiveness studies should be performed to provide important details for decision-makers.

TRIAL STATUS

This study is currently in the recruiting phase. The first patient was enrolled on March 10, 2014, data collection will be complete in approximately December 2015, and the article including results is expected in approximately 2016.

REFERENCES

1. Statistics Korea. Prevalence of Self-Recognition On Chronic Disease and Doctor's Diagnosis Rate by General Feature of The Aged (Over 65 Years Old) 2011. http://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_11771_2011N036&conn_path=I2.
2. Statistics Korea. Outpatient Benefits by Frequency of Disease (Male). 2013. http://kosis.kr/statHtml/statHtml.do?orgId=350&tblId=DT_35001_A080011&conn_path=I2.
3. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. The Journal of urology 2011;**185**(5):1793-803.
4. Oelke M, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. European urology 2013;**64**(1):118-40.
5. Shim SR, Kim JH, Choi H, et al. General effect of low-dose tamsulosin (0.2 mg) as a first-line treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia: a systematic review and meta-analysis. Current medical research and opinion 2014:1-36.
6. Cindolo L, Alvarez-Maestro M, Castellucci R, et al. Efficacy and safety of dutasteride for the treatment of symptomatic benign prostatic hyperplasia (BPH): a systematic review and meta-analysis. World journal of urology 2014.
7. Guang-Jun D, Feng-Bin G, Xun-Bo J. alpha-Blockers in the management of acute urinary retention secondary to benign prostatic hyperplasia: a systematic review and meta-analysis. Irish journal of medical science 2014.
8. Chapple CR, Montorsi F, Tammela TL, et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. European urology 2011;**59**(3):342-52.
9. Wu YJ, Dong Q, Liu LR, et al. A meta-analysis of efficacy and safety of the new alpha1A-adrenoceptor-selective antagonist silodosin for treating lower urinary tract symptoms associated with BPH. Prostate cancer and prostatic diseases 2013;**16**(1):79-84.
10. van Kerrebroec P, Jardin A, van Cangh P, et al. Long-term safety and efficacy of a once-daily formulation of

alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. European urology 2002;**41**(1):54-60; discussion 60-1.

11. Djavan B, Chapple C, Milani S, et al. State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urology 2004;**64**(6):1081-8.
12. Lowe F, Narayan P, Djavan B. Prospective, randomised, multicentre trial to evaluate the rapidity of onset and side effect profile of tamsulosin (TAM) vs terazosin (TER) in men with Benign Prostatic Hyperplasia (BPH). European Urology Supplements 2002;**1**(1):108.
13. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. The New England journal of medicine 2003;**349**(25):2387-98.
14. Abrams P, Kaplan S, De Koning Gans HJ, et al. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. The Journal of urology 2006;**175**(3 Pt 1):999-1004; discussion 04.
15. Fu YQ. Clinical observation on deep-oblique acupuncture with long needle at Guanyuan (CV 4) for urinary retention. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2013;**33**(12):1071-5.
16. Wang Y, Liu B, Yu J, et al. Electroacupuncture for moderate and severe benign prostatic hyperplasia: a randomized controlled trial. PloS one 2013;**8**(4):e59449.
17. Yu JS, Shen KH, Chen WC, et al. Effects of electroacupuncture on benign prostate hyperplasia patients with lower urinary tract symptoms: a single-blinded, randomized controlled trial. Evidence-based complementary and alternative medicine : eCAM 2011;**2011**:303198.
18. Xu ZJ. Efficacy observation on benign prostatic hyperplasia treated with acupuncture and moxibustion. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2014;**34**(3):241-4.
19. Li S, Lu A, Wang Y. Symptomatic comparison in efficacy on patients with benign prostatic hyperplasia treated with two therapeutic approaches. Complementary therapies in medicine 2010;**18**(1):21-7.
20. Kim KM. A literature study of acupuncture and moxibustion therapy in the [the Urine] section(in the Naegyeong Chapter) of [Dong-Ui-Bo-Gam]. The Journal of Daejeon Oriental Medicine 2010;**19**(1):129-42.
21. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics 2005;**4**(4):287-91.

22. Hwang MS, Heo KH, Cho HW, et al. Electroacupuncture as a complement to usual care for patients with non-acute pain after back surgery: a study protocol for a pilot randomised controlled trial. BMJ open 2015;**5**(2):e007031.

23. Kim KH, Ryu JH, Park MR, et al. Acupuncture as analgesia for non-emergent acute non-specific neck pain, ankle sprain and primary headache in an emergency department setting: a protocol for a parallel group, randomised, controlled pilot trial. BMJ Open 2014;**4**(6):e004994.

24. Witt CM, Reinhold T, Jena S, et al. Cost-effectiveness of acupuncture treatment in patients with headache. Cephalalgia : an international journal of headache 2008;**28**(4):334-45.

25. Li. D. Perplexities to acupuncture and moxibustion: Shanghai university of TCM press, 2007:112.

26. Song FJ, Jiang SH, Zheng SL, et al. [Electroacupuncture for post-stroke urinary incontinence: a multi-center randomized controlled study]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2013;**33**(9):769-73.

27. Huh J. Donguibogam. South Korea: Donguibogam publisher, 2005:357.

28. Korean Acupuncture & Moxibustion Society Textbook Compilation Committee. The Acupuncture and Moxibustion Medicine. Paju, Gyeongi, South Korea: Jipmoon, 2008:253.

29. Kim JW, Kim TG, Lee JH, Baek JU. A study on the selecting indications of Five - Viscera Source Point Acupuncture in Suwen. Journal of Korean Medical Classics 2013;**26**(4):23-42.

30. Yang T, Liu Z, Zhang X. Evaluation on therapeutic effects of electro acupuncture for benign prostatic hyperplasia: A prospective randomized controlled study. Chinese Journal of Rehabilitation Medicine 2008;**23**(11):1028-31.

31. Liu QG, Wang CY, Jiao S, et al. Electroacupuncture at Zhongji (CV 3) for treatment of benign hyperplasia of prostate: a multi-central randomized controlled study. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2008;**28**(8):555-9.

32. Korean Acupuncture & Moxibustion Society Textbook Compilation Committee. *The Acupuncture and Moxibustion Medicine*. Paju, Gyeongi, South Korea: Jipmoon, 2008.

33. Barry MJ, Fowler FJ, Jr., O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. The Journal of urology 1992;**148**(5):1549-57; discussion 64.

34. Choi HR CW, Shim BS, Kwon SW, Hong SJ, Chung BH et al. Translation validity and reliability of I-PSS Korean version. Korean J Urol 1996;**37**:659-65.

35. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of manipulative and physiological therapeutics 2004;**27**(1):26-35.

36. Han CW, Lee EJ, Iwaya T, et al. Development of the Korean version of Short-Form 36-Item Health Survey: health related QOL of healthy elderly people and elderly patients in Korea. The Tohoku journal of experimental medicine 2004;**203**(3):189-94.

37. Schafer W, Abrams P, Liao L, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourology and urodynamics 2002;**21**(3):261-74.

38. Chung BH. Medical management for benign prostatic hyperplasia. Korean Journal of Urology 2007;**48**(3):233-43.

39. Joung JY, Park JK, Park CH, et al. The role of alpha 1 (A) adrenoceptor antagonist tamsulosin for the treatment of patients with benign prostatic hyperplasia: the effect on lower urinary tract symptoms and nocturia. Korean Journal of Urology 2006;**47**(1):1-6.

40. Jeong DH, Park YI. Clinical experience of symptomatic management of BPH with terazosin, doxazosin or combination of terazosin and finasteride. Korean Journal of Urology 1998;**39**(8):772-76.

41. Lee ES. A study on utilization of oriental medical care. Korea Institute of Oriental Medicine 1999:1-5.

42. Lee SY, Byon YC. The present condition and the improvement method for western medicine-Korean medicine cooperative practice system. Korea Institute for Health and Social Affairs, Policy report 1997.

43. Lamb SE, Williamson EM, Heine PJ, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 2014.

44. Treweek S, Zwarenstein M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials 2009;**10**:37.

45. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC medical research methodology 2003;**3**:28.

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JNK, SDL and JGN conceived the study. JNK, SDL, JKN, JYH, YJY and HYL initiated the study design, and DHL, SHP, JHL and HLP helped with its implementation. JKN, DHL, JHY and HYL performed the intervention and discussed the optimal complementary medicine. HYL drafted the study protocol manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Competing interests

No, there are no competing interests.

Access to data

The data from this trial will be accessible by contacting the corresponding author.

Ethics approval

The study was approved by IRBs of both Pusan National University Korean Medicine Hospital (IRB approval number 2013021) and Pusan National University Yangsan Hospital (IRB approval number 03-2013-013).

Table 1. Trial progress

Period	Screening	Active treatment									F/U
Visit	Screening	1	2	3	4	5	6	7	8	9*	10
Week	0	1		2		3		4			12
Consent	●										
Demographic survey	●										
Medical history	●	○	○	○	○	○	○	○	○	●	●
Vital signs	●	○	○	○	○	○	○	○	○		●
Physical examination	●										
Conformity assessment	●										
Check PSA	●										
Check prostate size (TRUS)	●										
Inclusion/exclusion criteria	●										
Inform patient of the visit schedule	●	○	○	○	○	○	○	○	○	○	
Randomization	●										
Moxibustion		○	○	○	○	○	○	○	○		
IPSS	●					○				●	●
SF-36	●					○				●	●
PGIC			○	○	○	○	○	○	○	●	●
Qmax	●										●
PVR	●										●
FVC	●										●
Adverse event monitoring		○	○	○	○	○	○	○	○	○	○
Final compliance assessment											●

○: integrative group

●: both integrative group and conventional group

***visit 9: 1-3 days after visit 8**

PSA: prostate specific antigen; TRUS: transrectalultrasonography; IPSS: international prostate symptom; short-form 36-question health survey; PGIC: patients' global impression of changes; Qmax: maximum urinary flow rate; PVR: post-void residual urine volume; FVC: frequency-volume chart

Table 2. International prostate symptom score

1

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Nocturia	None	1 time	2 times	3 times	4 times	5 times or more
Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5
Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

2 **Total score:** 0-7, mildly symptomatic; 8-19, moderately symptomatic; 20-35, severely symptomatic.

3

Figures

Figure 1. Trial flowchart

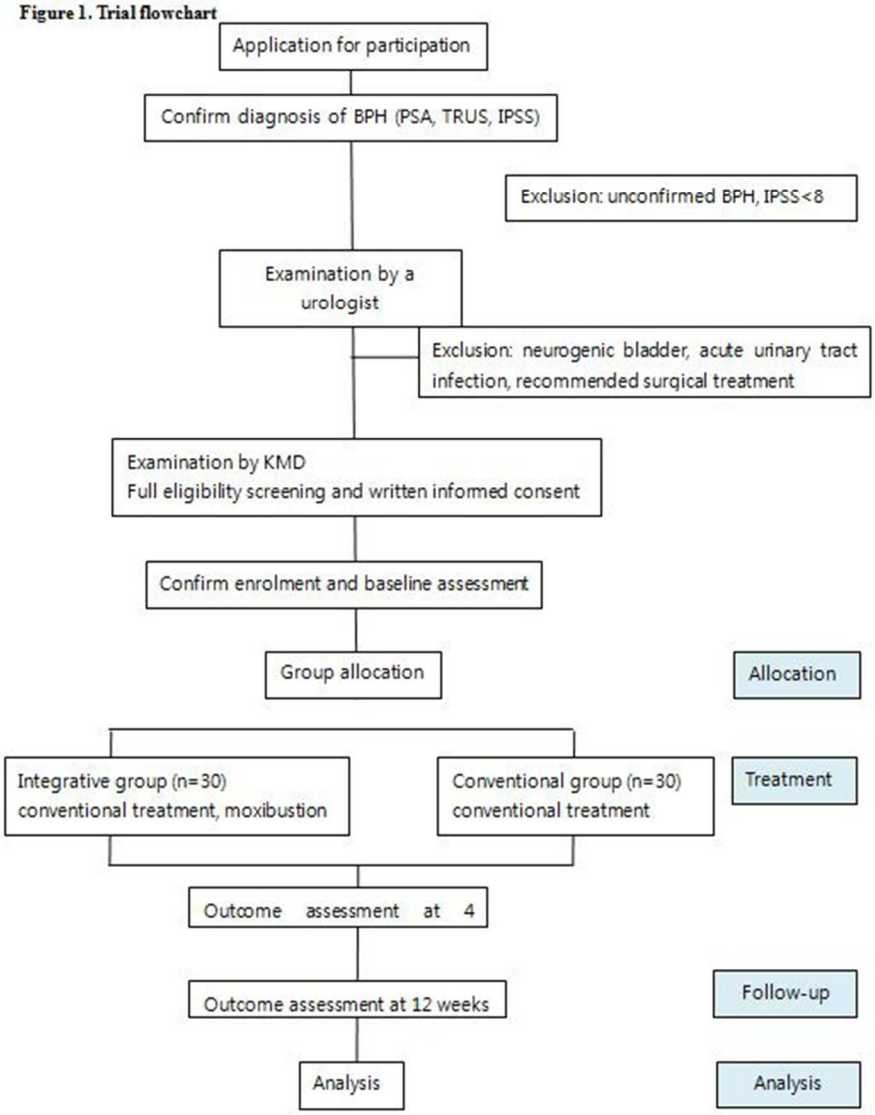
Figure 2. Timeframe of the integrative treatment group (IG) and conventional treatment group (TG).

Figure 3. Apparatus-type moxibustion on CV4

Figure 4. Mini-pillar-type moxibustion on bilateral SP6 and LR3

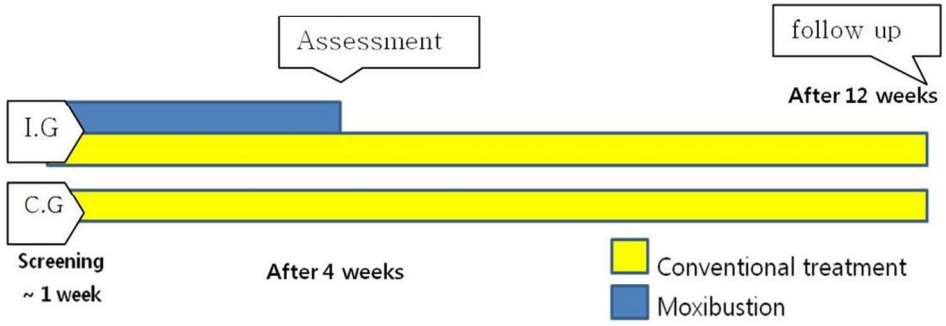
Data Category	Information
Primary Registry and Trial Identifying number	NCT02051036
Date of Registration in Primary Registry	01/26/2014.
Secondary Identifying Numbers	NC1307
Source(s) of Monetary or Material Support	Korea Institute of Oriental Medicine
Primary Sponsor	Korea Institute of Oriental Medicine
Secondary Sponsor(s)	National Clinical Research Center
Contact for Public Queries	Corresponding author
Contact for Scientific Queries	Corresponding author
Public Title	Moxibustion as a complement to benign prostatic hyperplasia accompanying lower urinary tract symptoms
Scientific Title	The effectiveness and safety of moxibustion as a complement for benign prostatic hyperplasia with lower urinary tract symptoms
Countries of Recruitment	Korea, Republic of
Health Condition(s) or Problem(s) Studied	Benign prostatic hyperplasia with lower urinary tract symptoms
Intervention(s)	Treatment: moxibustion plus usual care
	Control: usual care alone
Key Inclusion and Exclusion Criteria	Ages eligible for study: between 20 and 80 years; sexes eligible for study: male; accepts healthy volunteers: no
	Inclusion criteria: 1. Male patients diagnosed benign prostate hyperplasia aged from 20 to 80 years; prostate size over 20 gm 2. Greater than or equal to a score of eight on the IPSS 3. Submit written consent 4. Patients who can understand and answer the IPSS
	Exclusion criteria: 1. Prostate or bladder malignancy 2. Received herbal medication for lower urinary tract symptoms within one week 3. History of brain disease which can cause urinary difficulty 4. Difficulty answering IPSS due to cognitive impairment 5. Signs of acute urinary tract infection 6. Diabetic mellitus 7. Neurogenic bladder
Study Type	Randomized controlled trial, parallel, 1:1 ratio, pilot study
	Allocation: randomized; intervention model: parallel assignment
	Primary purpose: international prostate symptom score
Date of First Enrolment	2014/03/10
Target Sample Size	60
Recruitment Status	recruiting
Primary Outcome(s)	International prostatic symptom score
Key Secondary Outcomes	Maximum uroflow rate, post-void residual urine

Figure 1. Trial flowchart



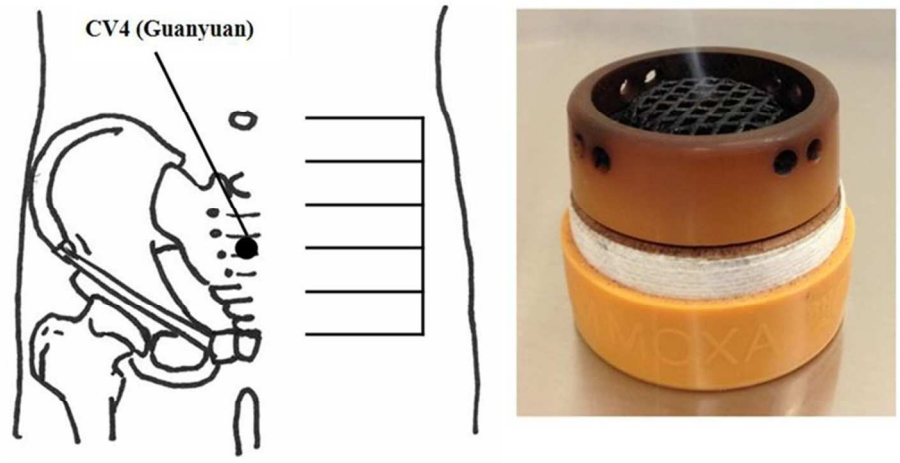
148x186mm (96 x 96 DPI)

Figure 2. Timeframe of the integrative treatment group (IG) and conventional treatment group (TG).



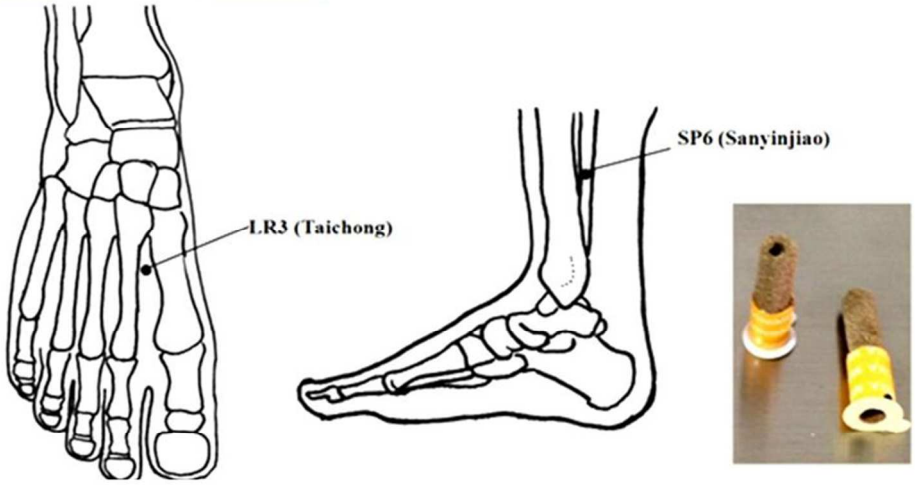
298x133mm (96 x 96 DPI)

Figure 3. Apparatus-type moxibustion on CV4



267x155mm (96 x 96 DPI)

Figure 4. Mini-pillar-type moxibustion on bilateral SP6 and LR3



264x161mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	32
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	25
	5b	Name and contact information for the trial sponsor	25
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	25

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10,11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11,12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7,8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12- 14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14,15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7,16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	none
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	25
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15,16
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.