Acupuncture for Prostatectomy Incontinence: Study Protocol for A Multicenter Single Blind Randomized Parallel Controlled Trial

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Research Article

Keywords: Acupuncture, Prostatectomy incontinence, Efficacy, Randomized control trial, Study protocol

Posted Date: June 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-530412/v1

Version of Record: A version of this preprint was published at Trials on January 4th, 2022. See the published version at https://doi.org/10.1186/s13063-021-05805-5.

Abstract

Background: Urinary incontinence is a common complication after prostatectomy. Acupuncture is considered an effective treatment for prostatectomy incontinence (PPI), but evidence is still limited. We propose to evaluate the effectiveness of acupuncture in a rigorously conducted trial.

Methods: Twenty hospitals will recruit 340 participants with urinary incontinence after prostatectomy in China from April 2021 to April 2022. Participants will be randomly allocated to acupuncture or sham acupuncture with a 1:1 ratio using computerized simple random sampling. The study plan consists of 1-week baseline, 6-week treatment, and 18-week follow up. Eighteen 30-mintute sessions of acupuncture or sham acupuncture treatment will be provided between weeks 1 and 6. The primary outcome is the change in the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF) score at the week 6 from the baseline. Secondary outcomes include the change in volume of urine leakage at weeks 4 and 6 from a baseline measured using the 1-h Pad Test;72-h incontinence episode frequency based on a 72-h voiding diary; change in the Expanded prostate cancer Index Composite scale (EPIC-26); change in the Self-Rating Anxiety Scale; weekly consumption of pads; the severity of urinary incontinence based on a 72-h bladder diary and self-assessment of the therapeutic effect. The safety of acupuncture will also be assessed.

Discussion: This trial will help to identify whether acupuncture is effective for PPI, and, if so, whether it exerts a therapeutic rather than a placebo effect.

Trial Registration: The trial was registered on www.Chictr.org.cn. ChiCTR2100042500. Retrospectively registered on 22 January 2021.

Background

Prostate cancer is one of the most common malignant tumors of the male genitourinary system and radical prostatectomy is the first-line treatment for localized prostate cancer [1]. Prostatectomy incontinence (PPI) is a known complication with an incidence rate ranging from 4–31% [2], which has a significant impact on men's quality of life (QoL) [3–4]. The complication may generate feelings of low self-esteem, anxiety, and depression. The patients' shame and discomfort arises from the inability to control the bladder. Patients who do not wish to wear a diaper daily, but always carry it for safety in their bag when leaving home [5]. The present study revealed that the postoperative period of 2 to 6 months had a severe impact on their QoL [6].

The treatments for PPI are mainly divided into two types. Conservative treatment includes bladder or pelvic floor muscle training [7–8], biofeedback [9–10], and drug therapy [11–12]. Surgical intervention mainly includes artificial urethral sphincter implantation [13], urethral suspension [14–15], or injection therapy [16]. All these treatments may benefit patients; although, it cannot be denied that anti muscarinic drugs such as duloxetine are often accompanied by symptoms of insomnia, nausea, loss of appetite, irritability, and other side effects [17, 18]. Further, surgical interventions are traumatic forms of treatment,

and are also costly [19]. Pelvic floor muscle training is the most used conservative treatment for urinary incontinence, but for elderly male patients with prostate cancer, whether functional training is carried out correctly is difficult to evaluate and assess, and it is challenging to implement.

Acupuncture, as a typical treatment modality of traditional Chinese medicine (TCM) [20, 21]. With few adverse effects, TCM may be used as an alternative treatment approach for patients. Many research centers, mostly in China, have conducted clinical trials to evaluate the safety and effectiveness of acupuncture in managing post-PPI. Liu et al. [22] conducted a multicenter, randomized clinical trial and revealed that women with stress urinary incontinence can benefit from electroacupuncture involving the lumbosacral region. Chen et al. [23] determined that acupuncture could be beneficial for men with post-PPI when applied alone or as an adjunct to other conservative therapies and medicines. Therefore, acupuncture could be considered an effective treatment for urinary incontinence.

Based on a systematic review [23], acupuncture may be an appropriate treatment for PPI; However, the quality of evidence has been low and inconclusive. Therefore, we plan to perform a multicenter randomized controlled trial (RCT) to investigate the efficacy and safety of acupuncture in the treatment of PPI in patients with prostate cancer.

Methods

Study design

This study is a multicenter, single blind, randomized parallel controlled prospective clinical trial with the objective of estimating the efficacy and safety of acupuncture on PPI by comparing a verum acupuncture group with a sham acupuncture group. Participants considered suitable for the study will be randomly allocated into the intervention group (verum acupuncture) or the control group (sham acupuncture) in a 1:1 ratio.

Study participants

Population

A target sample of 340 participants will be recruited from 20 hospitals across China: Tianjin Medical University General Hospital; The Second Hospital of Tianjin Medical University; Tianjin Medical University Cancer Hospital; Tianjin First Central Hospital; Tianjin Third Central Hospital; Peking University Third Hospital; Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine; West China Hospital of Sichuan University; Benxi Central Hospital; First Affiliated Hospital of Dalian Medical University; The Second Hospital of Dalian Medical University; The First Affiliated Hospital of Kunming Medical University; Qinghai University Affiliated Hospital; Jiangsu Province People's Hospital; First Hospital of Shanxi Medical University; Shandong Province Hospital; The Fifth People's Hospital of Jinan; Inner Mongolia People's Hospital; The Second Hospital of Anhui Medical University; and Guizhou Province People's Hospital. Informed consent will be obtained from all participants before randomization.

Baseline assessment

A baseline registration will be performed before treatment. Participants will provide a review of basic information, malignancy history including operation history, pathology, and QoL assessment including urinary incontinence. A safety evaluation will also be performed.

Recruitment

We will recruit participants who are attending the 20 above-mentioned hospitals in this trial. We will use WeChat to publish recruitment information, and use the "recruiters" applet to recruit and retrieve information for patients.

Inclusion criteria

Patients who meet all the following requirements will be allowed to enroll:

1. Patients who have received radical prostatectomy with definite pathological diagnosis of prostate cancer:

2. Diagnosis of urinary incontinence by the International Continuity Society criteria or patients who were evaluated by the urologist as experiencing urinary incontinence resulting from prostate surgery [24];

3. Karnofsky Score≥60 or Eastern Cooperative Oncology Group (ECOG) Score 0-2;

4. Willing to participate in the study and sign the consent forms.

Exclusion criteria

Patients who meet all the following criteria will be excluded:

1. Urgency urinary incontinence caused by detrusor hyperreflexia and bladder spasm, and urinary incontinence caused by central system or endocrine factors;

2. Urinary incontinence treated by cystostomy, urethral sphincter reconstruction, or urethral suspension;

3. Currently receiving less than 6 months treatment similar to acupuncture (such as electroacupuncture, warm moxibustion, warm acupuncture, etc.);

4. Irreversible urinary incontinence due to permanent nerve injury and complete loss of function of the external urethral sphincter;

5. Urinary tract infection (except asymptomatic lower urinary tract infection);

6. History of severe arrhythmia, severe cardiac insufficiency, acute myocarditis, constrictive pericarditis, pericardial tamponade, severe valvular disease, heart failure, or other serious heart diseases;

7. History of severe liver injury or potentially severe liver disease (ALT or AST > 10 times normal);

8. History of severe renal impairment (estimated GFR < 25 mL/min/1.73 m^2);

9. History of other important organ dysfunction or hematopoietic system disease, or other serious primary diseases(s);

10. Known to coagulation dysfunction (with typical clinical diagnosis or clear laboratory test results);

11. Patients with mental illness or cognitive impairment, or severe depression;

12. Patients who are not suitable to participate in this study or who are likely to withdraw from the study based on the judgment of the researchers;

13. Patients participating in other clinical trials.

Withdrawal from the study

Participants will be allowed or asked to withdraw from the study in the following circumstances:

1. Patients who express an unwillingness to being subjected to the assigned treatment for various reasons at any stage of the trial;

2. Patients experience an adverse events (AE) that necessitates their withdrawal from the trial;

3. Patients who cannot fully participate in the treatment or follow-up period;

4. Patients can withdraw from the study voluntarily for any reason.

Randomization and blinding

A total of 340 participants will be randomly allocated into the treatment group or the control group. Each hospital will recruit 17 patients. In this trial, we will carry out block randomization in a 1:1 ratio according to the sequence generated using SAS software version 9.4 (SAS Institute Inc. Cary, NC). Random allocation will be performed after eligible participants consent in written form and complete baseline assessments. The participants, outcome assessors, and statisticians will be blinded to treatment allocation. The acupuncturist will not be blinded to the participant's allocation. All participants in the study will sign a confidentiality commitment to avoid blind disclosure.

Ethics

The study will be performed in accordance with the principles of the Declaration of Helsinki, and has been approved by the ethics committee boards of the participating hospitals. Written informed consent will be obtained from each subject before the patients are enrolled in the trial. Ethical approval is provided as Additional file 1.

Interventions

According to the predetermined randomization results, participants will be randomly allocated to the verum or sham acupuncture group. All participants will go through a standardized interview, which will be recorded on the case report forms. To minimize bias, all the acupuncturists in this trial are specialists in acupuncture. They have a minimum of 2 years' experience in acupuncture treatment and hold licenses to perform acupuncture. Before performing this trial, all acupuncturists will receive special training regarding the purpose and content of the trial, treatment strategies, and quality control. The flowchart and study design schedule are presented in Figure 1 and Table 1, respectively.

The trial will last 24 weeks, including treatment and follow-up periods. All participants will receive treatment for 6 weeks. Participants in both groups will receive verum or sham acupuncture three times a week (recommended interval of one day). Each acupuncture session requires approximately 20 minutes to perform. Sterile needles for single use (0.25×40 mm; Jiangsu Medical Supplies Factory Co., Ltd.) will be used in this study. Needles in the treatment group will be inserted at a depth of 0.8-1 inches and manually manipulated by rotation methods. After acupuncture, the patient's "De Qi" should be taken as the criterion (the feeling of pain and numbness). In the control group, needles will be inserted about 0.5 inch in depth, and will not receive further manipulation. To prevent blind uncovering, the operator will pay attention to the depth and angle of the shallow stab. All participants will be evaluated by blind method at week 6 after acupuncture. The Blind Method Assessment is shown in Additional file 2.

Table 1 Study design schedule

Notes:

1. Vital signs: blood pressure, pulse, body temperature and respiration;
2. Blood routine: hemoglobin, red blood cell count, white blood cell count, lymphocyte, neutrophil, and platelet count;
3. Urine routine: white blood cell, red blood cell, protein, and ketone body;
4. Biochemical items: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, urea nitrogen, glomerular filtration rate, creatinine, glucose, triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein, potassium, sodium, calcium;
5. ECG: electrocardiogram;
6. BMI: body mass index;
7. ECOG score: Eastern Cooperative Oncology Group score;

Contents	Research period								
	Screening	Baseline	Treatment (W1-6)				Follow-up (W7-24)		
	W-1	W0	W1	W2	W4	W6	W12	W18	W24
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8
Name	×	×							
Age	×	×							
Contact information	×								
Inclusion/Exclusion criteria	×								
Informed consent	×								
Screening dispose	×								
Randomization	×								
Vital signs [1]	×	×	×	×	×	×			
Blood routine [2]	×	×				×			
Urine routine[3]	×	×				×			
Biochemical items [4]	×	×				×			
ECG [5]	×	×				×			
Height		×							
Weight		×							
BMI[6]		×							
Education and occupation		×							
Karnofsky score		×							
ECOG score[7]		×							
Personal history[8]		×							
Past History		×							
physical examination[9]		×	×	×	×	×			
Diagnosis time		×							
Pathological type		×							

Gleason score	×							
Clinical stages	×							
Operation type	×							
Treatment of PPI	×	×	×	×	×	×	×	×
Treatment of PCa	×	×	×	×	×	×	×	×
Daily water consumption	×	×	×	×	×	×	×	×
Drink preference	×	×	×	×	×	×	×	×
Postoperative extubation time	×							
Time of incontinence	×							
ICIQ-UI SF[10]	×				×	×	×	×
1-hour pad test	×			×	×			
72-h voiding diary	×	×	×	×	×	×	×	×
EPIC-26[11]	×				×	×	×	×
SAS[12]	×				×	×	×	×
Weekly consumption of pads	×	×	×	×	×	×	×	×
Severity of PPI	×				×	×	×	×
Self-assessment					×	×	×	×
Blind assessment					×			
Major AE of PCa[13]		×	×	×	×	×	×	×
AE[14]		×	×	×	×	×	×	×
SAE[15]		×	×	×	×	×	×	×

8. Personal history: including family history, smoking history, drinking history, drug and food allergy history, marriage history, occupational exposure history;
9. Physical examination: the researchers will conduct a comprehensive physical examination at baseline, including general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lung, heart, abdomen, back, lymph nodes, limbs, and nervous system examination. All other visits will have a brief physical examination, i.e., a general appearance examination;
10. ICIQ-UI SF: International Consultation Incontinence Questionnaire-Urinary Incontinence Short Form;

11. EPIC-26: The Expanded Prostate Cancer Index Composite 26-item version;
12. SAS: Self-Rating Anxiety Scale is a 20-item self-report assessment;
13. Major adverse event (AE) of prostate cancer (PCa): It refers to the AEs related to the progression of PCa from the time of enrollment to the end of follow-up;
14. AE: It refers to the AEs caused by the intervention measures of the project from the time of admission to the end of follow-up;
15. SAE: It refers to the serious adverse events caused by the intervention measures of the project during the period from enrollment to the end of follow-up.

Acupoints used in the treatment group

The stimulation points in the intervention group will be RN12 (Zhongwan), RN6 (Qihai), ST36 (Zusanli, bilaterally), SP6 (Sanyinjiao, bilaterally), SP9 (Yinlingquan, bilaterally), SP10 (Shuidao), RN3 (Zhongji), and RN2 (Qugu). All acupoints are located according to the National Standard of People's Republic of China (GB / T 12346-2006). The acupoint diagram is shown in Additional file 3.

Sham acupoints used in the control group

To ensure the quantity of stimulus is uniform between two groups, the same kind, size, and number of needles will be used for the control group. However, the control group will be treated with shallow needling at the non-meridian and non-acupoint positions. The acupuncture points shifted 1-inch from the actual location and have no therapeutic value.

Permitted and prohibited concomitant treatments

Both groups can receive conventional treatment for prostate cancer (such as endocrine therapy) and/or pelvic floor muscle training, which differ from acupuncture principles. Researchers need to keep a detailed record. Treatments like the principles of acupuncture are not allowed.

Outcome measures

Primary outcome measures

ICIQ-UI-SF The International Consultation Incontinence Questionnaire-Urinary Incontinence Short Form. Scores of the scale will be calculated to investigate the incidence of urinary incontinence and the impact of urinary incontinence on patients. It will be used at baseline, and at weeks 6, 12, 18, and 24. The scale is shown in Additional file 4.

Secondary outcome measures

1-h Pad Test It is a test to objectively evaluate urinary incontinence. It is measured to assess the change in volume of urine leakage from baseline at weeks 4 and 6.

72-hour Voiding Diary On the basis of not changing life status and urination habits, 72 hours of fluid intake and urination time are continuously recorded every week. It is used to assess the change in mean 72-hour incontinence-episode frequency (IEF) from baseline, and at weeks 1, 2, 4, 6, 12, 18, and 24. The scale is shown in Additional file 5.

EPIC-26 The Expanded Prostate Cancer Index Composite 26-item version includes three categories of questions aimed to evaluate the prostate function and QoL of patients with prostate cancer in the past 4 weeks. Evaluated at weeks 6, 12, 18, and 24, changes in scores from the baseline will be analyzed. The scale is shown in Additional file 6.

SAS Self-Rating Anxiety Scale is a 20-item self-report assessment used to measure anxiety levels, based on the scoring of 4 groups of symptoms: cognitive, autonomic, motor, and central nervous system symptoms. The scores will be evaluated at weeks 6, 12, 18, and 24, and changes in scores from the baseline values will be analyzed. The scale is shown in Additional file 7.

Weekly consumption of pads Changing and average weekly consumption of pads at weeks 1, 2, 4, 6, 12, 18, and 24 from the baseline will be calculated.

Severity of urinary incontinence It will be evaluated at weeks 6, 12, 18 and 24. The change in the number and percentage of severity ratings from the baseline value will be analyzed.

Self-report assessment of therapeutic effect A 4-point scale is used: no help, little help, medium help, and great help [25]. Treatment effects will be evaluated at weeks 6, 12, 18, and 24.

Safety assessment

To exclude any related serious diseases, patients will be asked to undergo necessary inspection before randomization, including vital signs, blood routine, urine routine, biochemical items, ECG. These tests will be performed at the week 6 of the study to evaluate the safety of this trial. If any AEs occur during the trial, patients will be treated as soon as possible.

Statistical methods

Sample size calculation

By enrolling approximately 340 (170 in each group) participants, the study will provide 90% power to detect a between-group difference of 2.5 in reduction of ICI-Q-SF score from baseline using a 2-sided alpha level of 0.05, and assuming a common standard deviation of 6.3 and a dropout rate of 20%. A difference of 2.5 points in the ICI-Q-SF score was selected for sample size calculations, which is indicative of a clinically significant change [25–27].

Statistical analysis

Summary tables (descriptive statistics and/or frequency tables) will be provided for all variables as appropriate. The primary outcome analysis will use the Cochran-Mantel-Haenszel (CMH) test. For continuous variables, means and standard deviations will be presented, unless the variable has a skewed distribution, in which medians, 25th and 75th percentiles will be presented. For other categorical data, between group comparisons will be performed using a Wilcoxon rank-sum test, chi-square test, or Fisher's exact test, as appropriate. AE incidences for each treatment group will be tested by the c2 test or Fisher's exact test as appropriate. All the statistical analysis will be performed using SAS version 9.4 (SAS Institute Inc) with 2-sided tests at a significance level of <0.05.

Discussion

PPI has a significant impact on the QoL of patients who undergo prostatectomy. It is closely associated with the trauma caused by surgery [28, 29]. Although urinary incontinence after prostate cancer heals within half a year, the need for active improvement of symptoms and the QoL of patients is widely recognized [30]. Surgical resection of prostate cancer mainly includes bladder neck, bilateral vas deferens ampulla, bilateral seminal vesicles, and the intact prostate. Although a complete resection of the tumor and avoidance of positive surgical edge can be achieved, often the bladder neck and part of the prostatic apex urethra are removed, which will lead to damage of the urinary control structure. In addition, due to intraoperative bleeding, tumor infiltration, and adhesion, the distal sphincter, fascia, ligament, and pelvic floor muscles may be damaged, which leads to postoperative urinary incontinence [31, 32]. The efficacy of acupuncture has been proved by many RCTs [33]. A systematic review demonstrated that acupuncture was an appropriate adjunctive therapy for PPI, but the supporting evidence was not sufficient. These limitations included small sample size, greater-than-anticipated withdrawal, the lack of a control group, and unclear statements about randomized allocation. Therefore, more powerful evidence is still needed to verify the efficacy and safety of acupuncture for PPI. We have presented the design of a RCT of verum acupuncture compared with sham acupuncture. Completion of this trial will contribute to verifying the efficacy of acupuncture for the treatment of PPI. This multicenter study covers 13 provinces and cities from south to north in China, we hope that the results will provide robust evidence to support the application of acupuncture in the treatment of postoperative incontinence of prostate cancer.

Declarations

Ethics approval and consent to participate: The trial has passed the ethical application, and the participants signed an informed consent form.

Competing interests: The authors declare that they have no competing interests. And agree to public the protocol and follow-up research data.

Funding: National Administration of Traditional Chinese Medicine : 2019 Project of building evidence based practice capacity for TCM(2019XZZX-ZL007).

Authors' contributions: Yingjie Jia and Xiaojiang Li drew up the research design. Yao Zhang drafted the protocol and wrote the manuscript in English. Shanqi Guo, Liang Wang and Peiying Yang participated in the design amendment. Yao Zhang, Shanqi Guo, Chaoran Wang and Xiaodi Liu contributed to protocol ethics and trial registration. Yan Liu and Jingbo Zhai revised the details and the language.Yan Liu made the statistical plan. All authors reviewed the manuscript content and approved the final version for submission.

Acknowledgements: Thanks to the China Academy of Chinese Medical Sciences of China Center for Evidence Based Traditional Chinese Medicine and Guang'anmen Hospital of China Academy of Chinese Medical Sciences for guiding the project. Thanks to the Key Laboratory of Chinese Internal Medicine of Ministry of Education, Dongzhimen Hospital, Beijing University of Chinese Medicine for Revising research plan.

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Figures

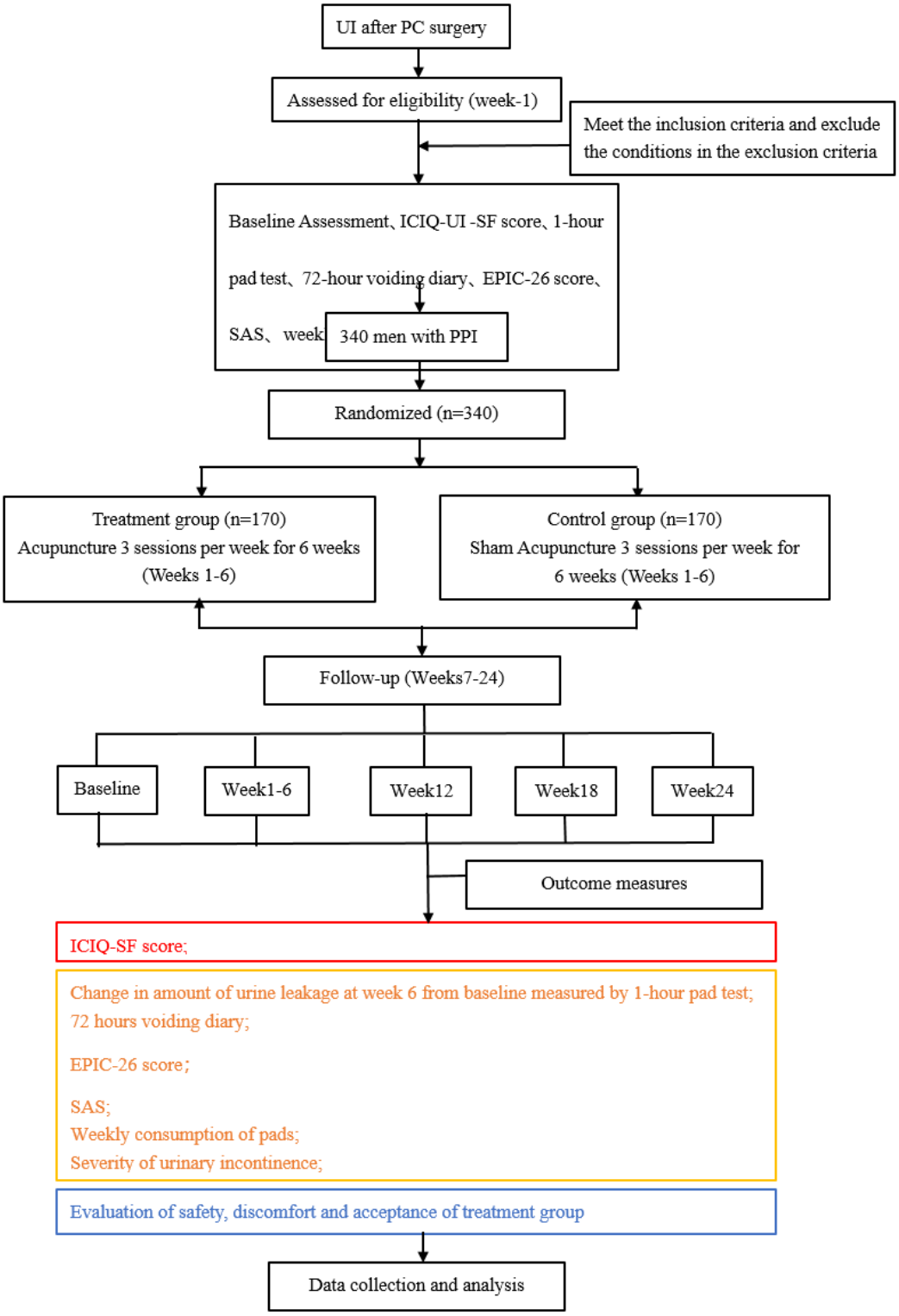

Figure 1

Trial flowchart. UI urinary incontinence; PC prostate cancer; PPI prostatectomy incontinence.

Supplementary Files

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