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# BMJ Open

## Effect of herbal extract granules combined with otilonium bromide on irritable bowel syndrome with diarrhea: study protocol for a randomized controlled trial

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4 **Effect of herbal extract granules combined with otilonium**  
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7 **bromide on irritable bowel syndrome with diarrhea: study**  
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10 **protocol for a randomized controlled trial**  
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**Key words:** Samryungbaekchulsan, otilonium bromide, irritable bowel syndrome, randomized controlled study, clinical trial protocol

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## ABSTRACT

### Introduction

Irritable bowel syndrome (IBS) is a collection of symptoms that occur together, generally including pain or discomfort in the abdomen and changes in bowel movement patterns. It is known as a functional gastrointestinal (GI) disorder. Due to the limitations of conventional treatments, alternative IBS treatments are used by many patients worldwide. Samryungbaekchulsan (SRS), an herbal formula, has long been used for alleviating diarrhea-predominant IBS (D-IBS) in traditional Korean medicine. Otilonium bromide (OB) is an antimuscarinic compound used to relieve spasmodic pain in the gut, especially in IBS. Although herbal formulas and western drugs have been administered simultaneously in many diseases including in D-IBS in Korea, only few studies have investigated the effects of combination therapy made up of an herbal formula and a western drug on any diseases including D-IBS.

### Methods and Analysis:

This trial is a randomized, double-blinded, placebo-controlled, double-dummy, four-arm, parallel study. After a 2-week preparation period, 80 patients with D-IBS will be randomly assigned to one of the four treatment groups consisting of SRS (water extract granules, 5 g/pack, 3 times a day) with OB (tablet form, 1 capsule 3 times a day) or their placebos, with treatment lasting for 8 weeks. Post-treatment follow-up will be conducted at 4 week after the end of treatment.. The primary outcome is the Subject's Global Assessment of Relief. The secondary outcomes are the severity of symptoms related to D-IBS using a 10-point scale and the change in symptoms.

### Discussion:

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4 The combination of OB and SRS is expected to improve multiple D-IBS symptoms at the  
5 same time—abdominal pain and discomfort (major efficacy of OB), and diarrhea (major  
6 efficacy of SRS). This trial is designed to examine the efficacy and safety of SRS and OB  
7 combination medication on D-IBS, and to provide clinical evidence for a new therapeutic  
8 regimen to treat D-IBS.  
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#### 14 15 16 17 **Ethics and dissemination:**

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19 This trial has full ethical approval of the ethics committee of Kwandong University  
20 International St. Mary's Hospital (IS15MISV0033), and Korean Ministry of Food and Drug  
21 Safety (30769). The results of the study will be disseminated through a peer-reviewed journal  
22 and/or conference presentations.  
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31 **Trial protocol version: IS15MISV0033 Version 4.0 (July 25, 2016)**

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35 **Trial registration number: KCT0001621**  
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## INTRODUCTION

Irritable bowel syndrome (IBS), a chronic gastro-intestinal (GI) disease and functional bowel disorder, is characterized by abnormal bowel habits and abdominal pain without structural, morphological, and histological abnormalities. It affects between 3–20% of the American population [1, 2]. Based on their predominant bowel habits, patients with IBS can be divided into diarrhea-predominant IBS (D-IBS), constipation-predominant IBS, or mixed IBS [3]. Recently, smooth-muscle relaxants, bulking agents, and anti-diarrheal agents have been commonly used in the treatment of IBS [4]. However, these methods are often not effective, and many IBS patients also use alternative treatments such as herbal medicine, acupuncture, psychological treatment, and lifestyle correction [2, 5, 6].

Samryungbaekchulsan (SRS; Shenlingbaizhu-san in Traditional Chinese Medicine; Jinryobyakujutsu-san in Kampo Medicine), which was introduced in the famous classical compendium of herbal formulas “*Formulary of Peaceful Benevolent Dispensary*”, consists of 10 herbs (Atractylodes rhizoma Alba, Poria sclerotium, Dioscoreae rhizoma, Glycyrrhizae radix et rhizoma, Coicis semen, Nelumbinis semen, Platycodonis radix, Dolichoris Semen, Amomi fructus, Ginseng radix). In traditional Korean and Chinese medicine, this herbal formula has been long used to treat GI disease, and various studies have been published on the treatment of IBS with SRS [7-10]. SRS has been shown to have anti-acetylcholine and anti-barium chloride effects, and to suppress gastric secretion and small intestine motility [11]. However, there have been no clinical trials studying the efficacy of SRS on IBS treatment when co-administered with a conventional drug.

Otilonium Bromide (OB) is widely used for the prevention and reduction of symptoms in patients with IBS [12]. OB has been shown to inhibit L- and T-type calcium channels, muscarinic receptors, and tachykininergic responses in human cultured smooth muscle cell and rat colon strips [10]. According to a recent randomized controlled trial (RCT), OB (40



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4 and 80 mg) is more effective in treating IBS than placebo, not only in the reduction of  
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6 bloating and abdominal pain, but also in protection from relapse due to its long-lasting effect.  
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8 [13].  
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11 Recently, several studies have been conducted to investigate the therapeutic effect of the  
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13 co-administration of herbal formulas and conventional drugs on IBS [14, 15]. However,  
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15 although both SRS and OB have been widely used in the treatment of IBS, there have been  
16  
17 no studies on the efficacy and safety of their combined treatment for IBS. Therefore, there is  
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19 a need to evaluate the efficacy and safety of SRS, OB, and co-administration of both drugs.  
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22 In this trial, we will evaluate the safety and efficacy of SRS, OB, and combination therapy  
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24 on D-IBS, by identifying Subject's Global Assessment of Relief and the severity of symptoms  
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26 related to D-IBS. The safety of SRS and OB will also be investigated via laboratory tests and  
27  
28 the subject's responses.  
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## 30 31 32 33 **METHODS AND ANALYSIS**

### 34 35 *Objectives*

36  
37 The purpose of this study is to identify efficacy and safety of the co-administration of SRS  
38  
39 and OB to patients with D-IBS.  
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### 43 44 *Necessity of the trial*

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46 Recently, co-administration of herbal medicines and western drugs has been utilized in  
47  
48 various medical therapies. This is true particularly in Korea, where very high percentage of  
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50 patients have used such combined administrations (76%) [16]. However, there are only a few  
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52 studies on the interaction between western and herbal medicines. Despite the need for  
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54 combined treatment in patients with various diseases, there are no standard clinical guidelines  
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56 or scientific evidence on co-administration due to a lack of research and data.  
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4 D-IBS is a disease that is difficult to cure and where many patients required treatment with  
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6 both western and herbal drugs in order to show an improvement in their symptoms. Therefore,  
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8 it is very important to proceed with the clinical study on the efficacy and safety of the  
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10 combined administration of SRS and OB in D-IBS patients.  
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### 13 14 15 ***Basis of drug selection*** 16

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18 According to guidelines for IBS treatment, the OB recommendation level is high (i.e., the  
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20 level of evidence is moderate, and many experts recommend using it), and it is the most  
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22 reasonable treatment option [17]. SRS is the herbal formula medicine used the most often by  
23  
24 clinical Korean and Chinese medical doctors for abdominal pain, abdominal discomfort, and  
25  
26 chronic diarrhea, which are typical symptoms of D-IBS [7-10]. Based on these studies and  
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28 clinical applications, OB and SRS were selected for this trial.  
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### 31 32 33 ***Hypothesis*** 34

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36 We hypothesize the following: (1) that co-administration of SRS and OB will have a more  
37  
38 positive effect on D-IBS symptoms than either SR or OB alone; (2) that after 8 weeks of  
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40 taking SRS, OB, or co-administration of both drugs, the Subject's Global Assessment of  
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42 Relief and severity of D-IBS symptoms will be improved more after treatment with placebo;  
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44 (3) that co-administration of SRS and OB will be safe for patients with D-IBS.  
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### 47 48 49 ***Design*** 50

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52 This study is a placebo-controlled, double-blind trial. Eighty patients will be enrolled and  
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54 randomly assigned to four separate arms of the trial. The trial will be conducted at Catholic  
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56 Kwandong University International St. Mary's Hospital, Incheon, South Korea.

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58 The study subjects will be required to participate in a 2-week preparation period (weeks -2  
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4 to 0) and an 8-week drug administration period (weeks 0 to 8). Visiting of the patients will  
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6 occur four times, on weeks 0, 4, 8, and 12. The primary outcome measurement will be  
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8 investigated at weeks 2, 4, 6, 8, and 12, and the secondary outcome measurement will be  
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10 investigated at weeks 0, 2, 4, 6, 8, and 12. Participants will be assessed for efficacy and safety  
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12 of the treatment through visits (0, 4, 8, 12 weeks) and telephone questionnaires (2, 6 weeks).  
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14 In addition, lab tests will be conducted at 0, 4, and 8 weeks. According to the intervention  
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16 protocols, CRC (Clinical Research Coordinator) will encourage patients and participants to  
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18 complete follow-up in every visits.  
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22 During the period of drug administration, SRS or its placebo will be given as 1 pack of  
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24 water extract granules, 3 times a day, 30 min before each meal. OB or its placebo will be  
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26 given as 1 tablet, 3 times a day, 30 min before each meal.  
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29 All participants will be divided into 4 groups: (1) the SRS and OB group; (2) SRS and  
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31 placebo-OB group; (3) placebo-SRS and OB group; (4) placebo-SRS and placebo-OB group.  
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33 The entire flow chart of the study is shown in Figure 1.  
34

35  
36 The entire protocol of this trial has been approved by the institutional review board (IRB)  
37  
38 and ethics committee of Kwandong University International St. Mary's Hospital. The IRB  
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40 permission number is IS15MISV0033, and CRIS (Clinical Research Information Service,  
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42 [www.cris.nih.go.kr](http://www.cris.nih.go.kr)) protocol identification number is KCT0001621. In addition, this study  
43  
44 received the first approval given by the Korean Ministry of Food and Drug Safety (KMFDS)  
45  
46 for a study of co-medication of a conventional drug and a Korean traditional herbal medicine  
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48 (approval number: 30769).  
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50  
51 After participants will be provided with sufficient information about the study, only those  
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53 who agree to the study protocol and sign the consent form, will be enrolled. The study will be  
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55 implemented according to the Good Clinical Practice and the revised version of the  
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57 Declaration of Helsinki.  
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### *Sample size calculation*

This trial is a pilot study of a new therapeutic regimen of SRS and OB combined treatment. In a former similar study using co-administration of western and herbal medicine (placebo-controlled, double-blind, and randomly 4-arm), each arm consisted of at least 15 patients and a total sample size of more than 60 participants [14]. In other similar pilot studies, clinical trials have been conducted on a total of 60–64 participants, consisting of 12–30 patients per group [18, 19]. Based on these previous studies, minimal clinical significance of the trial can be obtained by 16 participants who complete the trial. Since drop-out occurrence is expected to be 20%, each trial group will be made up of at least 20 participants. Therefore, the total sample size must be more than 80 participants.

### *Inclusion criteria*

Patients included in the study should match the following criteria: (1) 18–75 years old; (2) suffer from the Rome III criteria of IBS (recurrent abdominal pain or discomfort that began at least 6 months before the clinical trial and rates more than 3 on a 10 point scale, and at least 3 days/month in last 3 months associated with two or more of the following: improved with defecation, onset associated with a change in frequency of stools, and onset associated with a change in form of stool) [1, 20]; (3) in accordance with the Rome III criteria of IBS, D-IBS type defined as loose / mushy or watery stools—Bristol Stool Form (BSF) Scale 6-7  $\geq$  2 times / week [20, 21]; (4) urine pregnancy test is negative (childbearing age of women, within 7 days before clinical trial) and will use contraception during the administration period; (5) patients who can read the symptom questionnaire and understand its meaning; (6) patients who agree with the clinical plan and voluntarily sign the IRB-approved documents.

### *Exclusion criteria*

Patients who meet the following conditions will be excluded from the study: (1) chronic liver disease (cirrhosis, chronic hepatitis - B and C); (2) chronic renal failure or renal impairment (serum creatinine  $\geq 2$  times the upper limit of the normal); (3) liver dysfunction (AST / ALT  $\geq 3$  times the upper limit of the normal); (4) diabetes (HbA1c  $> 8\%$ , or not controlled by diet or medication), hypertension ( $\geq 160/100$  mmHg), thyroid dysfunction (exceptions in the following cases: if the disease is controlled during drug administration with a stable dose for 12 weeks before the screening, and the drug dose remains constant during the trial period), clinically significant hematologic, cardiac, pulmonary, neurological disorders or other severe systemic disorders; (5) abnormal findings on colonoscopy or colonography within the last 5 years; (6) history of surgery that affects gastrointestinal motility (i.e., gastrectomy, colonic resection, hysterectomy, except for appendectomy); (7) GI disease as follows, within 6 months before the clinical trial: inflammation or ulcer of esophagus, stomach, or duodenum; gastroesophageal reflux disease (at the discretion of the examiner, subjects may enroll if the disease is chronic and not acute); gastrointestinal bleeding; gastrointestinal stenosis or closure; infectious diarrhea; inflammatory bowel disease (i.e., Crohn's disease, diverticulitis, ulcerative colitis, infectious enteritis, ischemic colitis); pancreatic insufficiency; biliary abscess; (8) mental illness or an addiction to drugs or alcohol; (9) severe systemic organ diseases such as cancer, autoimmune disease, stroke (although patients in recurrence for more than 5 years from cancer unrelated to the GI tract can participate in trial); (10) pregnant and lactating women, and women who are not willing to use contraception during the trial; (11) a history of taking the following drugs within 2 weeks before the trial: antibiotics, anti-inflammatory drugs, analgesics, antidepressants, anti-anxiety agents, anti-inflammatory agents, anti-ulcer agents, anti-gastric secretion inhibitors, laxatives,

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4 antispasmodics, antacid agents, gastrointestinal stimulants, prostaglandin agents, and  
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6 corticosteroids; (12) use of medications that do not match the intent of this trial, or have a  
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8 clinical interaction with SRS or OB; (13) lactose intolerance (not controlled by food); (14)  
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10 glaucoma; (15) patients who have participated in other clinical studies within 30 days prior to  
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12 clinical screening, and have received other clinical trial medications (including placebo); (16)  
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14 hypersensitivity to clinical trial medicines; (17) other reasons considered inappropriate for  
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16 participation in clinical trials.  
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### 20 21 22 ***Recruitment, Randomization, Blinding and Unblinding*** 23

24 Advertisements of the study will be announced in the Catholic Kwandong University  
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26 International St. Mary's Hospital using banner ads and posters. We also plan to post the  
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28 advertisements on the homepage of the hospital, in the monthly hospital magazine, at the  
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30 internet café, and on the subway at least five times. All these advertisements will be  
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32 conducted with the approval of the IRB.  
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35 After recruitment, patients will randomized to one of the four trial arms. Randomization  
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37 will be performed using a list of block randomizations made by statisticians, independent of  
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39 this clinical trial. A researcher who is not involved in process of drug prescription and  
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41 evaluation will execute the randomization process.  
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44 During the treatment period, the subjects and all researchers (investigators, clinical  
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46 research coordinators, management pharmacists) will be blinded, except the researchers who  
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48 conducted the randomization procedure. Allocation concealment will be performed during  
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50 the process of medication administration. A management pharmacist who is not affect the  
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52 results of the trial and analysis, will refer to the randomization list and administer the  
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54 medication. The patients will take the drugs contained in the opaque envelope, which is  
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56 labeled with the assignment number.  
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4 Unblinding will be performed only in the following situations: (1) If the trial is terminated  
5 and there is a need for statistical analysis; (2) If a serious medical emergency occurs and  
6 information about the medication is needed; (3) If the chief investigator determines that  
7 unblinding is necessary.  
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12 The entire process of the study will be directed by the authorized clinical research  
13 organization (CRO), Dream CIS Corporation, Seoul, Korea.  
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### 17 18 19 **Intervention**

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21 The herbal formula SRS is commonly used by Korean traditional medical doctors for  
22 treatment of diarrhea and related diseases [7-10]. SRS used in this study  
23 (Samryungbaekchulsan granule<sup>®</sup>, Hankook shin yak, Co., Ltd., Nonsan, Korea) is extracted  
24 with water and mixed with starch and lactose in accordance with the Korean Good  
25 Manufacturing Practice (K-GMP). Production of SRS is regulated and allowed by the  
26 KMFDS. SRS contains 10 herbs, listed in Table 1. Placebo-SRS is made from cornstarch and  
27 has the same taste, shape, and color as SRS. SRS and placebo-SRS will be sealed in identical  
28 aluminum bags with the same labelling. These herbal drug packages will be administered by  
29 an independent pharmacist in an isolated room. After dissolving the granules in boiled water,  
30 the subjects will take them 30 min before each meal.  
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45 OB (Menocetyl Tab<sup>®</sup>, Dong Hwa Pharm Co., LTD., Seoul, Korea) is a tablet containing  
46 otilonium bromide 40 mg. Placebo-OB is a tablet made of Ludipress with same taste, shape,  
47 and color as OB. Patients will be instructed to swallow one tablet of OB or placebo-OB, 30  
48 min before each meal for the administration period. All of the drugs used in the trial (SRS,  
49 OB, placebo-SRS, placebo-OB) have been approved by the KMFDS. Patients will be asked at  
50 the end of the study whether the drugs that they have been taking are either real or placebo, to  
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measure the success of blinding. Compliance will be confirmed by counting returned SRS packets or OB tablets. Every patient will be instructed to write down any adverse events during the administration period, and these records will be checked at the follow-up. At the time of patients visit (0, 4, 8 week), we will check vital signs, physical examination, electrocardiogram, and perform laboratory tests to evaluate the safety of the patients. All side effects will be reported to the investigator.

**Table. 1 Ingredients of the herbal formula Samryungbaekchulsan (SRS)**

Scientific name	Part of use	Gram/day
Atractylodis Rhizoma Alba	Root	3.0
Poria Sclerotium	Dried core	4.0
Rhizoma Dioscoreae	Root	3.0
Glycyrrhizae Radix et Rhizoma	Root	1.5
Semen Coicis	Seed	8.0
Semen Nelumbinis	Fruit	4.0
Platycodonis Radix	Root	2.5
Dolichoris Semen	Seed	4.0
Amomi Fructus	Fruit	2.0
Ginseng Radix	Root	3.0

#### ***Rescue therapy and concomitant medications***

Participants are prohibited from taking any medication that could affect D-IBS during the entire course of the trial. However, if serious side effects or worsening of the symptoms occur, investigators will provide quick and appropriate treatment (including drug administration), based on their medical judgement. In this case, the direct investigators will record the



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4 treatment or drug administration, and report to the IRB within 24 hours to determine whether  
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6 the trial should be continued or discontinued.  
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### 9 10 11 ***Outcome Measurements***

#### 12 *Primary outcome*

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14 The primary outcome will be measured via a questionnaire that confirms the subjective  
15 symptom improvement. Participants will respond a total of five times during and after the  
16 administration period (2, 6 weeks: through telephone, and 4, 8, 12 weeks: through direct  
17 visits) to the following question: Subject's Global Assessment of Relief; "How much do you  
18 think the symptoms of D-IBS have improved compared to before the clinical trial?"  
19 According to the answers of patients to this survey, the improvement is given a score of 0, 1,  
20 2, 3, or 4.  
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#### 32 *Secondary outcomes*

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34 At 2, 4, 6, 8, and 12 weeks from the start of the treatment period, patients will be assessed  
35 for severity of D-IBS symptoms (abdominal pain, abdominal discomfort, satisfaction of  
36 defecation, frequency of abdominal pain, quality of life) by using a Likert scale ranging from  
37 0–10, [10, 14, 22]. Patients will also be instructed to record the number of defecations per day,  
38 BSF, and the degree of force used in bowel movements at 0, 2, 4, 6, 8, and 12 weeks [14, 19,  
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#### 50 *Safety assessments*

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52 The investigator will record all adverse events that occur during the trial along with any  
53 concomitant medications in the case reports. When an adverse event occurs, the investigator  
54 will record the symptoms and signs of the adverse reaction, the duration (start and end date),  
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4 severity, course, outcome, significance, causality with the trial drug, and any action taken in  
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6 relation to the adverse event. In the case of concomitant medicines, composition, dosage,  
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8 duration of administration, and reason for medication will be recorded in detail. Symptoms  
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10 that existed before the start of the clinical trial will not be recorded as adverse events.  
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### 13 14 15 *Laboratory tests*

16  
17 The purpose of laboratory tests in this study is to evaluate the safety and pharmacokinetic  
18  
19 profiles of SRS and OB. Because of the small number of patients assigned to this study and  
20  
21 the different baseline values for each individual patient, we will not perform a detailed  
22  
23 statistical analysis. However, if significant abnormal results are founded in the laboratory  
24  
25 tests, the clinical laboratory results will be described and the connection to the drug will be  
26  
27 considered.  
28  
29

30  
31 Blood tests will be conducted at 0, 2, 4, and 8 weeks, and urine tests will be performed at  
32  
33 0 and 4 weeks of the clinical trial. In the case of a participant who drops out or the early  
34  
35 termination of the clinical trial, blood and urine tests will be performed on the last day of the  
36  
37 trial.  
38

39  
40 Using the test results (comprehensive verifications of vital signs, laboratory tests,  
41  
42 electrocardiograms, and physical examinations) for each individual patient, the investigator  
43  
44 will determine adverse reaction of the drugs, and statistical tests will be conducted as needed  
45  
46 on clinically significant parameters.  
47  
48

### 49 50 51 *Test of human derivatives*

52  
53 IBS is known to be closely related to stress [6]. Therefore, we plan to quantify factors  
54  
55 associated with stress or that have been reported to worsen IBS symptoms as follows: 1)  
56  
57 cortisol; 2) corticotropin-releasing hormone (CRH); 3) serotonin; 4) cytokines group I (10  
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4 species); 5) cytokines group II (14 species); 6) growth factors (3 species) [23, 24]. Serum will  
5  
6 be separated from blood specimens collected at 0, 4, 8 weeks, stored frozen, and transferred  
7  
8 to the Korea Institute of Oriental Medicine (KIOM) for examination.  
9

#### 10 11 12 13 *Early termination or dropout*

14  
15 The criteria for early termination or dropout are as follows: 1) administration of other  
16  
17 drugs that are expected to affect the safety and efficacy of the clinical trial drugs; 2) request  
18  
19 of participants to discontinue the clinical trial, or withdrawal of the trial agreement; 3)  
20  
21 occurrence of significant adverse drug reaction or event that precludes continuing in the trial,  
22  
23 according to the judgment of the clinical investigator; 4) new discovery of violations of  
24  
25 significant clinical trial protocol during clinical trial; 5) Less than 70% trial drug compliance;  
26  
27 (6) any other reason that the clinical trial should be discontinued at the discretion of the  
28  
29 clinical trial manager or investigator.  
30  
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#### 35 *Data collection, access and management*

36  
37 The data of this trial will be managed according to the Standard work instructions of  
38  
39 Catholic Kwandong University International, St. Mary's Hospital. Other contents not  
40  
41 specified in the trial protocol shall follow the standards of The International Conference on  
42  
43 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human  
44  
45 Use (ICH)-Guideline for Good Clinical Practice (GCP) and guide line Korean Good Clinical  
46  
47 Practice (KGCP).  
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49

50  
51 The source document is recorded immediately when the data of case collected. After the  
52  
53 source document input is completed, it will be recorded in the case record form (CRF). All  
54  
55 the documents will be kept safe, so that it can be verified by the relevant government  
56  
57 agencies and IRB. Only research colleagues and others who have delegated the approval of  
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4 the principle investigator have access to all data obtained from this trial.  
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### 8 *Statistical analysis*

9  
10 The statistical analysis will be conducted by blinded professional statisticians. To evaluate  
11 the efficacy of the study, both the *intent-to-treat* (ITT) analysis (main analytical method) and  
12 the *per-protocol* (PP) analysis (secondary analytical method) will be performed  
13 simultaneously. The ITT analysis will be conducted on all patients who were followed up at  
14 least once after the randomization and will be able to evaluated for effectiveness, PP analysis  
15 will be performed on patients who have completed for 8 weeks treatment course meeting all  
16 of the inclusion and exclusion criteria.  
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24

25 To analyze for continuous variables of demographic information and pre-treatment  
26 characteristics between groups, a one-way analysis of variance (ANOVA) and Kruskal-Wallis  
27 test will be conducted. An ANOVA and Kruskal-Wallis test will be also used to test for  
28 symptom improvement compared to baseline (0 week), and the variables for analysis that  
29 include the following: (1) subjective symptom improvement (primary outcomes); (2) severity  
30 of symptoms related to D-IBS (abdominal pain, abdominal discomfort, satisfaction of  
31 defecation, frequency of abdominal pain, quality of life). All values will be shown as mean  $\pm$   
32 standard error of the mean (SEM). Comparisons of outcome assessments between the four  
33 groups will be performed using the paired t-test or Wilcoxon signed-rank test.  
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46 If the Subject's Global Assessment of Relief on the Likert scale is "0" or "1" for more than  
47 2 weeks between weeks 8 and 12, then the symptoms will be considered to have improved  
48 sufficiently. Based on this, we will calculate the symptom relief rate by dividing the number  
49 of participants who exhibited sufficient symptom relief by the total number of participants in  
50 the trial, and present descriptive statistics. The CATMOD procedure will be used to evaluate  
51 the relief rate improvement of symptom, compared with baseline. Comparisons between the  
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4 four groups will be conducted using the chi-square test or Fisher's exact test. These  
5  
6 statistical analyses will also be performed at 2, 4, 6, 8, and 10 weeks from the baseline. The  
7  
8 Cochran-Mantel-Haenszel (CMH) test will be used to confirm the difference between the  
9  
10 intervention groups, at each time-point.  
11

12  
13 A statistical analysis will also be conducted to evaluate safety. The incidence of adverse  
14  
15 events and abnormality of experimental results will be analyzed statistically according to the  
16  
17 groups, and non-parametric methods will be applied as necessary using a paired t-test for  
18  
19 continuous data, McNemar's test for categorical data, Fisher's exact test for adverse events,  
20  
21 and a generalized estimating equation for clinically significant changes between groups.  
22

23  
24 All statistical analysis will be conducted using SAS software, version 9.1.3 (SAS institute,  
25  
26 Cary, NC). A *P*-value <0.05 will be considered statistically significant.  
27

### 28 29 30 31 *Quality control and Data monitoring*

32  
33 To ensure the results and quality of clinical trials, assessments and monitoring will be  
34  
35 performed by the CRO (DreamCIS Corporation, Seoul, Korea), which is independent from  
36  
37 the sponsor and competing interests. During the trial, the CRO will monitor regularly whether  
38  
39 the study is proceeding in accordance with the protocol through the use of all related  
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41 documentation, including trial master files, case report forms, informed consent form, and  
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43 adverse event reports.  
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## DISCUSSION

Herbal medicine has been recognized as an effective treatment method based on accumulated clinical experience for thousands of years, and has more recently gained attention as an alternative therapy for treating various diseases which are difficult to treat or have unknown causes such as IBS [15, 25]. SRS has frequently been used for abdominal pain and diarrhea in Korean and Chinese traditional medicine. According to experimental research, SRS has an anti-cholinergic effect, increasing the recovery of intestinal digestion and absorption, and inhibiting intestinal movement, associated with the prevention of diarrhea and abdominal pain [11, 26]. In addition, clinical studies have shown that the use of SRS in D-IBS patients is effective in improving diarrhea [27, 28]. However, although there is a growing interest in the use of herbal medicine such as SRS in IBS, and related studies are continuously being published, there are only few well-designed RCTs. To overcome the limitations of these previous studies, this trial was designed as a double-blind, double-dummy, four-arm, parallel RCT. The efficacy of SRS will be evaluated via the Subject's Global Assessment of Relief and the improvement of symptoms associated with bowel movements and abdominal pain. The results of these assessments are expected to provide distinct clinical evidence for SRS in D-IBS treatment.

OB is one of the representative medicines for D-IBS treatment [12]. It is a spasmolytic agent, which exerts its activity primarily on the distal GI tract through the inhibition of  $Ca^{++}$  flux and direct activation of contractile proteins in the smooth muscle [29]. OB has also been shown to reduce hyper-motility and visceral sensation modulation, which are thought to help improve D-IBS symptoms [30]. RCTs using OB as an intervention for the treatment of D-IBS have been conducted. In these studies, OB showed a stronger improvement of symptoms related to D-IBS—defecation frequency, regular intestinal habits, reductions in frequency of diarrhea, abdominal pain and discomfort, severity of abdominal bloating—and protection

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4 from symptom relapse, than placebo [13, 31, 32].

5  
6 IBS is a disease with a high rate of disease progression and frequent recurrence. For this  
7  
8 reason, IBS patients often require various treatment methods [2]. Among these methods, the  
9  
10 combination of herbal and conventional drugs is widely used, and are more effective in  
11  
12 improving IBS symptoms than conventional drug alone [31]. However, there are several  
13  
14 limitations to the co-administration of herbal and conventional drugs in IBS. Specifically,  
15  
16 there is a high risk of bias in related studies, and there are insufficient clinical guidelines on  
17  
18 the interaction of herbal and conventional drugs in D-IBS, including SRS and OB. Therefore,  
19  
20 it is necessary to perform well-designed RCTs studying the co-administration of herbal and  
21  
22 conventional drugs.  
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25  
26 This RCT has several characteristic features. First, this trial will be the first study to  
27  
28 investigate the efficacy of SRS and OB combination therapy for D-IBS. The results of  
29  
30 previous studies suggest that the combination of OB and SRS will improve both major D-IBS  
31  
32 symptoms at the same time: abdominal pain and discomfort (major efficacy of OB), and  
33  
34 diarrhea (main efficacy of SRS). This study will assess this hypothesis, and provide a basis  
35  
36 for SRS and OB combination therapy in D-IBS. Second, the participants in this trial will be  
37  
38 grouped into four arms. Through this sorting, it will be possible to compare the efficacy of  
39  
40 combined treatment with the efficacy of each individual treatment effect. Third, this trial will  
41  
42 evaluate the safety of the subjects using several assessments: a periodic assessment of the  
43  
44 subjective symptom, physical measurements, and laboratory testing. The results of the safety  
45  
46 analysis may provide evidence for the combination treatment of herbal and conventional drug  
47  
48 on D-IBS. Fourth, this trial was the first clinical study related to the combination medication  
49  
50 of western and traditional herbal medicine in Korea to receive approval of the KMFDS.  
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52 Through the systematic management of the trial under the auspices of the KMFDS, a higher  
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54 quality of trial will be secured, and the results of this study will be more helpful in providing  
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4 information for use in clinical applications later.

5  
6 Although our study is a pilot study with a small sample size, it has a creative and  
7  
8 systematic research design, and will be able to be used as basic clinical evidence in the field  
9  
10 of integrated herbal and conventional drugs for the management of D-IBS.  
11  
12

### 13 14 15 **Trial status**

16  
17 The research plan and design began in April, 2015.

18  
19 The study received the IRB's final approval after two deliberations. The first deliberation  
20  
21 submission date was July 01, 2015; the result of first was a request for revision and  
22  
23 supplementation, which was received on July 13, 2015. We filed an application for re-review  
24  
25 on August 06, 2015, supplemented with the relevant information, and received IRB's final  
26  
27 approval on August 10, 2015. We also requested that the KMFD review the trial plan on  
28  
29 September 14, 2015 and received approval for the clinical research on December 21, 2015.  
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32  
33 The first participant was randomized on 29 March, 2016. Recruitment of the study is  
34  
35 ongoing.  
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37

### 38 39 **Ethics**

#### 40 41 *Research ethics approval*

42  
43 This trial has been approved by IRB and ethics committee of Kwandong University  
44  
45 International St. Mary's Hospital (approval number IS15MISV0033), and KMFD (approval  
46  
47 number 30769).  
48  
49

#### 50 51 *Protocol amendments*

52  
53 The investigator who wishes to change the protocol of a clinical trial plan should first  
54  
55 discuss it with the trial director. Thereafter, the examiner should obtain prior approval from  
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4 the IRB for changes to the protocol in advance (except to prevent immediate injury to the  
5 patient, in which case it will be reported to the IRB later). However, when a dangerous  
6 situation occurs to the patient and immediate treatment is needed, the investigator may report  
7 the protocol change to the IRB at a later time.  
8  
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### 13 14 15 *Consent*

16  
17 The patients who are recruited through the announcement will be explained the details of  
18 the trial in an easy-to-understand manner. The patients and investigators should have a mutual  
19 enough question and answer time, before signature to the clinical trial consent. Through these  
20 processes, if the patients agree to participate in the trial, the consent form will be written.  
21  
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### 28 29 *Confidentiality*

30  
31 All the information of patients will be anonymized with initials or symbols, and all related  
32 investigators should keep confidentiality of the trial results. The trial director should keep the  
33 signed consent form, and prepare the list, when to confirm the patient's identity.  
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### 40 41 *post-trial care*

42  
43 If the patients receive unexpected accidents or injuries, appropriate compensation will be  
44 performed by Federal Insurance Company Korea (12th Floor Ferrum Tower 66 Suha-Dong  
45 Jung-gu Seoul, 100210, South Korea), according to the patient's compensation rules of the  
46 trial. Also in the case of an emergency, the patients will receive an appropriate medical care  
47 with the Catholic Kwandong University International, St. Mary's Hospital  
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### 55 56 **Dissemination**

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4 The results of the trial will be disseminated through a peer-reviewed journal and/or  
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6 conference presentations.  
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For peer review only

## REFERENCES

- 1 Drossman DA. Introduction. The Rome Foundation and Rome III. *Neurogastroenterol Motil.* 2007;19:783-6.
- 2 Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. *J Gastroenterol Hepatol.* 2010;25:691-9.
- 3 Longstreth GF, Thompson WG, Chey WD, *et al.* Functional bowel disorders. *Gastroenterology.* 2006;130:1480-91.
- 4 Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000;133:136-47.
- 5 Liu JP, Yang M, Liu YX, *et al.* Grimsgaard S. Herbal medicines for treatment of irritable bowel syndrome. *Cochrane Database Syst. Rev.* 2006;1:CD004116.
- 6 Palsson OS, Drossman DA. Psychiatric and psychological dysfunction in irritable bowel syndrome and the role of psychological treatments. *Gastroenterol Clin North Am.* 2005;34:281-303.
- 7 Duan WK. Observation of sixty-five cases on irritable bowel syndrome treated by Trimebutine and Shenlingbaizhu-san granule [Chinese]. *Journal of Practical Traditional Chinese Medicine.* 2010;26:320.
- 8 Chen YJ. Clinical observation of irritable bowel syndrome treated by shenlingbaizhu-san granule and trimebutine [Chinese]. *Journal of Practical Traditional Chinese Medicine.* 2011;27:318-9.
- 9 Li Q, Jiang JL. Clinical observation of 80 cases on diarrhea - predominant irritable bowel syndrome treated by Shenlingbaizhu-san granule [Chinese]. *Guiding Journal of*

- 1  
2  
3  
4 Traditional Chinese Medicine and Pharmacy. 2013;19:41-2.  
5  
6 10 Martinez-Cutillas M, Gil V, Gallego D, *et al.* Jimenez M. Mechanisms of action of  
7  
8 otilonium bromide (OB) in human cultured smooth muscle cells and rat colonic strips.  
9  
10 Neurogastroenterol Motil. 2013;25:e803-12.  
11  
12 11 Song DS, Ryu BH, Park DW, *et al.* Experimental studies on the efficacy of  
13  
14 Samryungbaekchulsan. J Korean Med. 1977;14(1):179-95.  
15  
16 12 Boeckxstaens G, Clave P, Corazziari ES, *et al.* Irritable bowel syndrome: focus on  
17  
18 otilonium bromide. Expert Rev Gastroenterol Hepatol. 2014;8:131-7.  
19  
20 13 Chmielewska-Wilkoń D, Reggiardo G, Egan CG. Otilonium bromide in irritable  
21  
22 bowel syndrome: a dose-ranging randomized double-blind placebo-controlled trial.  
23  
24 World J Gastroenterol. 2014;20:12283-91.  
25  
26 14 Li CT, Wu MP, Wang LH, *et al.* Clinical observation of diarrhea - predominant  
27  
28 irritable bowel syndrome treated by Shenlingbaizhu-san and Paroxetine [Chinese].  
29  
30 Chinese Journal of Traditional Medical Science and Technology. 2010;17(2):154-5.  
31  
32 15 Leung WK, Wu JC, Liang SM, *et al.* Treatment of diarrhea predominant irritable  
33  
34 bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-  
35  
36 controlled trial. Am J Gastroenterol. 2006;101:1574-80.  
37  
38 16 Park JK, Choi SY, Koh KW, *et al.* Combined utilization with herbal products and  
39  
40 prescribed drugs: a result from health examinee-based national survey. Korean J  
41  
42 Health Policy Admin. 2006;16(1):1-16.  
43  
44 17 Kwon JG, Park KS, Park JH, *et al.* The Korean Society of Neurogastroenterology and  
45  
46 Motility. Guidelines for the treatment of irritable bowel syndrome. Korean J  
47  
48 Gastroenterol. 2011;57(2):82-99.  
49  
50 18 Cha BK, Jung SM, Choi CH, *et al.* The effect of a multispecies probiotic mixture on  
51  
52 the symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a  
53  
54  
55  
56  
57  
58  
59  
60

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3  
4 randomized, double-blind, placebo-controlled trial. *J Clin Gastroenterol.*  
5  
6 2012;46(3):220-7.  
7  
8  
9 19 Kim HJ, Vazquez Roque MI, Camilleri M, *et al.* A randomized controlled trial of a  
10 probiotic combination VSL #3 and placebo in irritable bowel syndrome with bloating.  
11 *Neurogastroenterol Motil.* 2005 ;17:687-96.  
12  
13  
14 20 Longstreth GF, Thompson WG, Chey WD, *et al.* Functional bowel disorders.  
15 *Gastroenterology.* 2006;130:1480-91.  
16  
17  
18 21 Lewis HJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time.  
19 *Scand J Gastroenterol.* 1997;32:920-4.  
20  
21  
22 22 Chambers CT, Giesbrecht K, Craig KD, *et al.* Comparison of faces scales for the  
23 measurement of pediatric pain: children's and parents' ratings. *Pain.* 1999; 83:25-35.  
24  
25  
26 23 Sugaya N, Izawa S., Saito K, *et al.* Effect of prolonged stress on the adrenal hormones  
27 of individuals with irritable bowel syndrome. *Biopsychosoc Med.* 2015;9:4.  
28  
29  
30 24 Fadgyas-Stanculete M., Buga AM, Popa-Wagner A, *et al.* The relationship between  
31 irritable bowel syndrome and psychiatric disorders: from molecular changes to  
32 clinical manifestations. *J Mol Psychiatry.* 2014;2(1):4.  
33  
34  
35 25 Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel  
36 syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.*  
37 2000;133:136-47.  
38  
39  
40 26 Li YL. Clinical and experimental study on the treatment of children diarrhea by  
41 granule of children-diarrhea fast-stopping. *Zhong Xi Yi Jie He Za Zhi.* 1991;11:79-82.  
42  
43  
44 27 Zhong YL, Wu YY. Forty cases of diarrhea - predominant irritable bowel syndrome  
45 treated by Shenlingbaizhu-san granule and Montmorillonite powder [Chinese].  
46 *Jiangxi Journal of Traditional Chinese Medicine.* 2013;44:45-6.  
47  
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57  
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3  
4 28 Xiong B. Thirty cases of irritable bowel syndrome treated by Shenlingbaizhu-san  
5 granule and Probiotics [Chinese]. Jiangxi Journal of Traditional Chinese Medicine.  
6 2011;42(5):22-3.  
7  
8  
9  
10  
11 29 Giachetti A. Pharmacological studies on otilonium bromide. Ital J Gastroenterol.  
12 1991;23:56-9.  
13  
14  
15 30 Evangelista S. Otilonium bromide: a selective spasmolytic for the gastrointestinal  
16 tract. J Int Med Res. 1999;27:207-22.  
17  
18  
19 31 Clave P, Acalovschi M, Triantafyllidis JK, *et al.* OBIS Study Investigators.  
20 Randomised clinical trial: otilonium bromide improves frequency of abdominal pain,  
21 severity of distention and time to relapse in patients with irritable bowel syndrome.  
22 Aliment Pharmacol Ther. 2011;34:432-42.  
23  
24  
25  
26  
27  
28 32 Battaglia G, Morselli-Labate AM, Camarri E, *et al.* Otilonium bromide in irritable  
29 bowel syndrome: a double-blind, placebo-controlled, 15-week study. Aliment  
30 Pharmacol Ther. 1998;12:1003-10.  
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### Authors' Contributions

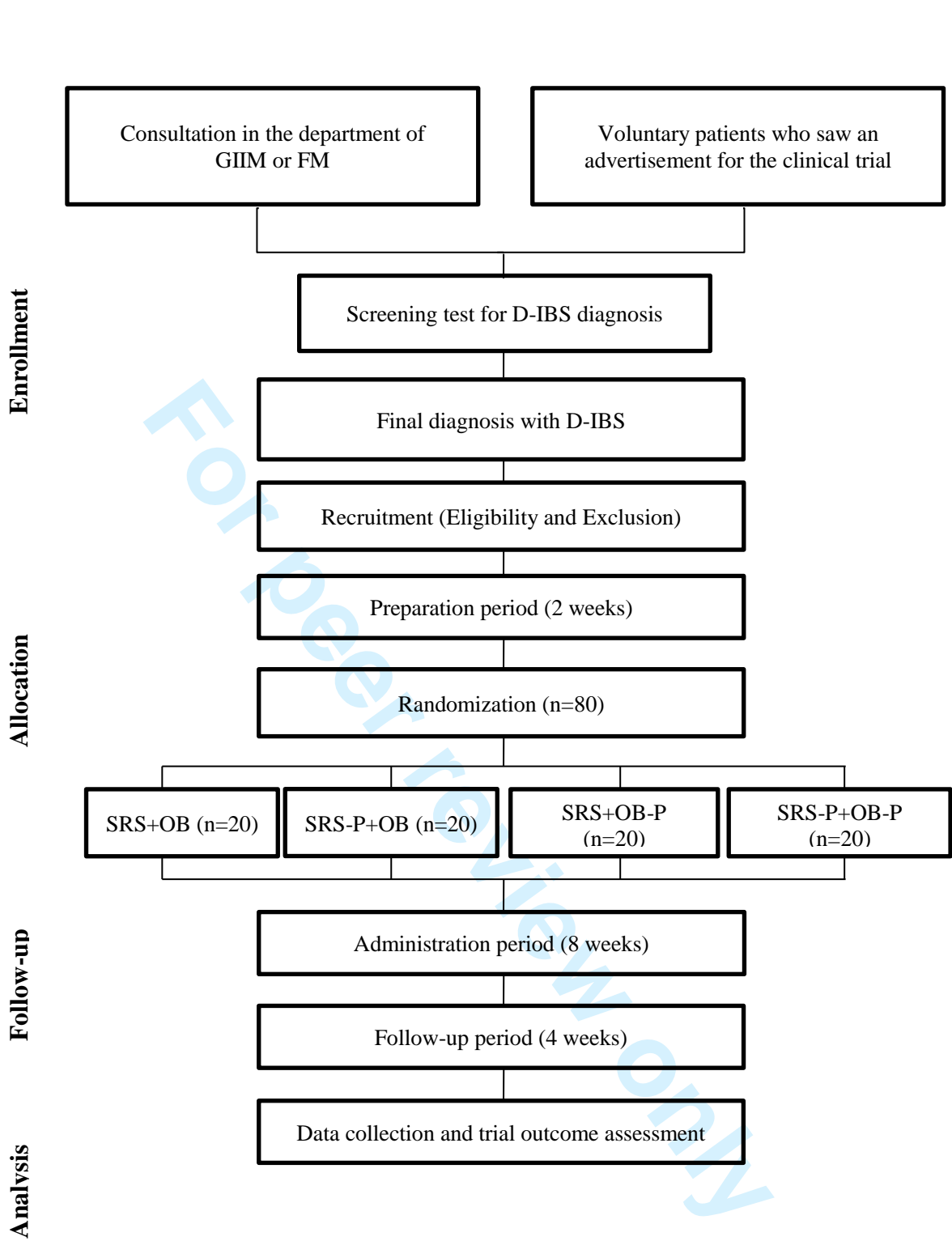
Joong-II Kim, Pumsoo Kim, Jin-Hyun Lee, and Jung-Han Lee contributed to making the protocol design and writing the manuscript. Hyekyung Ha is responsible for monitoring the process of the trial. Na-rae Yang, Yoo-Jin Kim, Myong Ki Baeg, Ja Sung Choi, Hye-Jung Kim and Ja-Young Kim provide advice on the process of the trial. Tae-Yong Park is responsible for writing the manuscript and also managing and supervising the clinical research. All authors approved of the final manuscript.

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### Competing interests

The authors have no competing interests to declare.



**Figure 1. Flow chart of Trial.** GIIM: Gastrointestinal internal medicine, FM: Family medicine, D-IBS: diarrhea-irritable bowel syndrome, P: placebo, OB: otilonium bromide, SRS: Samryungbaekchulsan

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P4
	2b	All items from the World Health Organization Trial Registration Data Set	Attachment
Protocol version	3	Date and version identifier	P4
Funding	4	Sources and types of financial, material, and other support	P1, P28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1, P28
	5b	Name and contact information for the trial sponsor	P1
	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	N/A
	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)	P17-19
<b>Introduction</b>			
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	P5-6
	6b	Explanation for choice of comparators	P6
Objectives	7	Specific objectives or hypotheses	P7
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)	P7-8

**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	P7
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)	P10-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P13-14
	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)	P14, P15-16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P17
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	P15-16
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)	P9, Figure1
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	P10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P12

**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	P12
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2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	P12
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	P12
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	P12
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13				
14		17b	If blinded, circumstances under which unblinding is permissible, and	P12
15			procedure for revealing a participant's allocated intervention during	
16			the trial	
17				
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19	<b>Methods: Data collection, management, and analysis</b>			
20				
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	P17-19
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27				
28		18b	Plans to promote participant retention and complete follow-up,	P8
29			including list of any outcome data to be collected for participants who	
30			discontinue or deviate from intervention protocols	
31				
32				
33	Data	19	Plans for data entry, coding, security, and storage, including any	P17
34	management		related processes to promote data quality (eg, double data entry;	
35			range checks for data values). Reference to where details of data	
36			management procedures can be found, if not in the protocol	
37				
38	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	P17-19
39	methods		Reference to where other details of the statistical analysis plan can be	
40			found, if not in the protocol	
41				
42		20b	Methods for any additional analyses (eg, subgroup and adjusted	P17
43			analyses)	
44				
45		20c	Definition of analysis population relating to protocol non-adherence	P17
46			(eg, as randomised analysis), and any statistical methods to handle	
47			missing data (eg, multiple imputation)	
48				
49				
50	<b>Methods: Monitoring</b>			
51				
52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	P19
53			and reporting structure; statement of whether it is independent from	
54			the sponsor and competing interests; and reference to where further	
55			details about its charter can be found, if not in the protocol.	
56			Alternatively, an explanation of why a DMC is not needed	
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1		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	P17,19
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6	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	P15-16
7				
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P19
11				
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15	<b>Ethics and dissemination</b>			
16				
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P1, P22
18				
19				
20	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)	P22-23
21				
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24				
25	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P23
26				
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28		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A.
29				
30				
31	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	P23
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36	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P29
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39	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	P17
40				
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43	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	P23
44				
45				
46	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	P4, P23-24
47				
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52		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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55		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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**Appendices**

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attachment
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	P16

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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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# BMJ Open

## Effect of herbal extract granules combined with octylonium bromide on irritable bowel syndrome with diarrhea: a pilot study protocol for a randomized controlled trial

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Keywords:	Samryungbaekchulsan, octylonium bromide, irritable bowel syndrome, randomized controlled study, clinical trial protocol

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1 **Effect of herbal extract granules combined with octylonium bromide**  
2 **on irritable bowel syndrome with diarrhea: a pilot study protocol for a**  
3 **randomized controlled trial**

4  
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21  
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23  
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**Keywords:** Samryungbaekchulsan, octylonium bromide, irritable bowel syndrome, randomized controlled study, clinical trial protocol

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## 1 ABSTRACT

### 2 Introduction

3 Irritable bowel syndrome (IBS), known as a functional and organic gastrointestinal (GI)  
4 disorder, is a collection of symptoms that occur together and generally include pain or  
5 discomfort in the abdomen and changes in bowel movement patterns. Due to the limitations  
6 of conventional treatments, alternative IBS treatments are used by many patients worldwide.  
7 Samryungbaekchulsan (SRS), a herbal formula, has long been used for alleviating diarrhea-  
8 predominant IBS (D-IBS) in traditional Korean medicine. Octylonium bromide (OB) is an  
9 antimuscarinic compound used to relieve spasmodic pain in the gut, especially in IBS.  
10 Although herbal formulas and western drugs are commonly co-administered for various  
11 diseases in Korea, few clinical studies have been conducted regarding the synergic effects of  
12 these treatments for any disease, including D-IBS.

### 14 Methods and Analysis

15 This trial is a randomized, double-blinded, placebo-controlled, double-dummy, four-arm,  
16 parallel study. After a 2-week preparation period, 80 patients with D-IBS will be randomly  
17 assigned to one of four treatment groups consisting of SRS (water extract granules, 5 g/pack,  
18 3 times a day) with OB (tablet form, 1 capsule 3 times a day) or their placebos, with  
19 treatment lasting for 8 weeks. Post-treatment follow-up will be conducted 4 weeks after the  
20 end of treatment. The primary outcome is the finding obtained using the Subject's Global  
21 Assessment of Relief method. The secondary outcomes are the severity of symptoms related  
22 to D-IBS, determined using a 10-point scale, and the change in symptoms.

### 24 Ethics and dissemination

25 This trial has full ethical approval of the ethics committee of Catholic Kwandong University  
26 International St. Mary's Hospital (IS15MISV0033) and the Korean Ministry of Food and  
27 Drug Safety (30769). The results of the study will be disseminated through a peer-reviewed  
28 journal and/or conference presentations.

1

2 **Trial protocol version: IS15MISV0033 Version 4.0 (July 25, 2016)**

3

4 **Trial registration number: KCT0001621 (Approval date: Aug 10, 2015)**

5

6 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

7 ■ In Korea, herbal and western medicine have been co-administered without sufficient  
8 evidence for various diseases; however, this study will provide basic evidence for such co-  
9 administration and will contribute to the development of integrative medicine.

10 ■ This randomized controlled trial is the first Korean clinical trial approved by the Korean  
11 Ministry of Food and Drug Safety (KMFDS) to investigate the efficacy and safety of  
12 Samryungbaekchulsan (SRS; herbal formula) and octylonium bromide (OB; western drug) in  
13 diarrhea-predominant irritable bowel syndrome (D-IBS).

14 ■ The primary outcome is the improvement in the patient's symptoms according to the  
15 Subject's Global Assessment of Relief and the secondary outcome is the severity of D-IBS  
16 symptoms.

17 ■ This study is conducted with a small sample size (four arms, 20 participants per group)  
18 because it is a pilot study and further clinical trials with powerful sample sizes will be  
19 required to more adequately determine the effectiveness of SRS and/or OB for D-IBS.

20

## 1 INTRODUCTION

2 Irritable bowel syndrome (IBS), a chronic gastrointestinal (GI) disease and functional  
3 bowel disorder, is characterized by abnormal bowel habits and abdominal pain without  
4 structural, morphological, and histological abnormalities. It affects approximately 20% of the  
5 population worldwide, according to population-based studies<sup>1-6</sup>. In addition, recent evidence  
6 suggests that IBS is not only a functional disease, but also an organic disease with a complex  
7 of symptoms, including infection, immune activation, serotonin dysregulation, bacterial  
8 overgrowth, central dysregulation, brain-gut interaction, and genetics<sup>4-6</sup>. Based on their  
9 predominant bowel habits, patients with IBS can be divided into diarrhea-predominant IBS  
10 (D-IBS), constipation-predominant IBS, or mixed IBS<sup>6,7</sup>. Recently, smooth-muscle relaxants,  
11 bulking agents, and anti-diarrheal agents have been used in the treatment of IBS<sup>8</sup>. However,  
12 these methods are often not effective and many IBS patients also use complementary  
13 treatments, such as herbal medicine, acupuncture, psychological treatment, and lifestyle  
14 correction<sup>3,9,10</sup>.

15 Samryungbaekchulsan (SRS; Shenlingbaizhu-san in Traditional Chinese Medicine;  
16 Jinryobyakujutsu-san in Kampo Medicine), which was introduced in the famous classical  
17 compendium of herbal formulas “Formulary of Peaceful Benevolent Dispensary,” consists of  
18 10 herbs (*Atractylodes rhizoma Alba*, *Poria sclerotium*, *Dioscoreae rhizoma*, *Glycyrrhizae*  
19 *radix et rhizoma*, *Coicis semen*, *Nelumbinis semen*, *Platycodonis radix*, *Dolichoris semen*,  
20 *Amomi fructus*, and *Ginseng radix*). In traditional Korean and Chinese medicine, this herbal  
21 formula has been used to treat GI disease, and various studies have been published regarding  
22 the treatment of IBS with SRS<sup>11-13</sup>. SRS has been shown to have anti-acetylcholine and anti-  
23 barium chloride effects and to suppress gastric secretion and small intestine motility<sup>14</sup>.  
24 However, no clinical trials have evaluated the efficacy of SRS for IBS when co-administered  
25 with a conventional drug.

1 Octylonium bromide (OB) is widely used for the prevention and reduction of symptoms in  
2 patients with IBS<sup>15</sup>. OB has been shown to inhibit L- and T-type calcium channels,  
3 muscarinic receptors, and tachykininergic responses in human cultured smooth muscle cells  
4 and rat colon strips<sup>16</sup>. According to a recent randomized controlled trial (RCT), OB (40 and  
5 80 mg) is more effective for treating IBS than placebo, not only for the reduction of bloating  
6 and abdominal pain, but also for protection from relapse owing to its long-lasting effect<sup>17 18</sup>.

7 According to the guidelines of the Korean Society of Gastroenterology, antispasmodic  
8 agents are recommended for the treatment of D-IBS (Grade 1B),<sup>19</sup> and SRS is the preferred  
9 drug for diarrhea treatment in Korean medicine<sup>20</sup>. Recently, several studies have been  
10 conducted to evaluate the therapeutic effect of the co-administration of herbal formulas and  
11 conventional drugs for IBS in China<sup>21 22</sup>. However, there has been no such clinical study in  
12 Korea, even though both herbal medicine and conventional drugs are widely used for IBS  
13 treatment in the clinical field. Therefore, there is a need to evaluate the efficacy and safety of  
14 SRS, OB, and the co-administration of both drugs.

15 In this study, we expect that the combined administration of OB and SRS will result in  
16 synergistic effects that improve D-IBS symptoms, including abdominal pain, discomfort (the  
17 main effect of OB), and diarrhea-like stool patterns (the main effect of SRS).

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## 1 METHODS AND ANALYSIS

### 2 *Objectives*

3 The purpose of this study is to evaluate the efficacy and safety of the co-administration of  
4 SRS and OB to patients with D-IBS.

### 6 *Necessity of the trial*

7 Recently, herbal medicines and western drugs have been co-administered for various  
8 medical therapies. This is particularly true in Korea, where approximately 76% of patients  
9 have used the combination of herbal medicines and western drugs<sup>23</sup>. However, only a few  
10 studies have evaluated the interaction between western and herbal medicines. Despite the  
11 need for combined treatment in patients with various diseases, there are no standard clinical  
12 guidelines or scientific evidence regarding co-administration because of a lack of research  
13 and data.

14 D-IBS is a disease that is difficult to cure and many patients require treatment with both  
15 western and herbal drugs to experience an improvement in their symptoms. Therefore, it is  
16 very important to conduct a clinical study regarding the efficacy and safety of the combined  
17 administration of SRS and OB in patients with D-IBS.

### 19 *Basis of drug selection*

20 According to guidelines for IBS treatment, the OB recommendation level is high (i.e., the  
21 level of evidence is moderate and many experts recommend using it) and it is the most  
22 reasonable treatment option<sup>21</sup>. SRS is the herbal formula used most often by clinical Korean  
23 and Chinese medical doctors for abdominal pain, abdominal discomfort, and chronic diarrhea,  
24 which are typical symptoms of D-IBS<sup>11-13 19</sup>. Based on these studies and clinical applications,  
25 OB and SRS were selected for this trial.

1

## 2 *Hypothesis*

3 We hypothesize the following: (1) that co-administration of SRS and OB will have a more  
4 positive effect on D-IBS symptoms than either SRS or OB alone; (2) that after 8 weeks of  
5 treatment with SRS, OB, or both drugs, the Subject's Global Assessment of Relief and  
6 severity of D-IBS symptoms will be more improved than after treatment with placebo; and (3)  
7 that co-administration of SRS and OB will be safe for patients with D-IBS.

## 9 *Design*

10 This study is a placebo-controlled, double-blind trial. Eighty patients will be enrolled and  
11 randomly assigned to four separate arms of the trial. The trial will be conducted at Catholic  
12 Kwandong University International St. Mary's Hospital, Incheon, South Korea.

13 The study subjects will be required to participate in a 2-week preparation period (weeks -2  
14 to 0) and an 8-week drug administration period (weeks 0 to 8). The patients will visit four  
15 times, on weeks 0, 4, 8, and 12. The primary outcome measurement will be evaluated at  
16 weeks 2, 4, 6, 8, and 12, and the secondary outcome measurement will be evaluated at weeks  
17 0, 2, 4, 6, 8, and 12. Participants will be assessed for efficacy and safety of the treatment  
18 through visits (0, 4, 8, 12 weeks) and telephone questionnaires (2, 6 weeks). In addition, lab  
19 tests will be conducted at 0, 4, and 8 weeks. According to the intervention protocols, the  
20 clinical research coordinator (CRC) will encourage patients and participants to complete  
21 follow-up at every visit.

22 During the drug administration period, SRS or its placebo will be given as 1 pack of water  
23 extract granules 3 times a day, 30 min before each meal. OB or its placebo will be given as 1  
24 tablet 3 times a day, 30 min before each meal.

25 Participants will be divided into 4 groups: (1) SRS and OB group; (2) SRS and placebo-

1 OB group; (3) placebo-SRS and OB group; and (4) placebo-SRS and placebo-OB group. The  
2 entire flow chart of the study is shown in Figure 1.

3 The protocol of this trial has been approved by the institutional review board (IRB) and  
4 ethics committee of Catholic Kwandong University International St. Mary's Hospital. The  
5 IRB permission number is IS15MISV0033 and CRIS (Clinical Research Information Service,  
6 www.cris.nih.go.kr) protocol identification number is KCT0001621. In addition, this study  
7 received the first approval given by the Korean Ministry of Food and Drug Safety (KMFDS)  
8 for a study of the co-administration of a conventional drug and a Korean traditional herbal  
9 medicine (approval number: 30769).

10 Potential participants will be provided with sufficient information about the study and only  
11 those who agree to the study protocol and sign the consent form will be enrolled. The study  
12 will be implemented according to Good Clinical Practice and the revised version of the  
13 Declaration of Helsinki.

### 14 ***Sample size calculation***

15 This trial is a pilot study for a new therapeutic regimen of SRS and OB combination  
16 treatment. In a similar study conducted previously by using co-administration of a probiotics  
17 mixture and an herbal medicine (placebo-controlled, double-blind, and randomly 4-arm),  
18 each arm consisted of at least 15 patients and the total sample size was more than 60  
19 participants<sup>24</sup>. In other similar pilot studies, clinical trials have been conducted with a total of  
20 60–64 participants, consisting of 12–30 patients per group<sup>25-27</sup>. Based on these previous studies,  
21 the minimal clinical significance of the trial can be obtained when only 16 participants  
22 complete the trial. Because the drop-out rate is expected to be 20%, each trial group will be  
23 made up of at least 20 participants. Therefore, the total sample size must be more than 80  
24 participants.  
25



1

***Inclusion criteria***

The following patients would be included: (1) patients aged 18–75 years; (2) patients satisfying the Rome III criteria of IBS (recurrent abdominal pain or discomfort that began at least 6 months before the clinical trial, with a rating of more than 3 on a 10-point scale, frequency of at least 3 days/month in the last 3 months, and associated with two or more of the following: improvement associated with defecation, onset associated with a change in frequency of stools, and onset associated with a change in form of stool)<sup>2 7</sup>; (3) patients satisfying the Rome III criteria of IBS, whereby D-IBS type is defined as loose/mushy or watery stools—Bristol Stool Form (BSF) Scale 6-7  $\geq$  2 times/week<sup>2 27</sup>; (4) patients with a negative urine pregnancy test (in women of a childbearing age, within 7 days before the clinical trial) and who consent to using contraception during the administration period; (5) patients with the ability to read the symptom questionnaire and understand it; and (6) patients who agree with the clinical plan and voluntarily sign the IRB-approved documents.

15

***Exclusion criteria***

The exclusion criteria are as follows: (1) chronic liver disease (cirrhosis, chronic hepatitis B or C); (2) chronic renal failure or renal impairment (serum creatinine  $\geq$  2 times the upper limit of normal); (3) liver dysfunction (AST/ALT  $\geq$  3 times the upper limit of normal); (4) diabetes (HbA1c  $>$  8% or not controlled by diet or medication), hypertension ( $\geq$  160/100 mmHg), thyroid dysfunction (exceptions in the following cases: if the disease is controlled by drug administration with a stable dose for 12 weeks before the screening, and the drug dose remains constant during the trial period), clinically significant hematologic, cardiac, pulmonary, neurological disorders, or other severe systemic disorders; (5) abnormal findings on colonoscopy or colonography within the last 5 years; (6) history of surgery that affects

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1 gastrointestinal motility (i.e., gastrectomy, colonic resection, hysterectomy, except for  
2 appendectomy); (7) GI disease characterized by the following symptoms within 6 months  
3 before the clinical trial: inflammation of or ulcer in the esophagus, stomach, or duodenum;  
4 gastroesophageal reflux disease (at the discretion of the examiner, subjects may enroll if the  
5 disease is chronic and not acute); gastrointestinal bleeding; gastrointestinal stenosis or closure;  
6 infectious diarrhea; inflammatory bowel disease (i.e., Crohn's disease, diverticulitis,  
7 ulcerative colitis, infectious enteritis, ischemic colitis); pancreatic insufficiency; biliary  
8 abscess; (8) mental illness or an addiction to drugs or alcohol; (9) severe systemic organ  
9 diseases such as cancer, autoimmune disease, stroke (although patients in remission for more  
10 than 5 years from a cancer unrelated to the GI tract can participate in the trial); (10)  
11 pregnancy, breastfeeding, and unwillingness to use contraception during the trial; (11) a  
12 history of taking the following drugs within 2 weeks before the trial: antibiotics, analgesics,  
13 antidepressants, anti-anxiety agents, anti-inflammatory agents, anti-ulcer agents, anti-gastric  
14 secretion inhibitors, laxatives, antispasmodics, antacid agents, gastrointestinal stimulants,  
15 prostaglandin agents, and corticosteroids; (12) use of medications that do not match the intent  
16 of this trial or have a clinical interaction with SRS or OB; (13) lactose intolerance (not  
17 controlled by food); (14) glaucoma; (15) participation in other clinical studies within 30 days  
18 prior to clinical screening and have received other clinical trial medications (including  
19 placebo); (16) hypersensitivity to clinical trial medicines; and (17) other reasons considered  
20 inappropriate for participation in clinical trials.

21

### 22 ***Recruitment, randomization, blinding, and unblinding***

23 Advertisements for the study will be posted at the Catholic Kwandong University  
24 International St. Mary's Hospital using banner ads and posters. We also plan to post the  
25 advertisements on the hospital homepage, in the monthly hospital magazine, at the internet

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4 1 café, and on the subway at least five times. All these advertisements will be done with the  
5  
6 2 approval of the IRB.  
7

8 3 After recruitment, patients will be randomized to one of the four trial arms. Randomization  
9  
10 4 will be performed using a list of block randomizations made by statisticians, independent of  
11  
12 5 this clinical trial. A researcher who is not involved in process of drug prescription and  
13  
14 6 evaluation will execute the randomization process.  
15

16  
17 7 During the treatment period, the patients and all researchers (investigators and clinical  
18  
19 8 research coordinators) will be blinded, except the researchers who conducted the  
20  
21 9 randomization procedure. In addition, the researchers will not know the kind of medication  
22  
23 10 that is being administered to the patient or any other information that could lead to bias.  
24

25  
26 11 Allocation concealment will be performed during the process of medication administration.  
27  
28 12 The management pharmacist, who will not be involved in analyzing the results of the trial,  
29  
30 13 will use the randomization table to label the medication with the assignment number and  
31  
32 14 provide the medication. The patients will take the drugs contained in the opaque envelope,  
33  
34 15 which will be labeled with the assignment number.  
35

36  
37 16 Unblinding will be performed only in the following situations: (1) if the trial is terminated  
38  
39 17 and there is a need for statistical analysis; (2) if a serious medical emergency occurs and  
40  
41 18 information about the medication is needed; and (3) if the chief investigator determines that  
42  
43 19 unblinding is necessary.  
44

45  
46 20 The entire process of the study will be directed by the authorized clinical research  
47  
48 21 organization (CRO), Dream CIS Corporation, Seoul, Korea.  
49

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51  
52  
53 ***Intervention***  
54

55 24 The herbal formula SRS is commonly used by Korean traditional medical doctors for  
56  
57 25 treatment of diarrhea and related diseases<sup>11-13 16</sup>. SRS used in this study  
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1 (Samryungbaekchulsan granule®, Hankook shin yak, Co., Ltd., Nonsan, Korea) is extracted  
2 with water and mixed with starch and lactose in accordance with Korean Good  
3 Manufacturing Practice (K-GMP). Production of SRS is regulated and allowed by the  
4 KMFDS. SRS contains 10 herbs, listed in Table 1. Placebo-SRS is made from cornstarch and  
5 has the same taste, shape, color, and similar scent as SRS. SRS and placebo-SRS will be  
6 sealed in identical aluminum bags with the same labeling. These herbal drug packages will be  
7 distributed by an independent pharmacist in an isolated room. According to the recommended  
8 dosing methods of KMFDS, after SRS or placebo-SRS is dissolved in boiled water, the  
9 subjects will take them 30 min before each meal (5 g/pack, 3 times a day).

10 OB (Menocetyl Tab®, Dong Hwa Pharm Co., LTD., Seoul, Korea) is a tablet containing  
11 octylonium bromide 40 mg. Placebo-OB is a tablet made of Ludipress with the same taste,  
12 shape, and color as OB. Patients will be instructed to swallow one tablet of OB or placebo-  
13 OB 30 min before each meal over the administration period. The drugs used in the trial (SRS,  
14 OB, placebo-SRS, placebo-OB) have been approved by the KMFDS. Patients will be asked at  
15 the end of the study whether the drugs that they have been taking are either real or placebo, to  
16 measure the success of blinding. Compliance will be confirmed by counting returned SRS  
17 packets or OB tablets. Every patient will be instructed to write down any adverse events  
18 during the administration period and these records will be evaluated at the follow-up. At the  
19 patient visits (at 0, 4, and 8 weeks), we will perform a check of vital signs, physical  
20 examination, electrocardiogram, and laboratory tests to evaluate safety for the patients. All  
21 side effects will be reported to the investigator.

22  
23

**Table. 1 Ingredients in the herbal formula Samryungbaekchulsan (SRS)**

Scientific name	Part used	Grams/day
Atractylodis Rhizoma Alba	Root	3.0
Poria Sclerotium	Dried core	4.0
Rhizoma Dioscoreae	Root	3.0
Glycyrrhizae Radix et Rhizoma	Root	1.5
Semen Coicis	Seed	8.0
Semen Nelumbinis	Fruit	4.0
Platycodonis Radix	Root	2.5
Dolichoris Semen	Seed	4.0
Amomi Fructus	Fruit	2.0
Ginseng Radix	Root	3.0

### ***Rescue therapy and concomitant medications***

Participants are prohibited from taking any medication that could affect D-IBS during the entire course of the trial. However, if serious side effects occur or symptoms worsen, investigators will provide quick and appropriate treatment (including drug administration), based on their medical judgement. In this case, the direct investigators will record the treatment or drug administration and report to the IRB within 24 h to determine whether the trial should be continued or discontinued.

### ***Outcome Measurements***

#### ***Primary outcome***

The primary outcome will be measured via a questionnaire that confirms subjective

1 symptom improvement. Participants will respond a total of five times during and after the  
2 administration period (at 2 and 6 weeks via telephone, and at 4, 8, and 12 weeks during direct  
3 visits) to the following question: Subject's Global Assessment of Relief; "How much do you  
4 think the symptoms of D-IBS have improved compared to before the clinical trial?"  
5 According to the answers given by the patients to this survey, the improvement is given a  
6 score of 0, 1, 2, 3, or 4.

### 7 8 *Secondary outcomes*

9 At 2, 4, 6, 8, and 12 weeks from the start of the treatment period, patients will be assessed  
10 for severity of D-IBS symptoms (abdominal pain, abdominal discomfort, satisfaction of  
11 defecation, frequency of abdominal pain, quality of life) using a Likert scale ranging from 0  
12 to 10<sup>28</sup>. Patients will also be instructed to record the number of defecations per day, BSF, and  
13 the degree of force used in bowel movements at 0, 2, 4, 6, 8, and 12 weeks<sup>29</sup>.

### 14 15 *Safety assessments*

16 The investigator will record all adverse events that occur during the trial along with any  
17 concomitant medications in the case reports. When an adverse event occurs, the investigator  
18 will record the symptoms and signs of the adverse reaction, the duration (start and end date),  
19 severity, course, outcome, significance, causality by the trial drug, and any action taken in  
20 relation to the adverse event. In the case of concomitant medicines, composition, dosage,  
21 duration of administration, and reason for medication will be recorded in detail. Symptoms  
22 that existed before the start of the clinical trial will not be recorded as adverse events.

### 23 24 *Laboratory tests*

25 The purpose of laboratory tests in this study is to evaluate the safety and pharmacokinetic

1 profiles of SRS and OB. Because of the small number of patients assigned to this study and  
2 the different baseline values for each individual patient, we will not perform a detailed  
3 statistical analysis. However, if significant abnormal results are found in the laboratory tests,  
4 the clinical laboratory results will be described and the connection to the drug will be  
5 considered.

6 Blood tests will be conducted at 0, 2, 4, and 8 weeks and urine tests will be performed at  
7 0 and 4 weeks during the clinical trial. In the case of a participant who drops out or the early  
8 termination of the clinical trial, blood and urine tests will be performed on the last day of the  
9 trial.

10 Using the test results (comprehensive verification of vital signs, laboratory tests,  
11 electrocardiograms, and physical examinations) for each individual patient, the investigator  
12 will determine adverse reactions caused by the drugs and statistical tests will be conducted as  
13 needed on clinically significant parameters.

#### 14 *Test of human derivatives*

15 IBS is known to be closely related to stress<sup>10</sup>. Therefore, we plan to quantify factors  
16 associated with stress or that have been reported to worsen IBS symptoms as follows: 1)  
17 cortisol; 2) corticotropin-releasing hormone (CRH); 3) serotonin; 4) group I cytokines (10  
18 species); 5) group II cytokines (14 species); and 6) growth factors (3 species)<sup>30 31</sup>. Serum will  
19 be separated from blood specimens collected at 0, 4, 8 weeks, stored frozen, and transferred  
20 to the Korea Institute of Oriental Medicine (KIOM) for examination.

#### 21 *Early termination or dropout*

22 The criteria for early termination or dropout are as follows: 1) administration of other  
23 drugs that are expected to affect the safety and efficacy of the clinical trial drugs; 2) request



1 of participants to discontinue the clinical trial, or withdrawal of the trial agreement; 3)  
2 occurrence of significant adverse drug reactions or events that preclude continuing the trial,  
3 according to the judgment of the clinical investigator; 4) new discovery of violations of  
4 significant clinical trial protocol during clinical trial; 5) less than 70% trial drug compliance;  
5 and 6) any other reason that the clinical trial should be discontinued at the discretion of the  
6 clinical trial manager or investigator.

#### 8 *Data collection, access, and management*

9 The data of this trial will be managed according to the standard work instructions of  
10 Catholic Kwandong University International, St. Mary's Hospital. Other contents not  
11 specified in the trial protocol shall follow the standards of The International Conference on  
12 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human  
13 Use (ICH) Guideline for Good Clinical Practice (GCP) and Korean Good Clinical Practice  
14 (KGCP) guideline.

15 The source document is recorded immediately when the data are collected. After the source  
16 document input is completed, it will be recorded in the case record form (CRF). All the  
17 documents will be kept safe, so that the data can be verified by the relevant government  
18 agencies and the IRB. Only research colleagues and others who have been approved by the  
19 principle investigator will have access to all data obtained from this trial.

#### 21 *Statistical analysis*

22 The statistical analysis will be conducted by blinded professional statisticians. To evaluate  
23 the efficacy of the study, both an intent-to-treat (ITT) analysis (primary analytical method)  
24 and a per-protocol (PP) analysis (secondary analytical method) will be performed. The ITT  
25 analysis will be conducted for all patients who were followed up at least once after



1 randomization and will be able to be evaluated for effectiveness. The PP analysis will be  
2 performed for patients who complete the 8-week treatment course and meet the inclusion and  
3 exclusion criteria.

4 To analyze the continuous variables in the demographic information and pre-treatment  
5 characteristics between groups, a one-way analysis of variance (ANOVA) and Kruskal-Wallis  
6 test will be conducted. An ANOVA and Kruskal-Wallis test will also be used to test for  
7 symptom improvement compared to baseline (0 week) and the variables for analysis that  
8 include the following: (1) subjective symptom improvement (primary outcomes); and (2)  
9 severity of symptoms related to D-IBS (abdominal pain, abdominal discomfort, satisfaction  
10 of defecation, frequency of abdominal pain, quality of life). All values will be shown as mean  
11  $\pm$  standard error of the mean (SEM). Comparisons of outcome assessments between the four  
12 groups will be performed using the paired t-test or Wilcoxon signed-rank test.

13 If the Subject's Global Assessment of Relief on the Likert scale is "0" or "1" for more than  
14 2 weeks between weeks 8 and 12, then the symptoms will be considered to have improved  
15 sufficiently. Based on this, we will calculate the symptom relief rate by dividing the number  
16 of participants who exhibited sufficient symptom relief by the total number of participants in  
17 the trial and present descriptive statistics. The CATMOD procedure will be used to evaluate  
18 the relief rate improvement of symptoms compared with baseline. Comparisons between the  
19 four groups will be conducted using the chi-square test or Fisher's exact test. These statistical  
20 analyses will also be performed at 2, 4, 6, 8, and 10 weeks from baseline. The Cochran-  
21 Mantel-Haenszel (CMH) test will be used to confirm the difference between the intervention  
22 groups at each time-point.

23 A statistical analysis will also be conducted to evaluate safety. The incidence of adverse  
24 events and abnormality of experimental results will be analyzed statistically according to the  
25 groups and non-parametric methods will be applied as necessary using a paired t-test for

1 continuous data, McNemar's test for categorical data, Fisher's exact test for adverse events,  
2 and a generalized estimating equation for clinically significant changes between groups.

3 All statistical analysis will be conducted using SAS software, version 9.1.3 (SAS institute,  
4 Cary, NC). A P-value < 0.05 will be considered statistically significant.

### 5 6 *Quality control and data monitoring*

7 To ensure the results and quality of the clinical trial, assessments and monitoring will be  
8 performed by the CRO, DreamCIS Corporation (Seoul, Korea), which is independent from  
9 the sponsor and competing interests. During the trial, the CRO will regularly monitor whether  
10 the study is proceeding in accordance with the protocol through the use of all related  
11 documentation, including trial master files, case report forms, informed consent forms, and  
12 adverse event reports.

## 13 14 **DISCUSSION**

15 Herbal medicine is a recognized effective treatment method based on clinical experience  
16 accumulated over thousands of years and more recently gained attention as an alternative  
17 therapy for treating various diseases that are difficult to treat or have unknown causes, such  
18 as IBS<sup>8 22</sup>. SRS is frequently used for abdominal pain and diarrhea in Korean and Chinese  
19 traditional medicine. According to experimental research, SRS has an anti-cholinergic effect  
20 that improves intestinal digestion and absorption and inhibits intestinal movement, resulting  
21 in the prevention of diarrhea and abdominal pain<sup>14</sup>. In addition, clinical studies have shown  
22 that the use of SRS in patients with D-IBS is effective for improving diarrhea<sup>32 33</sup>. Some  
23 studies have reported that co-administration with SRS and trimebutine maleate or SRS and  
24 paroxetine is more effective than trimebutine maleate alone for the improvement in IBS  
25 symptoms<sup>11 12 21</sup>. Other studies have reported that SRS exerted more beneficial effects on IBS

1 patients compared with Smecta or probiotics<sup>13 33</sup>.

2 However, although there is a growing interest in the use of herbal medicines such as SRS  
3 in IBS and related studies are continuously being published, there have been only a few well-  
4 designed RCTs. To overcome the limitations of the previous studies, this trial was designed as  
5 a double-blind, double-dummy, four-arm, parallel-group RCT. The efficacy of SRS will be  
6 evaluated via the Subject's Global Assessment of Relief and the improvement in symptoms  
7 associated with bowel movements and abdominal pain. The results of these assessments are  
8 expected to provide distinct clinical evidence for the use of SRS in D-IBS treatment.

9 OB is a representative conventional medicine used for D-IBS treatment<sup>15</sup>. It is a  
10 spasmolytic agent that exerts its activity primarily in the distal GI tract through the inhibition  
11 of Ca<sup>++</sup> flux and direct activation of contractile proteins in the smooth muscle. OB has also  
12 been shown to reduce hyper-motility and modulate visceral sensation, the effect of which is  
13 to improve D-IBS symptoms<sup>34 35</sup>. RCTs using OB for the treatment of D-IBS have been  
14 conducted. In these studies, treatment with OB resulted in a greater improvement in  
15 symptoms related to D-IBS (defecation frequency, regular intestinal habits, reductions in  
16 frequency of diarrhea, abdominal pain and discomfort, severity of abdominal bloating) and  
17 better protection from symptom relapse compared to placebo<sup>17 18 36</sup>.

18 IBS is a disease with a high rate of progression and frequent recurrence. For this reason,  
19 patients with IBS often require a variety of treatment methods<sup>3</sup>. Among these methods, the  
20 combination of herbal and conventional drugs is widely used and is more effective for  
21 improving IBS symptoms than conventional drugs alone<sup>3 37</sup>. However, there are several  
22 limitations to the co-administration of herbal and conventional drugs in IBS. Specifically,  
23 there is a high risk of bias in related studies and there are insufficient clinical guidelines  
24 regarding the interaction of herbal and conventional drugs in D-IBS, including SRS and OB.  
25 Therefore, it is necessary to perform well-designed RCTs to evaluate the co-administration of

1 herbal and conventional drugs.

2 This RCT has several characteristic features. First, this trial will be the first to investigate  
3 the efficacy of SRS and OB combination therapy for D-IBS. The results of previous studies  
4 suggested that the combination of OB and SRS will improve two major D-IBS symptoms at  
5 the same time: abdominal pain and discomfort (major effect of OB) and diarrhea (main effect  
6 of SRS). This study will assess this hypothesis and provide a basis for the use of SRS and OB  
7 combination therapy for D-IBS. Second, the participants in this trial will be grouped into four  
8 arms, making it possible to compare the efficacy of combined treatment with the efficacy of  
9 each individual treatment. Third, this trial will evaluate the safety of the subjects using  
10 several assessments, including a periodic assessment of subjective symptoms, physical  
11 measurements, and laboratory testing. The results of the safety analysis may provide evidence  
12 for the safety of treatment with the combination of herbal and conventional drugs in D-IBS.  
13 Fourth, this trial was the first clinical study related to combination treatment with western and  
14 traditional herbal medicine in Korea to receive approval from the KMFDS. Through the  
15 systematic management of the trial under the auspices of the KMFDS, a high quality trial will  
16 be performed and the results of this study will provide information for use in further clinical  
17 applications.

18 Although our study is a pilot study with a small sample size, it has a creative and  
19 systematic research design and the results will be useful basic clinical evidence in the field of  
20 integrated herbal and conventional drugs for the management of D-IBS.

21

## 22 **Trial status**

23 The research plan and design began in April 2015.

24 The study received the IRB's final approval after two deliberations. The first submission  
25 date was July 01, 2015; the result was a request for revision and supplementation, which was

1 received on July 13, 2015. We filed an application for re-review on August 06, 2015,  
2 supplemented with the relevant information, and received the IRB's final approval on August  
3 10, 2015. We also requested that the KMFDS review the trial plan on September 14, 2015  
4 and received approval for the clinical research on December 21, 2015.

5 The first participant was randomized on March 29, 2016. Recruitment for the study is  
6 ongoing. The primary completion date for this trial is anticipated to be December 31, 2017,  
7 and the study completion date is expected to be February 28, 2018.

## 8 9 **Ethics**

### 10 *Research ethics approval*

11 This trial was approved by the IRB and ethics committee of Catholic Kwandong  
12 University International St. Mary's Hospital (approval number IS15MISV0033) and the  
13 KMFDS (approval number 30769).

### 14 15 *Protocol amendments*

16 An investigator who wishes to change the protocol of the clinical trial plan should first  
17 discuss it with the trial director. Thereafter, the examiner should obtain prior approval from  
18 the IRB for changes to the protocol (except to prevent immediate injury to the patient, in  
19 which case it will be reported to the IRB later). However, when a dangerous situation occurs  
20 and immediate treatment is needed, the investigator may report the protocol change to the  
21 IRB at a later time.

### 22 23 *Consent*

24 Patients recruited through the announcement will receive a full explanation of the details of  
25 the trial in an easy-to-understand manner. The patients and investigators will have a mutual

1 question and answer time before the patient is asked to sign the clinical trial consent. Through  
2 these processes, if the patient agrees to participate in the trial, a signed consent form will be  
3 obtained.

#### 4 5 *Confidentiality*

6 All patient information will be anonymized with initials or symbols and all related  
7 investigators will keep the trial results confidential. The trial director will keep the signed  
8 consent forms and prepare a list that will be used to confirm the patient identities.

#### 9 10 *Post-trial care*

11 If the patients experience unexpected accidents or injuries, appropriate compensation will  
12 be made by the Federal Insurance Company Korea (12th Floor Ferrum Tower 66 Suha-Dong  
13 Jung-gu Seoul, 100210, South Korea), according to the patient compensation rules of the trial.  
14 Additionally, in the case of an emergency, the patients will receive appropriate medical care  
15 at the Catholic Kwandong University International, St. Mary's Hospital.

#### 16 17 **Dissemination**

18 The results of the trial will be disseminated through a peer-reviewed journal and/or  
19 conference presentations.

#### 20 21 **Contributors**

22 Joong Il Kim, Pumsoo Kim, Jin-Hyun Lee, and Jung-Han Lee contributed to the protocol  
23 design and writing of the manuscript. Hyekyung Ha is responsible for monitoring the process  
24 of the trial. Na-rae Yang, Yoo-Jin Kim, Myong Ki Baeg, Ja Sung Choi, Hye-Jung Kim, and  
25 Ja-Young Kim provide advice on the process of the trial. Tae-Yong Park is responsible for

1 writing the manuscript and also managing and supervising the clinical research. All authors  
2 approved the final manuscript.

3

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6 Formulas (K15250)” grant from the Korea Institute of Oriental Medicine (KIOM).  
7 (Telephone: +82-42-868-9513)

8

#### 9 **Competing interests**

10 The authors have no competing interests to declare.

11

#### 12 **Ethics approval**

13 This trial has been approved by the IRB and ethics committee of Catholic Kwandong  
14 University International St. Mary’s Hospital (approval number IS15MISV0033).

15

#### 16 **Provenance and peer review**

17 Not commissioned; externally peer reviewed.

18

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## 1 REFERENCES

1. Maxion-Bergemann S, Thielecke F, Abel F, et al. Costs of irritable bowel syndrome in the UK and US. *Pharmacoeconomics* 2006;24(1):21-37.
2. Drossman DA. Introduction. The Rome Foundation and Rome III. *Neurogastroenterol Motil* 2007;19(10):783-6. doi: 10.1111/j.1365-2982.2007.01001.x
3. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. *J Gastroenterol Hepatol* 2010;25(4):691-9. doi: 10.1111/j.1440-1746.2009.06120.x
4. Soares RL. Irritable bowel syndrome: a clinical review. *World J Gastroenterol* 2014;20(34):12144-60. doi: 10.3748/wjg.v20.i34.12144
5. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol* 2014;20(22):6759-73. doi: 10.3748/wjg.v20.i22.6759
6. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015;313(9):949-58. doi: 10.1001/jama.2015.0954
7. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130(5):1480-91. doi: 10.1053/j.gastro.2005.11.061
8. Jaiwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med* 2000;133(2):136-47.
9. Liu JP, Yang M, Liu YX, et al. Herbal medicines for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2006(1):CD004116. doi: 10.1002/14651858.CD004116.pub2
10. Palsson OS, Drossman DA. Psychiatric and psychological dysfunction in irritable bowel syndrome and the role of psychological treatments. *Gastroenterol Clin North Am*

- 1  
2  
3  
4 1 2005;34(2):281-303. doi: 10.1016/j.gtc.2005.02.004
- 5  
6 2 11. Duan W. Observation of sixty-five cases on Irritable Bowel Syndrome treated by  
7  
8 3 Trimebutine and Shenlingbaizhu-san granule [Chinese]. *Journal of Practical*  
9  
10 4 *Traditional Chinese Medicine* 2010;26(5):320.
- 11  
12 5 12. Chen Y. Clinical observation of irritable bowel syndrome treated by shenlingbaizhu-san  
13  
14 6 granule and trimebutine [Chinese]. *Journal of Practical Traditional Chinese Medicine*  
15  
16 7 2011;27(5):318-9.
- 17  
18 8 13. Li Z, Jiang J. Clinical observation of 80 cases on diarrhea - predominant irritable bowel  
19  
20 9 syndrome treated by Shenlingbaizhu-san granule [Chinese]. *Guiding Journal of*  
21  
22 10 *Traditional Chinese Medicine and Pharmacy* 2013;20(5):41-2.
- 23  
24 11 14. Song DS, Ryu BH, Park DW, et al. Experimental studies on the efficacy of  
25  
26 12 Samryungbaekchulsan. *J Korean Med* 1993;14(1):179-95.
- 27  
28 13 15. Boeckstaens G, Clave P, Corazziari ES, et al. Irritable bowel syndrome: focus on  
29  
30 14 otilonium bromide. *Expert Rev Gastroenterol Hepatol* 2014;8(2):131-7. doi:  
31  
32 15 10.1586/17474124.2014.869477
- 33  
34 16 16. Martinez-Cutillas M, Gil V, Gallego D, et al. Mechanisms of action of otilonium bromide  
35  
36 17 (OB) in human cultured smooth muscle cells and rat colonic strips.  
37  
38 18 *Neurogastroenterol Motil* 2013;25(12):e803-12. doi: 10.1111/nmo.12206
- 39  
40 19 17. Chmielewska-Wilkon D, Reggiardo G, Egan CG. Otilonium bromide in irritable bowel  
41  
42 20 syndrome: a dose-ranging randomized double-blind placebo-controlled trial. *World J*  
43  
44 21 *Gastroenterol* 2014;20(34):12283-91. doi: 10.3748/wjg.v20.i34.12283
- 45  
46 22 18. Clave P, Acalovschi M, Triantafillidis JK, et al. Randomised clinical trial: otilonium  
47  
48 23 bromide improves frequency of abdominal pain, severity of distention and time to  
49  
50 24 relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*  
51  
52 25 2011;34(4):432-42. doi: 10.1111/j.1365-2036.2011.04730.x
- 53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 19. Kwon JG, Park KS, Park JH, et al. [Guidelines for the treatment of irritable bowel  
5  
6 syndrome]. *Korean J Gastroenterol* 2011;57(2):82-99.  
7  
8  
9 20. Shin B, Lee B. Frequency Analysis of Clinical Prescriptions in the Korean Medicine  
10  
11 Hospital, Pusan National University based on Herb Weight Ratio(2) - Focusing on  
12  
13 Prescriptions of Herbal Formula Study Textbook[Korean]. *Herbal Formula Science*  
14  
15 2015;23(1):77-89. doi: dx.doi.org/10.14374/HFS.2015.23.1.077  
16  
17 21. Li C, Zuo M, Wang L, et al. Clinical observation of diarrhea - predominant irritable bowel  
18  
19 syndrome treated by Shenlingbaizhu-san and Paroxetine [Chinese]. *Chinese Journal*  
20  
21 *of Traditional Medical Science and Technology* 2010;17(2):154-5.  
22  
23  
24 22. Leung WK, Wu JC, Liang SM, et al. Treatment of diarrhea-predominant irritable bowel  
25  
26 syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled  
27  
28 trial. *Am J Gastroenterol* 2006;101(7):1574-80. doi: 10.1111/j.1572-  
29  
30 0241.2006.00576.x  
31  
32  
33 23. Park JK, Choi SY, Koh KW, et al. Combined utilization with herbal products and  
34  
35 prescribed drugs: A result from health examinee-based national survey. *Korean J*  
36  
37 *Health Policy Adm* 2006;16(1):1-16.  
38  
39  
40 24. Ko SJ, Han G, Kim SK, et al. Effect of korean herbal medicine combined with a probiotic  
41  
42 mixture on diarrhea-dominant irritable bowel syndrome: a double-blind, randomized,  
43  
44 placebo-controlled trial. *Evid Based Complement Alternat Med* 2013;2013:824605.  
45  
46 doi: 10.1155/2013/824605  
47  
48  
49 25. Whitehead AL, Julious SA, Cooper CL, et al. Estimating the sample size for a pilot  
50  
51 randomised trial to minimise the overall trial sample size for the external pilot and  
52  
53 main trial for a continuous outcome variable. *Stat Methods Med Res* 2016;25(3):1057-  
54  
55 73. doi: 10.1177/0962280215588241  
56  
57  
58 26. Cha BK, Jung MS, Choi CH, et al. The effect of a multispecies probiotic mixture on the  
59  
60

- 1 symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a  
2 randomized, double-blind, placebo-controlled trial. *J Clin Gastroenterol*  
3 2012;46(3):220-7. doi: 10.1097/MCG.0b013e31823712b1
- 4 27. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a  
5 probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating.  
6 *Neurogastroenterol Motil* 2005;17(5):687-96. doi: 10.1111/j.1365-2982.2005.00695.x
- 7 28. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a  
8 disease-specific quality-of-life questionnaire. *Am J Gastroenterol* 2000;95(4):999-  
9 1007. doi: 10.1111/j.1572-0241.2000.01941.x
- 10 29. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand*  
11 *J Gastroenterol* 1997;32(9):920-4. doi: 10.3109/00365529709011203
- 12 30. Sugaya N, Izawa S, Saito K, et al. Effect of prolonged stress on the adrenal hormones of  
13 individuals with irritable bowel syndrome. *Biopsychosoc Med* 2015;9(1):4. doi:  
14 10.1186/s13030-015-0031-7
- 15 31. Fadgyas-Stanculete M, Buga AM, Popa-Wagner A, et al. The relationship between  
16 irritable bowel syndrome and psychiatric disorders: from molecular changes to  
17 clinical manifestations. *J Mol Psychiatry* 2014;2(1):4. doi: 10.1186/2049-9256-2-4
- 18 32. Zhong Y, Wu Y. Forty cases of diarrhea - predominant irritable bowel syndrome treated  
19 by Shenlingbaizhu-san granule and Montmorillonite powder [Chinese]. *Jiangxi*  
20 *Journal of Traditional Chinese Medicine* 2013;44(7):45-6.
- 21 33. Xiong B. Thirty cases of irritable bowel syndrome treated by Shenlingbaizhu-san granule  
22 and Probiotics [Chinese]. *Jiangxi Journal of Traditional Chinese Medicine*  
23 2011;42(5):22-3.
- 24 34. Giachetti A. Pharmacological studies on otilonium bromide. *Ital J Gastroenterol*  
25 1991;23(8 Suppl 1):56-9.

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4 1 35. Evangelista S. Otilonium bromide: a selective spasmolytic for the gastrointestinal tract. *J*  
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6 2 *Int Med Res* 1999;27(5):207-22. doi: 10.1177/030006059902700501  
7  
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9 3 36. Battaglia G, Morselli-Labate AM, Camarri E, et al. Otilonium bromide in irritable bowel  
10 4 syndrome: a double-blind, placebo-controlled, 15-week study. *Aliment Pharmacol*  
11 5 *Ther* 1998;12(10):1003-10.  
12  
13 6 37. Shi J, Tong Y, Shen JG, et al. Effectiveness and safety of herbal medicines in the  
14 7 treatment of irritable bowel syndrome: a systematic review. *World J Gastroenterol*  
15 8 2008;14(3):454-62.  
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24 10 **Figure legend**

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26 11 **Figure 1.** Flow chart of Trial. GIIM: Gastrointestinal internal medicine, FM: Family  
27 12 medicine, D-IBS: diarrhea-irritable bowel syndrome, P: placebo, OB: octyloonium bromide,  
28 13 SRS: Samryungbaekchulsan  
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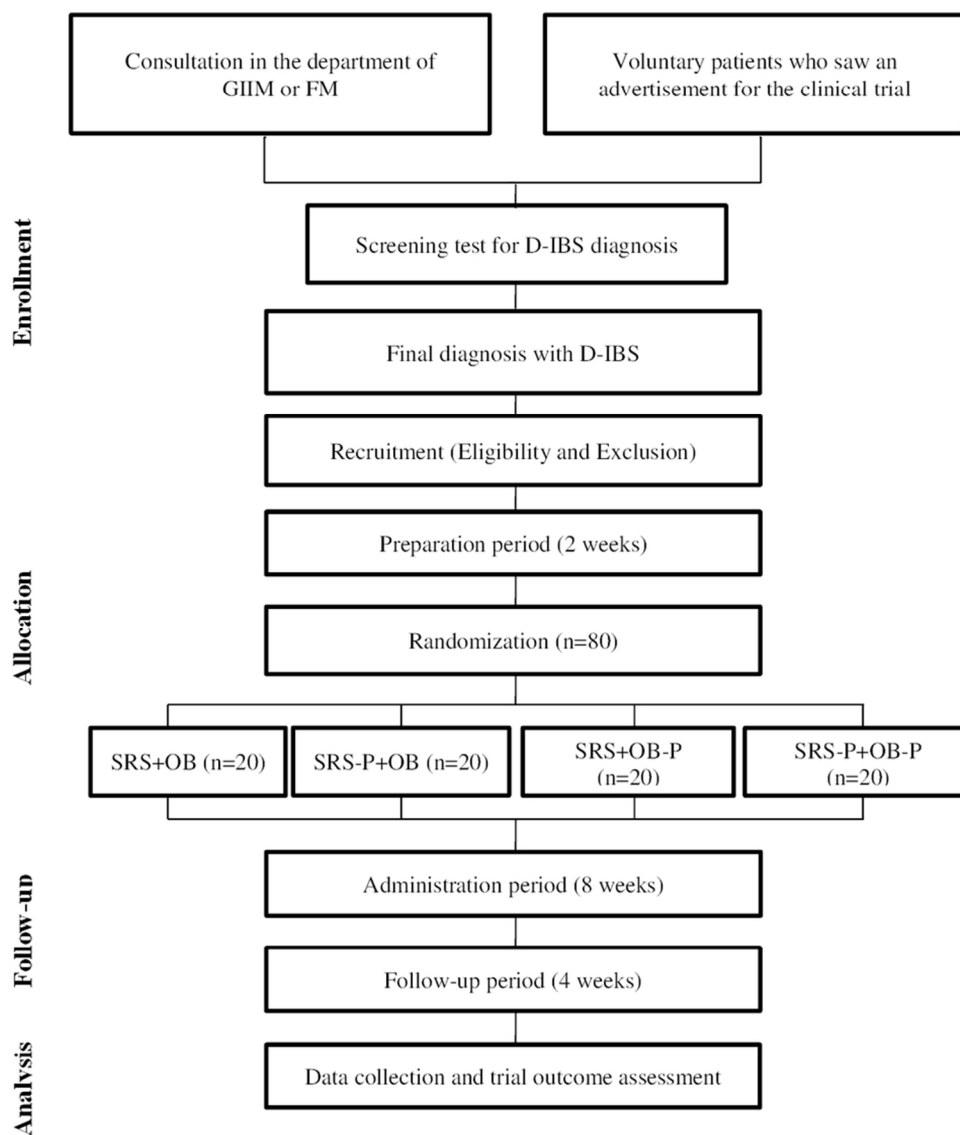


Figure 1. Flow chart of Trial. GIIM: Gastrointestinal internal medicine, FM: Family medicine, D-IBS: diarrheal-irritable bowel syndrome, P: placebo, OB: octylonium bromide, SRS: Samryungbaekchulsan

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>P1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>P4</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Attachment</u>
Protocol version	3	Date and version identifier	<u>P4</u>
Funding	4	Sources and types of financial, material, and other support	<u>P1, P24</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>P1, P23</u>
	5b	Name and contact information for the trial sponsor	<u>P1, P24</u>
	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	<u>N/A</u>
	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)	<u>P8-9, P11-13, P17-19</u>

## 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	<u>P5-6</u>
	6b	Explanation for choice of comparators	<u>P6</u>
Objectives	7	Specific objectives or hypotheses	<u>P7-8</u>
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)	<u>P8-9</u>

## 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	<u>P8</u>
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)	<u>P9-12</u>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>P12-14</u>
	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)	<u>P14-17</u>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>P14-17,19</u>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>P14</u>
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	<u>P14-16</u>
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)	<u>P8-9, Figure1</u>



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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 P9

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size P11-12

**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 P11-12

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 P12

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P11-12

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P11-12

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial P11-12

**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 P17-19

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 P8-9

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3	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	<u><a href="#">P17,19</a></u>
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7	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	<u><a href="#">P17-19</a></u>
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u><a href="#">P17-19</a></u>
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12		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)	<u><a href="#">P17-19</a></u>
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16	<b>Methods: Monitoring</b>			
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18	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	<u><a href="#">P19</a></u>
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23		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	<u><a href="#">P17,19</a></u>
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26	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	<u><a href="#">P15-17</a></u>
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u><a href="#">P19</a></u>
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33	<b>Ethics and dissemination</b>			
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35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u><a href="#">P3, P22</a></u>
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38	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)	<u><a href="#">P22</a></u>
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>P22-23</u>
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>N/A</u>
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9	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	<u>P23</u>
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>P24</u>
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15	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	<u>P17</u>
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18	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	<u>P23</u>
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21	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	<u>P3, 23</u>
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
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28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
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30	<b>Appendices</b>			
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32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>Attachment</u>
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35	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	<u>P15-16</u>
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Effect of herbal extract granules combined with otilonium bromide on irritable bowel syndrome with diarrhea: a pilot study protocol for a randomized controlled trial

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<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Samryungbaekchulsan, otilonium bromide, irritable bowel syndrome, randomized controlled study, clinical trial protocol

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1 **Effect of herbal extract granules combined with otilonium bromide on**  
2 **irritable bowel syndrome with diarrhea: a pilot study protocol for a**  
3 **randomized controlled trial**

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6 Myong Ki Baeg<sup>1</sup>, Ja Sung Choi<sup>1</sup>, Hye-Jung Kim<sup>1</sup>, Ja-Young Kim<sup>1</sup>, Yun-Young Sunwoo<sup>1</sup>,  
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22 **\* These authors contributed equally to the study**

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25 Medicine Formulas (K15250)” grant from the Korea Institute of Oriental Medicine (KIOM).  
26 (Telephone: +82-42-868-9513)

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28 **Word Count:** 5898

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**Keywords:** Samryungbaekchulsan, otilonium bromide, irritable bowel syndrome, randomized controlled study, clinical trial protocol

For peer review only

## 1 ABSTRACT

### 2 Introduction

3 Irritable bowel syndrome (IBS), known as a functional and organic gastrointestinal (GI)  
4 disorder, is a collection of symptoms that occur together and generally include pain or  
5 discomfort in the abdomen and changes in bowel movement patterns. Due to the limitations  
6 of conventional treatments, alternative IBS treatments are used by many patients worldwide.  
7 Samryungbaekchulsan (SRS), a herbal formula, has long been used for alleviating diarrhea-  
8 predominant IBS (D-IBS) in traditional Korean medicine. Otilonium bromide (OB) is an  
9 antimuscarinic compound used to relieve spasmodic pain in the gut, especially in IBS.  
10 Although herbal formulas and western drugs are commonly co-administered for various  
11 diseases in Korea, few clinical studies have been conducted regarding the synergic effects of  
12 these treatments for any disease, including D-IBS.

### 14 Methods and Analysis

15 This trial is a randomized, double-blinded, placebo-controlled, double-dummy, four-arm,  
16 parallel study. After a 2-week preparation period, 80 patients with D-IBS will be randomly  
17 assigned to one of four treatment groups consisting of SRS (water extract granules, 5 g/pack,  
18 3 times a day) with OB (tablet form, 1 capsule 3 times a day) or their placebos, with  
19 treatment lasting for 8 weeks. Post-treatment follow-up will be conducted 4 weeks after the  
20 end of treatment. The primary outcome is the finding obtained using the Subject's Global  
21 Assessment of Relief method. The secondary outcomes are the severity of symptoms related  
22 to D-IBS, determined using a 10-point scale, and the change in symptoms.

### 24 Ethics and dissemination

25 This trial has full ethical approval of the ethics committee of Catholic Kwandong University  
26 International St. Mary's Hospital (IS15MISV0033) and the Korean Ministry of Food and  
27 Drug Safety (30769). The results of the study will be disseminated through a peer-reviewed  
28 journal and/or conference presentations.



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2 **Trial protocol version: IS15MISV0033 Version 4.0 (July 25, 2016)**

3

4 **Trial registration number: KCT0001621 (Approval date: Aug 10, 2015)**

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6 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

7 ■ This randomized controlled trial is the first Korean clinical trial approved by the Korean  
8 Ministry of Food and Drug Safety (KMFDS) to investigate the efficacy and safety of  
9 Samryungbaekchulsan (SRS; herbal formula) and otilonium bromide (OB; western drug) in  
10 diarrhea-predominant irritable bowel syndrome (D-IBS).

11 ■ To evaluate the therapeutic effect and safety of the co-administration of SRS and OB, this  
12 study is proposed as a double-blind, double-dummy, four-arm, parallel-group randomized  
13 controlled trial.

14 ■ The primary outcome is the improvement in the patient's symptoms according to the  
15 Subject's Global Assessment of Relief and the secondary outcome is the severity of D-IBS  
16 symptoms.

17 ■ This study is conducted with a small sample size (four arms, 20 participants per group)  
18 because it is a pilot study and further clinical trials with powerful sample sizes will be  
19 required to more adequately determine the effectiveness of SRS and/or OB for D-IBS.

20

21

## 1 INTRODUCTION

2 Irritable bowel syndrome (IBS), a chronic gastrointestinal (GI) disease and functional  
3 bowel disorder, is characterized by abnormal bowel habits and abdominal pain without  
4 structural, morphological, and histological abnormalities. It affects approximately 20% of the  
5 population worldwide, according to population-based studies<sup>1-6</sup>. In addition, recent evidence  
6 suggests that IBS is not only a functional disease, but also an organic disease with a complex  
7 of symptoms, including infection, immune activation, serotonin dysregulation, bacterial  
8 overgrowth, central dysregulation, brain-gut interaction, and genetics<sup>4-8</sup>. Based on their  
9 predominant bowel habits, patients with IBS can be divided into diarrhea-predominant IBS  
10 (D-IBS), constipation-predominant IBS, or mixed IBS<sup>2,6,9</sup>. Recently, smooth-muscle relaxants,  
11 bulking agents, and anti-diarrheal agents have been used in the treatment of IBS<sup>10</sup>. However,  
12 these methods are often not effective and many IBS patients also use complementary  
13 treatments, such as herbal medicine, acupuncture, psychological treatment, and lifestyle  
14 correction<sup>2,11,12</sup>.

15 Samryungbaekchulsan (SRS; Shenlingbaizhu-san in Traditional Chinese Medicine;  
16 Jinryobyakujutsu-san in Kampo Medicine), which was introduced in the famous classical  
17 compendium of herbal formulas “Formulary of Peaceful Benevolent Dispensary,” consists of  
18 10 herbs (*Atractylodes rhizoma Alba*, *Poria sclerotium*, *Dioscoreae rhizoma*, *Glycyrrhizae*  
19 *radix et rhizoma*, *Coicis semen*, *Nelumbinis semen*, *Platycodonis radix*, *Dolichoris semen*,  
20 *Amomi fructus*, and *Ginseng radix*). In traditional Korean and Chinese medicine, this herbal  
21 formula has been used to treat GI disease, and various studies have been published regarding  
22 the treatment of IBS with SRS<sup>13-18</sup>. SRS has been shown to have anti-acetylcholine and anti-  
23 barium chloride effects and to suppress gastric secretion and small intestine motility<sup>13</sup>.  
24 However, no clinical trials have evaluated the efficacy of SRS for IBS when co-administered  
25 with a conventional drug.

1 Otilonium bromide (OB) is widely used for the prevention and reduction of symptoms in  
2 patients with IBS<sup>7 8</sup>. OB has been shown to inhibit L- and T-type calcium channels,  
3 muscarinic receptors, and tachykininergic responses in human cultured smooth muscle cells  
4 and rat colon strips<sup>19-21</sup>. According to a recent randomized controlled trial (RCT), OB (40 and  
5 80 mg) is more effective for treating IBS than placebo, not only for the reduction of bloating  
6 and abdominal pain, but also for protection from relapse owing to its long-lasting effect<sup>22 23</sup>.

7 According to the guidelines of the Korean Society of Gastroenterology, antispasmodic  
8 agents are recommended for the treatment of D-IBS (Grade 1B),<sup>24</sup> and SRS is the preferred  
9 drug for diarrhea treatment in Korean medicine<sup>18</sup>. Recently, several studies have been  
10 conducted to evaluate the therapeutic effect of the co-administration of herbal formulas and  
11 conventional drugs for IBS in China<sup>25 26</sup>. However, there has been no such clinical study in  
12 Korea, even though both herbal medicine and conventional drugs are widely used for IBS  
13 treatment in the clinical field. Therefore, there is a need to evaluate the efficacy and safety of  
14 SRS, OB, and the co-administration of both drugs.

15 In this study, we expect that the combined administration of OB and SRS will result in  
16 synergistic effects that improve D-IBS symptoms, including abdominal pain, discomfort (the  
17 main effect of OB), and diarrhea-like stool patterns (the main effect of SRS).

## 1 METHODS AND ANALYSIS

### 2 *Objectives*

3 The purpose of this study is to evaluate the efficacy and safety of the co-administration of  
4 SRS and OB to patients with D-IBS.

### 6 *Necessity of the trial*

7 Recently, herbal medicines and western drugs have been co-administered for various  
8 medical therapies. This is particularly true in Korea, where approximately 76% of patients  
9 have used the combination of herbal medicines and western drugs<sup>14</sup>. However, only a few  
10 studies have evaluated the interaction between western and herbal medicines. Despite the  
11 need for combined treatment in patients with various diseases, there are no standard clinical  
12 guidelines or scientific evidence regarding co-administration because of a lack of research  
13 and data.

14 D-IBS is a disease that is difficult to cure and many patients require treatment with both  
15 western and herbal drugs to experience an improvement in their symptoms. Therefore, it is  
16 very important to conduct a clinical study regarding the efficacy and safety of the combined  
17 administration of SRS and OB in patients with D-IBS.

### 19 *Basis of drug selection*

20 According to guidelines for IBS treatment, the OB recommendation level is high (i.e., the  
21 level of evidence is moderate and many experts recommend using it) and it is the most  
22 reasonable treatment option<sup>25</sup>. SRS is the herbal formula used most often by clinical Korean  
23 and Chinese medical doctors for abdominal pain, abdominal discomfort, and chronic diarrhea,  
24 which are typical symptoms of D-IBS<sup>15-17 24</sup>. Based on these studies and clinical applications,  
25 OB and SRS were selected for this trial.

1

## 2 *Hypothesis*

3 We hypothesize the following: (1) that co-administration of SRS and OB will have a more  
4 positive effect on D-IBS symptoms than either SRS or OB alone; (2) that after 8 weeks of  
5 treatment with SRS, OB, or both drugs, the Subject's Global Assessment of Relief and  
6 severity of D-IBS symptoms will be more improved than after treatment with placebo; and (3)  
7 that co-administration of SRS and OB will be safe for patients with D-IBS.

## 9 *Design*

10 This study is a placebo-controlled, double-blind trial. Eighty patients will be enrolled and  
11 randomly assigned to four separate arms of the trial. The trial will be conducted at Catholic  
12 Kwandong University International St. Mary's Hospital, Incheon, South Korea.

13 The study subjects will be required to participate in a 2-week preparation period (weeks -2  
14 to 0) and an 8-week drug administration period (weeks 0 to 8). The patients will visit four  
15 times, on weeks 0, 4, 8, and 12. The primary outcome measurement will be evaluated at  
16 weeks 2, 4, 6, 8, and 12, and the secondary outcome measurement will be evaluated at weeks  
17 0, 2, 4, 6, 8, and 12. Participants will be assessed for efficacy and safety of the treatment  
18 through visits (0, 4, 8, 12 weeks) and telephone questionnaires (2, 6 weeks). In addition, lab  
19 tests will be conducted at 0, 4, and 8 weeks. According to the intervention protocols, the  
20 clinical research coordinator (CRC) will encourage patients and participants to complete  
21 follow-up at every visit.

22 During the drug administration period, SRS or its placebo will be given as 1 pack of water  
23 extract granules 3 times a day, 30 min before each meal. OB or its placebo will be given as 1  
24 tablet 3 times a day, 30 min before each meal.

25 Participants will be divided into 4 groups: (1) SRS and OB group; (2) SRS and placebo-

1 OB group; (3) placebo-SRS and OB group; and (4) placebo-SRS and placebo-OB group. The  
2 entire flow chart of the study is shown in Figure 1.

3 The protocol of this trial has been approved by the institutional review board (IRB) and  
4 ethics committee of Catholic Kwandong University International St. Mary's Hospital. The  
5 IRB permission number is IS15MISV0033 and CRIS (Clinical Research Information Service,  
6 www.cris.nih.go.kr) protocol identification number is KCT0001621. In addition, this study  
7 received the first approval given by the Korean Ministry of Food and Drug Safety (KMFDS)  
8 for a study of the co-administration of a conventional drug and a Korean traditional herbal  
9 medicine (approval number: 30769).

10 Potential participants will be provided with sufficient information about the study and only  
11 those who agree to the study protocol and sign the consent form will be enrolled. The study  
12 will be implemented according to Good Clinical Practice and the revised version of the  
13 Declaration of Helsinki.

#### 14 ***Sample size calculation***

15 This trial is a pilot study for a new therapeutic regimen of SRS and OB combination  
16 treatment. In a similar study conducted previously by using co-administration of a probiotics  
17 mixture and an herbal medicine (placebo-controlled, double-blind, and randomly 4-arm),  
18 each arm consisted of at least 15 patients and the total sample size was more than 60  
19 participants<sup>27</sup>. In other similar pilot studies, clinical trials have been conducted with a total of  
20 60–64 participants, consisting of 12–30 patients per group<sup>28-30</sup>. Based on these previous studies,  
21 the minimal clinical significance of the trial can be obtained when only 16 participants  
22 complete the trial. Because the drop-out rate is expected to be 20%, each trial group will be  
23 made up of at least 20 participants. Therefore, the total sample size must be more than 80  
24 participants.  
25

1

***Inclusion criteria***

The following patients would be included: (1) patients aged 18–75 years; (2) patients satisfying the Rome III criteria of IBS (recurrent abdominal pain or discomfort that began at least 6 months before the clinical trial, with a rating of more than 3 on a 10-point scale, frequency of at least 3 days/month in the last 3 months, and associated with two or more of the following: improvement associated with defecation, onset associated with a change in frequency of stools, and onset associated with a change in form of stool)<sup>19</sup>; (3) patients satisfying the Rome III criteria of IBS, whereby D-IBS type is defined as loose/mushy or watery stools—Bristol Stool Form (BSF) Scale 6-7  $\geq$  2 times/week<sup>130</sup>; (4) patients with a negative urine pregnancy test (in women of a childbearing age, within 7 days before the clinical trial) and who consent to using contraception during the administration period; (5) patients with the ability to read the symptom questionnaire and understand it; and (6) patients who agree with the clinical plan and voluntarily sign the IRB-approved documents.

15

***Exclusion criteria***

The exclusion criteria are as follows: (1) chronic liver disease (cirrhosis, chronic hepatitis B or C); (2) chronic renal failure or renal impairment (serum creatinine  $\geq$  2 times the upper limit of normal); (3) liver dysfunction (AST/ALT  $\geq$  3 times the upper limit of normal); (4) diabetes (HbA1c  $>$  8% or not controlled by diet or medication), hypertension ( $\geq$  160/100 mmHg), thyroid dysfunction (exceptions in the following cases: if the disease is controlled by drug administration with a stable dose for 12 weeks before the screening, and the drug dose remains constant during the trial period), clinically significant hematologic, cardiac, pulmonary, neurological disorders, or other severe systemic disorders; (5) abnormal findings on colonoscopy or colonography within the last 5 years; (6) history of surgery that affects

25



1 gastrointestinal motility (i.e., gastrectomy, colonic resection, hysterectomy, except for  
2 appendectomy); (7) GI disease characterized by the following symptoms within 6 months  
3 before the clinical trial: inflammation of or ulcer in the esophagus, stomach, or duodenum;  
4 gastroesophageal reflux disease (at the discretion of the examiner, subjects may enroll if the  
5 disease is chronic and not acute); gastrointestinal bleeding; gastrointestinal stenosis or closure;  
6 infectious diarrhea; inflammatory bowel disease (i.e., Crohn's disease, diverticulitis,  
7 ulcerative colitis, infectious enteritis, ischemic colitis); pancreatic insufficiency; biliary  
8 abscess; (8) mental illness or an addiction to drugs or alcohol; (9) severe systemic organ  
9 diseases such as cancer, autoimmune disease, stroke (although patients in remission for more  
10 than 5 years from a cancer unrelated to the GI tract can participate in the trial); (10)  
11 pregnancy, breastfeeding, and unwillingness to use contraception during the trial; (11) a  
12 history of taking the following drugs within 2 weeks before the trial: antibiotics, analgesics,  
13 antidepressants, anti-anxiety agents, anti-inflammatory agents, anti-ulcer agents, anti-gastric  
14 secretion inhibitors, laxatives, antispasmodics, antacid agents, gastrointestinal stimulants,  
15 prostaglandin agents, and corticosteroids; (12) use of medications that do not match the intent  
16 of this trial or have a clinical interaction with SRS or OB; (13) lactose intolerance (not  
17 controlled by food); (14) glaucoma; (15) participation in other clinical studies within 30 days  
18 prior to clinical screening and have received other clinical trial medications (including  
19 placebo); (16) hypersensitivity to clinical trial medicines; and (17) other reasons considered  
20 inappropriate for participation in clinical trials.

21

### 22 ***Recruitment, randomization, blinding, and unblinding***

23 Advertisements for the study will be posted at the Catholic Kwandong University  
24 International St. Mary's Hospital using banner ads and posters. We also plan to post the  
25 advertisements on the hospital homepage, in the monthly hospital magazine, at the internet



1 café, and on the subway at least five times. All these advertisements will be done with the  
2 approval of the IRB.

3 After recruitment, patients will be randomized to one of the four trial arms. Randomization  
4 will be performed using a list of block randomizations made by statisticians, independent of  
5 this clinical trial. A researcher who is not involved in process of drug prescription and  
6 evaluation will execute the randomization process.

7 During the treatment period, the patients and all researchers (investigators and clinical  
8 research coordinators) will be blinded, except the researchers who conducted the  
9 randomization procedure. In addition, the researchers will not know the kind of medication  
10 that is being administered to the patient or any other information that could lead to bias.

11 Allocation concealment will be performed during the process of medication administration.  
12 The management pharmacist, who will not be involved in analyzing the results of the trial,  
13 will use the randomization table to label the medication with the assignment number and  
14 provide the medication. The patients will take the drugs contained in the opaque envelope,  
15 which will be labeled with the assignment number.

16 Unblinding will be performed only in the following situations: (1) if the trial is terminated  
17 and there is a need for statistical analysis; (2) if a serious medical emergency occurs and  
18 information about the medication is needed; and (3) if the chief investigator determines that  
19 unblinding is necessary.

20 The entire process of the study will be directed by the authorized clinical research  
21 organization (CRO), Dream CIS Corporation, Seoul, Korea.

### 23 ***Intervention***

24 The herbal formula SRS is commonly used by Korean traditional medical doctors for  
25 treatment of diarrhea and related diseases<sup>13-18</sup>. SRS used in this study (Samryungbaekchulsan

1 granule®, Hankook shin yak, Co., Ltd., Nonsan, Korea) is extracted with water and mixed  
2 with starch and lactose in accordance with Korean Good Manufacturing Practice (K-GMP).  
3 Production of SRS is regulated and allowed by the KMFDS. SRS contains 10 herbs, listed in  
4 Table 1. Placebo-SRS is made from cornstarch and has the same taste, shape, color, and  
5 similar scent as SRS. SRS and placebo-SRS will be sealed in identical aluminum bags with  
6 the same labeling. These herbal drug packages will be distributed by an independent  
7 pharmacist in an isolated room. According to the recommended dosing methods of KMFDS,  
8 after SRS or placebo-SRS is dissolved in boiled water, the subjects will take them 30 min  
9 before each meal (5 g/pack, 3 times a day).

10 OB (Menocetyl Tab®, Dong Hwa Pharm Co., LTD., Seoul, Korea) is a tablet containing  
11 otilonium bromide 40 mg. Placebo-OB is a tablet made of Ludipress with the same taste,  
12 shape, and color as OB. Patients will be instructed to swallow one tablet of OB or placebo-  
13 OB 30 min before each meal over the administration period. The drugs used in the trial (SRS,  
14 OB, placebo-SRS, placebo-OB) have been approved by the KMFDS. Patients will be asked at  
15 the end of the study whether the drugs that they have been taking are either real or placebo, to  
16 measure the success of blinding. Compliance will be confirmed by counting returned SRS  
17 packets or OB tablets. Every patient will be instructed to write down any adverse events  
18 during the administration period and these records will be evaluated at the follow-up. At the  
19 patient visits (at 0, 4, and 8 weeks), we will perform a check of vital signs, physical  
20 examination, electrocardiogram, and laboratory tests to evaluate safety for the patients. All  
21 side effects will be reported to the investigator.

22  
23

**Table. 1 Ingredients in the herbal formula Samryungbaekchulsan (SRS)**

Scientific name	Part used	Grams/day
Atractylodis Rhizoma Alba	Root	3.0
Poria Sclerotium	Dried core	4.0
Rhizoma Dioscoreae	Root	3.0
Glycyrrhizae Radix et Rhizoma	Root	1.5
Semen Coicis	Seed	8.0
Semen Nelumbinis	Fruit	4.0
Platycodonis Radix	Root	2.5
Dolichoris Semen	Seed	4.0
Amomi Fructus	Fruit	2.0
Ginseng Radix	Root	3.0

### ***Rescue therapy and concomitant medications***

Participants are prohibited from taking any medication that could affect D-IBS during the entire course of the trial. However, if serious side effects occur or symptoms worsen, investigators will provide quick and appropriate treatment (including drug administration), based on their medical judgement. In this case, the direct investigators will record the treatment or drug administration and report to the IRB within 24 h to determine whether the trial should be continued or discontinued.

### ***Outcome Measurements***

#### ***Primary outcome***

The primary outcome will be measured via a questionnaire that confirms subjective

1 symptom improvement. Participants will respond a total of five times during and after the  
2 administration period (at 2 and 6 weeks via telephone, and at 4, 8, and 12 weeks during direct  
3 visits) to the following question: Subject's Global Assessment of Relief; "How much do you  
4 think the symptoms of D-IBS have improved compared to before the clinical trial?"  
5 According to the answers given by the patients to this survey, the improvement is given a  
6 score of 0, 1, 2, 3, or 4.

### 7 8 *Secondary outcomes*

9 At 2, 4, 6, 8, and 12 weeks from the start of the treatment period, patients will be assessed  
10 for severity of D-IBS symptoms (abdominal pain, abdominal discomfort, satisfaction of  
11 defecation, frequency of abdominal pain, quality of life) using a Likert scale ranging from 0  
12 to 10<sup>31</sup>. Patients will also be instructed to record the number of defecations per day, BSF, and  
13 the degree of force used in bowel movements at 0, 2, 4, 6, 8, and 12 weeks<sup>32</sup>.

### 14 15 *Safety assessments*

16 The investigator will record all adverse events that occur during the trial along with any  
17 concomitant medications in the case reports. When an adverse event occurs, the investigator  
18 will record the symptoms and signs of the adverse reaction, the duration (start and end date),  
19 severity, course, outcome, significance, causality by the trial drug, and any action taken in  
20 relation to the adverse event. In the case of concomitant medicines, composition, dosage,  
21 duration of administration, and reason for medication will be recorded in detail. Symptoms  
22 that existed before the start of the clinical trial will not be recorded as adverse events.

### 23 24 *Laboratory tests*

25 The purpose of laboratory tests in this study is to evaluate the safety and pharmacokinetic

1 profiles of SRS and OB. Because of the small number of patients assigned to this study and  
2 the different baseline values for each individual patient, we will not perform a detailed  
3 statistical analysis. However, if significant abnormal results are found in the laboratory tests,  
4 the clinical laboratory results will be described and the connection to the drug will be  
5 considered.

6 Blood tests will be conducted at 0, 2, 4, and 8 weeks and urine tests will be performed at  
7 0 and 4 weeks during the clinical trial. In the case of a participant who drops out or the early  
8 termination of the clinical trial, blood and urine tests will be performed on the last day of the  
9 trial.

10 Using the test results (comprehensive verification of vital signs, laboratory tests,  
11 electrocardiograms, and physical examinations) for each individual patient, the investigator  
12 will determine adverse reactions caused by the drugs and statistical tests will be conducted as  
13 needed on clinically significant parameters.

#### 14 *Test of human derivatives*

15 IBS is known to be closely related to stress<sup>12</sup>. Therefore, we plan to quantify factors  
16 associated with stress or that have been reported to worsen IBS symptoms as follows: 1)  
17 cortisol; 2) corticotropin-releasing hormone (CRH); 3) serotonin; 4) group I cytokines (10  
18 species); 5) group II cytokines (14 species); and 6) growth factors (3 species)<sup>33 34</sup>. Serum will  
19 be separated from blood specimens collected at 0, 4, 8 weeks, stored frozen, and transferred  
20 to the Korea Institute of Oriental Medicine (KIOM) for examination.

#### 21 *Early termination or dropout*

22 The criteria for early termination or dropout are as follows: 1) administration of other  
23 drugs that are expected to affect the safety and efficacy of the clinical trial drugs; 2) request

1 of participants to discontinue the clinical trial, or withdrawal of the trial agreement; 3)  
2 occurrence of significant adverse drug reactions or events that preclude continuing the trial,  
3 according to the judgment of the clinical investigator; 4) new discovery of violations of  
4 significant clinical trial protocol during clinical trial; 5) less than 70% trial drug compliance;  
5 and 6) any other reason that the clinical trial should be discontinued at the discretion of the  
6 clinical trial manager or investigator.

#### 8 *Data collection, access, and management*

9 The data of this trial will be managed according to the standard work instructions of  
10 Catholic Kwandong University International, St. Mary's Hospital. Other contents not  
11 specified in the trial protocol shall follow the standards of The International Conference on  
12 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human  
13 Use (ICH) Guideline for Good Clinical Practice (GCP) and Korean Good Clinical Practice  
14 (KGCP) guideline.

15 The source document is recorded immediately when the data are collected. After the source  
16 document input is completed, it will be recorded in the case record form (CRF). All the  
17 documents will be kept safe, so that the data can be verified by the relevant government  
18 agencies and the IRB. Only research colleagues and others who have been approved by the  
19 principle investigator will have access to all data obtained from this trial.

#### 21 *Statistical analysis*

22 The statistical analysis will be conducted by blinded professional statisticians. To evaluate  
23 the efficacy of the study, both an intent-to-treat (ITT) analysis (primary analytical method)  
24 and a per-protocol (PP) analysis (secondary analytical method) will be performed. The ITT  
25 analysis will be conducted for all patients who were followed up at least once after

1 randomization and will be able to be evaluated for effectiveness. The PP analysis will be  
2 performed for patients who complete the 8-week treatment course and meet the inclusion and  
3 exclusion criteria.

4 To analyze the continuous variables in the demographic information and pre-treatment  
5 characteristics between groups, a one-way analysis of variance (ANOVA) and Kruskal-Wallis  
6 test will be conducted. An ANOVA and Kruskal-Wallis test will also be used to test for  
7 symptom improvement compared to baseline (0 week) and the variables for analysis that  
8 include the following: (1) subjective symptom improvement (primary outcomes); and (2)  
9 severity of symptoms related to D-IBS (abdominal pain, abdominal discomfort, satisfaction  
10 of defecation, frequency of abdominal pain, quality of life). All values will be shown as mean  
11  $\pm$  standard error of the mean (SEM). Comparisons of outcome assessments between the four  
12 groups will be performed using the paired t-test or Wilcoxon signed-rank test.

13 If the Subject's Global Assessment of Relief on the Likert scale is "0" or "1" for more than  
14 2 weeks between weeks 8 and 12, then the symptoms will be considered to have improved  
15 sufficiently. Based on this, we will calculate the symptom relief rate by dividing the number  
16 of participants who exhibited sufficient symptom relief by the total number of participants in  
17 the trial and present descriptive statistics. The CATMOD procedure will be used to evaluate  
18 the relief rate improvement of symptoms compared with baseline. Comparisons between the  
19 four groups will be conducted using the chi-square test or Fisher's exact test. These statistical  
20 analyses will also be performed at 2, 4, 6, 8, and 10 weeks from baseline. The Cochran-  
21 Mantel-Haenszel (CMH) test will be used to confirm the difference between the intervention  
22 groups at each time-point.

23 A statistical analysis will also be conducted to evaluate safety. The incidence of adverse  
24 events and abnormality of experimental results will be analyzed statistically according to the  
25 groups and non-parametric methods will be applied as necessary using a paired t-test for



1 continuous data, McNemar's test for categorical data, Fisher's exact test for adverse events,  
2 and a generalized estimating equation for clinically significant changes between groups.

3 All statistical analysis will be conducted using SAS software, version 9.1.3 (SAS institute,  
4 Cary, NC). A P-value < 0.05 will be considered statistically significant.

### 5 6 *Quality control and data monitoring*

7 To ensure the results and quality of the clinical trial, assessments and monitoring will be  
8 performed by the CRO, DreamCIS Corporation (Seoul, Korea), which is independent from  
9 the sponsor and competing interests. During the trial, the CRO will regularly monitor whether  
10 the study is proceeding in accordance with the protocol through the use of all related  
11 documentation, including trial master files, case report forms, informed consent forms, and  
12 adverse event reports.

## 13 14 **DISCUSSION**

15 Herbal medicine is a recognized effective treatment method based on clinical experience  
16 accumulated over thousands of years and more recently gained attention as an alternative  
17 therapy for treating various diseases that are difficult to treat or have unknown causes, such  
18 as IBS<sup>5 7 10 26 35</sup>. SRS is frequently used for abdominal pain and diarrhea in Korean and  
19 Chinese traditional medicine. According to experimental research, SRS has an anti-  
20 cholinergic effect that improves intestinal digestion and absorption and inhibits intestinal  
21 movement, resulting in the prevention of diarrhea and abdominal pain<sup>13</sup>. In addition, clinical  
22 studies have shown that the use of SRS in patients with D-IBS is effective for improving  
23 diarrhea<sup>36 37</sup>. Some studies have reported that co-administration with SRS and trimebutine  
24 maleate or SRS and paroxetine is more effective than trimebutine maleate alone for the  
25 improvement in IBS symptoms<sup>15 16 25</sup>. Other studies have reported that SRS exerted more



1 beneficial effects on IBS patients compared with Smecta or probiotics<sup>17 37</sup>.

2 However, although there is a growing interest in the use of herbal medicines such as SRS  
3 in IBS and related studies are continuously being published, there have been only a few well-  
4 designed RCTs<sup>22 23 26</sup>. To overcome the limitations of the previous studies, this trial was  
5 designed as a double-blind, double-dummy, four-arm, parallel-group RCT. The efficacy of  
6 SRS will be evaluated via the Subject's Global Assessment of Relief and the improvement in  
7 symptoms associated with bowel movements and abdominal pain. The results of these  
8 assessments are expected to provide distinct clinical evidence for the use of SRS in D-IBS  
9 treatment.

10 OB is a representative conventional medicine used for D-IBS treatment<sup>8 21 23 38 39</sup>. It is a  
11 spasmolytic agent that exerts its activity primarily in the distal GI tract through the inhibition  
12 of Ca<sup>++</sup> flux and direct activation of contractile proteins in the smooth muscle<sup>20 21</sup>. OB has  
13 also been shown to reduce hyper-motility and modulate visceral sensation, the effect of which  
14 is to improve D-IBS symptoms<sup>39 40</sup>. RCTs using OB for the treatment of D-IBS have been  
15 conducted. In these studies, treatment with OB resulted in a greater improvement in  
16 symptoms related to D-IBS (defecation frequency, regular intestinal habits, reductions in  
17 frequency of diarrhea, abdominal pain and discomfort, severity of abdominal bloating) and  
18 better protection from symptom relapse compared to placebo<sup>22 23 38</sup>.

19 IBS is a disease with a high rate of progression and frequent recurrence. For this reason,  
20 patients with IBS often require a variety of treatment methods<sup>2 6 10</sup>. Among these methods, the  
21 combination of herbal and conventional drugs is widely used and is more effective for  
22 improving IBS symptoms than conventional drugs alone<sup>2 35</sup>. However, there are several  
23 limitations to the co-administration of herbal and conventional drugs in IBS. Specifically,  
24 there is a high risk of bias in related studies and there are insufficient clinical guidelines  
25 regarding the interaction of herbal and conventional drugs in D-IBS, including SRS and OB.

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4 1 Therefore, it is necessary to perform well-designed RCTs to evaluate the co-administration of  
5  
6 2 herbal and conventional drugs.  
7

8  
9 3 Because only a few studies have evaluated the combination of herbal and conventional  
10  
11 4 drugs, our proposed study will significantly contribute to overcoming the limitations of  
12  
13 5 previous studies and provide basic medical evidence for the co-administration of SRS and  
14  
15 6 OB for D-IBS treatment. Therefore, this RCT has several characteristic features. First, this  
16  
17 7 trial will be the first to investigate the efficacy of SRS and OB combination therapy for D-  
18  
19 8 IBS. The results of previous studies suggested that the combination of OB and SRS will  
20  
21 9 improve two major D-IBS symptoms at the same time: abdominal pain and discomfort (major  
22  
23 10 effect of OB) and diarrhea (main effect of SRS). This study will assess this hypothesis and  
24  
25 11 provide a basis for the use of SRS and OB combination therapy for D-IBS. Second, the  
26  
27 12 participants in this trial will be grouped into four arms, making it possible to compare the  
28  
29 13 efficacy of combined treatment with the efficacy of each individual treatment. Third, this trial  
30  
31 14 will evaluate the safety of the subjects using several assessments, including a periodic  
32  
33 15 assessment of subjective symptoms, physical measurements, and laboratory testing. The  
34  
35 16 results of the safety analysis may provide evidence for the safety of treatment with the  
36  
37 17 combination of herbal and conventional drugs in D-IBS. Fourth, this trial was the first clinical  
38  
39 18 study related to combination treatment with western and traditional herbal medicine in Korea  
40  
41 19 to receive approval from the KMFDS. Through the systematic management of the trial under  
42  
43 20 the auspices of the KMFDS, a high quality trial will be performed and the results of this study  
44  
45 21 will provide information for use in further clinical applications.  
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51 22 Although our study is a pilot study with a small sample size, it has a creative and  
52  
53 23 systematic research design and the results will be useful basic clinical evidence in the field of  
54  
55 24 integrated herbal and conventional drugs for the management of D-IBS.  
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## 1 **Trial status**

2 The research plan and design began in April 2015.

3 The study received the IRB's final approval after two deliberations. The first submission  
4 date was July 01, 2015; the result was a request for revision and supplementation, which was  
5 received on July 13, 2015. We filed an application for re-review on August 06, 2015,  
6 supplemented with the relevant information, and received the IRB's final approval on August  
7 10, 2015. We also requested that the KMFDS review the trial plan on September 14, 2015  
8 and received approval for the clinical research on December 21, 2015.

9 The first participant was randomized on March 29, 2016. Recruitment for the study is  
10 ongoing. The primary completion date for this trial is anticipated to be December 31, 2017,  
11 and the study completion date is expected to be February 28, 2018.

## 13 **Ethics**

### 14 *Research ethics approval*

15 This trial was approved by the IRB and ethics committee of Catholic Kwandong  
16 University International St. Mary's Hospital (approval number IS15MISV0033) and the  
17 KMFDS (approval number 30769).

### 19 *Protocol amendments*

20 An investigator who wishes to change the protocol of the clinical trial plan should first  
21 discuss it with the trial director. Thereafter, the examiner should obtain prior approval from  
22 the IRB for changes to the protocol (except to prevent immediate injury to the patient, in  
23 which case it will be reported to the IRB later). However, when a dangerous situation occurs  
24 and immediate treatment is needed, the investigator may report the protocol change to the  
25 IRB at a later time.

1

## 2 *Consent*

3 Patients recruited through the announcement will receive a full explanation of the details of  
4 the trial in an easy-to-understand manner. The patients and investigators will have a mutual  
5 question and answer time before the patient is asked to sign the clinical trial consent. Through  
6 these processes, if the patient agrees to participate in the trial, a signed consent form will be  
7 obtained.

8

## 9 *Confidentiality*

10 All patient information will be anonymized with initials or symbols and all related  
11 investigators will keep the trial results confidential. The trial director will keep the signed  
12 consent forms and prepare a list that will be used to confirm the patient identities.

13

## 14 *Post-trial care*

15 If the patients experience unexpected accidents or injuries, appropriate compensation will  
16 be made by the Federal Insurance Company Korea (12th Floor Ferrum Tower 66 Suha-Dong  
17 Jung-gu Seoul, 100210, South Korea), according to the patient compensation rules of the trial.  
18 Additionally, in the case of an emergency, the patients will receive appropriate medical care  
19 at the Catholic Kwandong University International, St. Mary's Hospital.

20

## 21 **Dissemination**

22 The results of the trial will be disseminated through a peer-reviewed journal and/or  
23 conference presentations.

24

## 25 **Contributors**

1 Joong Il Kim, Pumsoo Kim, Jin-Hyun Lee, and Jung-Han Lee contributed to the protocol  
2 design and writing of the manuscript. Hyekyung Ha is responsible for monitoring the process  
3 of the trial. Na-rae Yang, Yoo-Jin Kim, Myong Ki Baeg, Ja Sung Choi, Hye-Jung Kim, Ja-  
4 Young Kim and Yun-Young Sunwoo provide advice on the process of the trial. Tae-Yong  
5 Park is responsible for writing the manuscript and also managing and supervising the clinical  
6 research. All authors approved the final manuscript.

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10 Formulas (K15250)” grant from the Korea Institute of Oriental Medicine (KIOM).  
11 (Telephone: +82-42-868-9513)

### 13 **Competing interests**

14 The authors have no competing interests to declare.

### 16 **Ethics approval**

17 This trial has been approved by the IRB and ethics committee of Catholic Kwandong  
18 University International St. Mary’s Hospital (approval number IS15MISV0033).

### 20 **Provenance and peer review**

21 Not commissioned; externally peer reviewed.

### 23 **Open Access**

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## 8 REFERENCES

- 9 1. Drossman DA. Introduction. The Rome Foundation and Rome III. *Neurogastroenterol*  
10 *Motil* 2007;19(10):783-6. doi: 10.1111/j.1365-2982.2007.01001.x
- 11 2. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment:  
12 an update for health-care practitioners. *J Gastroenterol Hepatol* 2010;25(4):691-9. doi:  
13 10.1111/j.1440-1746.2009.06120.x
- 14 3. Masion-Bergemann S, Thielecke F, Abel F, et al. Costs of irritable bowel syndrome in the  
15 UK and US. *Pharmacoeconomics* 2006;24(1):21-37.
- 16 4. Soares RL. Irritable bowel syndrome: a clinical review. *World J Gastroenterol*  
17 2014;20(34):12144-60. doi: 10.3748/wjg.v20.i34.12144
- 18 5. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based  
19 medicine. *World J Gastroenterol* 2014;20(22):6759-73. doi:  
20 10.3748/wjg.v20.i22.6759
- 21 6. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*  
22 2015;313(9):949-58. doi: 10.1001/jama.2015.0954
- 23 7. Boeckxstaens G, Corazziari ES, Mearin F, et al. IBS and the role of otilonium bromide. *Int*  
24 *J Colorectal Dis* 2013;28(3):295-304. doi: 10.1007/s00384-012-1598-0
- 25 8. Boeckxstaens G, Clave P, Corazziari ES, et al. Irritable bowel syndrome: focus on

- 1  
2  
3  
4 1 otilonium bromide. *Expert Rev Gastroenterol Hepatol* 2014;8(2):131-7. doi:  
5  
6 2 10.1586/17474124.2014.869477  
7  
8  
9 3 9. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders.  
10  
11 4 *Gastroenterology* 2006;130(5):1480-91. doi: 10.1053/j.gastro.2005.11.061  
12  
13 5 10. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel  
14  
15 6 syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med*  
16  
17 7 2000;133(2):136-47.  
18  
19 8 11. Liu JP, Yang M, Liu YX, et al. Herbal medicines for treatment of irritable bowel  
20  
21 9 syndrome. *Cochrane Database Syst Rev* 2006(1):CD004116. doi:  
22  
23 10 10.1002/14651858.CD004116.pub2  
24  
25 11 12. Palsson OS, Drossman DA. Psychiatric and psychological dysfunction in irritable bowel  
26  
27 12 syndrome and the role of psychological treatments. *Gastroenterol Clin North Am*  
28  
29 13 2005;34(2):281-303. doi: 10.1016/j.gtc.2005.02.004  
30  
31 14 13. Song DS, Ryu BH, Park DW, et al. Experimental studies on the efficacy of  
32  
33 15 Samryungbaekchulsan. *J Korean Med* 1993;14(1):179-95.  
34  
35 16 14. Park JK, Choi SY, Koh KW, et al. Combined utilization with herbal products and  
36  
37 17 prescribed drugs: A result from health examinee-based national survey. *Korean J*  
38  
39 18 *Health Policy Adm* 2006;16(1):1-16.  
40  
41 19 15. Duan W. Observation of sixty-five cases on Irritable Bowel Syndrome treated by  
42  
43 20 Trimebutine and Shenlingbaizhu-san granule [Chinese]. *Journal of Practical*  
44  
45 21 *Traditional Chinese Medicine* 2010;26(5):320.  
46  
47 22 16. Chen Y. Clinical observation of irritable bowel syndrome treated by shenlingbaizhu-san  
48  
49 23 granule and trimebutine [Chinese]. *Journal of Practical Traditional Chinese Medicine*  
50  
51 24 2011;27(5):318-9.  
52  
53 25 17. Li Z, Jiang J. Clinical observation of 80 cases on diarrhea - predominant irritable bowel  
54  
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4 1 syndrome treated by Shenlingbaizhu-san granule [Chinese]. *Guiding Journal of*  
5  
6 2 *Traditional Chinese Medicine and Pharmacy* 2013;20(5):41-2.  
7  
8  
9 3 18. Shin B, Lee B. Frequency Analysis of Clinical Prescriptions in the Korean Medicine  
10  
11 4 Hospital, Pusan National University based on Herb Weight Ratio(2) - Focusing on  
12  
13 5 Prescriptions of Herbal Formula Study Textbook[Korean]. *Herbal Formula Science*  
14  
15 6 2015;23(1):77-89. doi: dx.doi.org/10.14374/HFS.2015.23.1.077  
16  
17 7 19. Martinez-Cutillas M, Gil V, Gallego D, et al. Mechanisms of action of otilonium bromide  
18  
19 8 (OB) in human cultured smooth muscle cells and rat colonic strips.  
20  
21 9 *Neurogastroenterol Motil* 2013;25(12):e803-12. doi: 10.1111/nmo.12206  
22  
23  
24 10 20. Traini C, Cipriani G, Evangelista S, et al. Chronic treatment with otilonium bromide  
25  
26 11 induces changes in L-type Ca(2)(+) channel, tachykinins, and nitric oxide synthase  
27  
28 12 expression in rat colon muscle coat. *Neurogastroenterol Motil* 2013;25(11):e728-39.  
29  
30 13 doi: 10.1111/nmo.12197  
31  
32  
33 14 21. Traini C, Evangelista S, Girod V, et al. Repeated otilonium bromide administration  
34  
35 15 prevents neurotransmitter changes in colon of rats underwent to wrap restraint stress.  
36  
37 16 *J Cell Mol Med* 2017;21(4):735-45. doi: 10.1111/jcmm.13016  
38  
39  
40 17 22. Chmielewska-Wilkon D, Reggiardo G, Egan CG. Otilonium bromide in irritable bowel  
41  
42 18 syndrome: a dose-ranging randomized double-blind placebo-controlled trial. *World J*  
43  
44 19 *Gastroenterol* 2014;20(34):12283-91. doi: 10.3748/wjg.v20.i34.12283  
45  
46 20 23. Clave P, Acalovschi M, Triantafillidis JK, et al. Randomised clinical trial: otilonium  
47  
48 21 bromide improves frequency of abdominal pain, severity of distention and time to  
49  
50 22 relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*  
51  
52 23 2011;34(4):432-42. doi: 10.1111/j.1365-2036.2011.04730.x  
53  
54  
55 24 24. Kwon JG, Park KS, Park JH, et al. [Guidelines for the treatment of irritable bowel  
56  
57 25 syndrome]. *Korean J Gastroenterol* 2011;57(2):82-99.  
58  
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- 1  
2  
3  
4 1 25. Li C, Zuo M, Wang L, et al. Clinical observation of diarrhea - predominant irritable bowel  
5  
6 2 syndrome treated by Shenlingbaizhu-san and Paroxetine [Chinese]. *Chinese Journal*  
7  
8 3 *of Traditional Medical Science and Technology* 2010;17(2):154-5.  
9  
10  
11 4 26. Leung WK, Wu JC, Liang SM, et al. Treatment of diarrhea-predominant irritable bowel  
12  
13 5 syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled  
14  
15 6 trial. *Am J Gastroenterol* 2006;101(7):1574-80. doi: 10.1111/j.1572-  
16  
17 7 0241.2006.00576.x  
18  
19  
20 8 27. Ko SJ, Han G, Kim SK, et al. Effect of korean herbal medicine combined with a probiotic  
21  
22 9 mixture on diarrhea-dominant irritable bowel syndrome: a double-blind, randomized,  
23  
24 10 placebo-controlled trial. *Evid Based Complement Alternat Med* 2013;2013:824605.  
25  
26 11 doi: 10.1155/2013/824605  
27  
28  
29 12 28. Whitehead AL, Julious SA, Cooper CL, et al. Estimating the sample size for a pilot  
30  
31 13 randomised trial to minimise the overall trial sample size for the external pilot and  
32  
33 14 main trial for a continuous outcome variable. *Stat Methods Med Res* 2016;25(3):1057-  
34  
35 15 73. doi: 10.1177/0962280215588241  
36  
37  
38 16 29. Cha BK, Jung MS, Choi CH, et al. The effect of a multispecies probiotic mixture on the  
39  
40 17 symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a  
41  
42 18 randomized, double-blind, placebo-controlled trial. *J Clin Gastroenterol*  
43  
44 19 2012;46(3):220-7. doi: 10.1097/MCG.0b013e31823712b1  
45  
46  
47 20 30. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a  
48  
49 21 probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating.  
50  
51 22 *Neurogastroenterol Motil* 2005;17(5):687-96. doi: 10.1111/j.1365-2982.2005.00695.x  
52  
53  
54 23 31. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a  
55  
56 24 disease-specific quality-of-life questionnaire. *Am J Gastroenterol* 2000;95(4):999-  
57  
58 25 1007. doi: 10.1111/j.1572-0241.2000.01941.x  
59  
60

- 1  
2  
3  
4 1 32. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand*  
5  
6 2 *J Gastroenterol* 1997;32(9):920-4. doi: 10.3109/00365529709011203  
7  
8  
9 3 33. Sugaya N, Izawa S, Saito K, et al. Effect of prolonged stress on the adrenal hormones of  
10  
11 4 individuals with irritable bowel syndrome. *Biopsychosoc Med* 2015;9(1):4. doi:  
12  
13 5 10.1186/s13030-015-0031-7  
14  
15 6 34. Fadgyas-Stanculete M, Buga AM, Popa-Wagner A, et al. The relationship between  
16  
17 7 irritable bowel syndrome and psychiatric disorders: from molecular changes to  
18  
19 8 clinical manifestations. *J Mol Psychiatry* 2014;2(1):4. doi: 10.1186/2049-9256-2-4  
20  
21 9 35. Shi J, Tong Y, Shen JG, et al. Effectiveness and safety of herbal medicines in the  
22  
23 10 treatment of irritable bowel syndrome: a systematic review. *World J Gastroenterol*  
24  
25 11 2008;14(3):454-62.  
26  
27  
28 12 36. Zhong Y, Wu Y. Forty cases of diarrhea - predominant irritable bowel syndrome treated  
29  
30 13 by Shenlingbaizhu-san granule and Montmorillonite powder [Chinese]. *Jiangxi*  
31  
32 14 *Journal of Traditional Chinese Medicine* 2013;44(7):45-6.  
33  
34  
35 15 37. Xiong B. Thirty cases of irritable bowel syndrome treated by Shenlingbaizhu-san granule  
36  
37 16 and Probiotics [Chinese]. *Jiangxi Journal of Traditional Chinese Medicine*  
38  
39 17 2011;42(5):22-3.  
40  
41  
42 18 38. Battaglia G, Morselli-Labate AM, Camarri E, et al. Otilonium bromide in irritable bowel  
43  
44 19 syndrome: a double-blind, placebo-controlled, 15-week study. *Aliment Pharmacol*  
45  
46 20 *Ther* 1998;12(10):1003-10.  
47  
48  
49 21 39. Evangelista S. Otilonium bromide: a selective spasmolytic for the gastrointestinal tract. *J*  
50  
51 22 *Int Med Res* 1999;27(5):207-22. doi: 10.1177/030006059902700501  
52  
53 23 40. Giachetti A. Pharmacological studies on otilonium bromide. *Ital J Gastroenterol*  
54  
55 24 1991;23(8 Suppl 1):56-9.  
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4 **1 Figure legend**

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6 **2 Figure 1.** Flow chart of Trial. GIIM: Gastrointestinal internal medicine, FM: Family  
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8 medicine, D-IBS: diarrhea-irritable bowel syndrome, P: placebo, OB: otilonium bromide,  
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11 **4 SRS:** Samryungbaekchulsan  
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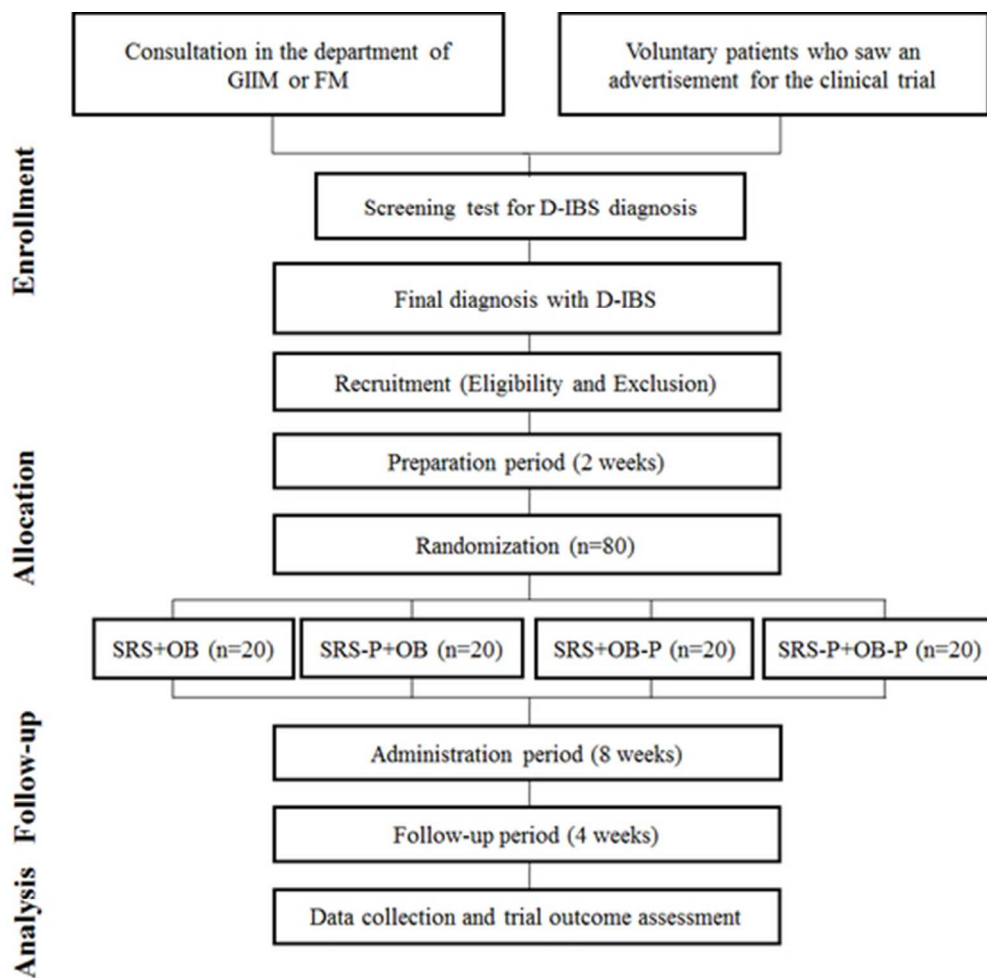


Figure 1. Flow chart of Trial. GIIM: Gastrointestinal internal medicine, FM: Family medicine, D-IBS: diarrhea-irritable bowel syndrome, P: placebo, OB: otilonium bromide, SRS: Samryungbaekchulsan

44x43mm (300 x 300 DPI)



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>P1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>P4</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Attachment</u>
Protocol version	3	Date and version identifier	<u>P4</u>
Funding	4	Sources and types of financial, material, and other support	<u>P1, P24</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>P1, P23</u>
	5b	Name and contact information for the trial sponsor	<u>P1, P24</u>
	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	<u>N/A</u>
	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)	<u>P8-9, P11-13, P17-19</u>

## 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	<u>P5-6</u>
	6b	Explanation for choice of comparators	<u>P6</u>
Objectives	7	Specific objectives or hypotheses	<u>P7-8</u>
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)	<u>P8-9</u>

## 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	<u>P8</u>
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)	<u>P9-12</u>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>P12-14</u>
	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)	<u>P14-17</u>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>P14-17,19</u>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>P14</u>
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	<u>P14-16</u>
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)	<u>P8-9, Figure1</u>

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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 P9

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size P11-12

**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 P11-12

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 P12

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P11-12

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P11-12

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial P11-12

**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 P17-19

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 P8-9

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3	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	<u>P17,19</u>
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7	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	<u>P17-19</u>
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>P17-19</u>
11				
12		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)	<u>P17-19</u>
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16	<b>Methods: Monitoring</b>			
17				
18	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	<u>P19</u>
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23		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	<u>P17,19</u>
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26	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	<u>P15-17</u>
27				
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>P19</u>
30				
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33	<b>Ethics and dissemination</b>			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>P3, P22</u>
36				
37				
38	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)	<u>P22</u>
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>P22-23</u>
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>N/A</u>
7				
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9	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	<u>P23</u>
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>P24</u>
13				
14				
15	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	<u>P17</u>
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18	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	<u>P23</u>
19				
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21	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	<u>P3, 23</u>
22				
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
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30	<b>Appendices</b>			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>Attachment</u>
33				
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35	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	<u>P15-16</u>
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Effect of herbal extract granules combined with otilonium bromide on irritable bowel syndrome with diarrhea: a study protocol for a randomized controlled trial

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<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Samryungbaekchulsan, otilonium bromide, irritable bowel syndrome, randomized controlled study, clinical trial protocol

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1 **Effect of herbal extract granules combined with otilonium bromide on**  
2 **irritable bowel syndrome with diarrhea: a study protocol for a**  
3 **randomized controlled trial**

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**Keywords:** Samryungbaekchulsan, otilonium bromide, irritable bowel syndrome, randomized controlled study, clinical trial protocol

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## 1 ABSTRACT

### 2 Introduction

3 Irritable bowel syndrome (IBS), known as a functional and organic gastrointestinal (GI)  
4 disorder, is a collection of symptoms that occur together and generally include pain or  
5 discomfort in the abdomen and changes in bowel movement patterns. Due to the limitations  
6 of conventional treatments, alternative IBS treatments are used by many patients worldwide.  
7 Samryungbaekchulsan (SRS), a herbal formula, has long been used for alleviating diarrhea-  
8 predominant IBS (D-IBS) in traditional Korean medicine. Otilonium bromide (OB) is an  
9 antimuscarinic compound used to relieve spasmodic pain in the gut, especially in IBS.  
10 Although herbal formulas and western drugs are commonly co-administered for various  
11 diseases in Korea, few clinical studies have been conducted regarding the synergic effects of  
12 these treatments for any disease, including D-IBS.

### 14 Methods and Analysis

15 This trial is a randomized, double-blinded, placebo-controlled, double-dummy, four-arm,  
16 parallel study. After a 2-week preparation period, 80 patients with D-IBS will be randomly  
17 assigned to one of four treatment groups consisting of SRS (water extract granules, 5 g/pack,  
18 3 times a day) with OB (tablet form, 1 capsule 3 times a day) or their placebos, with  
19 treatment lasting for 8 weeks. Post-treatment follow-up will be conducted 4 weeks after the  
20 end of treatment. The primary outcome is the finding obtained using the Subject's Global  
21 Assessment of Relief method. The secondary outcomes are the severity of symptoms related  
22 to D-IBS, determined using a 10-point scale, and the change in symptoms.

### 24 Ethics and dissemination

25 This trial has full ethical approval of the ethics committee of Catholic Kwandong University  
26 International St. Mary's Hospital (IS15MISV0033) and the Korean Ministry of Food and  
27 Drug Safety (30769). The results of the study will be disseminated through a peer-reviewed  
28 journal and/or conference presentations.

1

2 **Trial protocol version: IS15MISV0033 Version 4.0 (July 25, 2016)**

3

4 **Trial registration number: KCT0001621 (Approval date: Aug 10, 2015)**

5

6 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

7 ■ This randomized controlled trial is the first Korean clinical trial approved by the Korean  
8 Ministry of Food and Drug Safety (KMFDS) to investigate the efficacy and safety of  
9 Samryungbaekchulsan (SRS; herbal formula) and otilonium bromide (OB; western drug) in  
10 diarrhea-predominant irritable bowel syndrome (D-IBS).

11 ■ To evaluate the therapeutic effect and safety of the co-administration of SRS and OB, this  
12 study is proposed as a double-blind, double-dummy, four-arm, parallel-group randomized  
13 controlled trial.

14 ■ The primary outcome is the improvement in the patient's symptoms according to the  
15 Subject's Global Assessment of Relief and the secondary outcome is the severity of D-IBS  
16 symptoms.

17 ■ This study is conducted with a small sample size (four arms, 20 participants per group), so  
18 further clinical trials with powerful sample sizes will be required to more adequately  
19 determine the effectiveness of SRS and/or OB for D-IBS.

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## 1 INTRODUCTION

2 Irritable bowel syndrome (IBS), a chronic gastrointestinal (GI) disease and functional  
3 bowel disorder, is characterized by abnormal bowel habits and abdominal pain without  
4 structural, morphological, and histological abnormalities. It affects approximately 20% of the  
5 population worldwide, according to population-based studies<sup>1-6</sup>. In addition, recent evidence  
6 suggests that IBS is not only a functional disease, but also an organic disease with a complex  
7 of symptoms, including infection, immune activation, serotonin dysregulation, bacterial  
8 overgrowth, central dysregulation, brain-gut interaction, and genetics<sup>4-8</sup>. Based on their  
9 predominant bowel habits, patients with IBS can be divided into diarrhea-predominant IBS  
10 (D-IBS), constipation-predominant IBS, or mixed IBS<sup>2,6,9</sup>. Recently, smooth-muscle relaxants,  
11 bulking agents, and anti-diarrheal agents have been used in the treatment of IBS<sup>10</sup>. However,  
12 these methods are often not effective and many IBS patients also use complementary  
13 treatments, such as herbal medicine, acupuncture, psychological treatment, and lifestyle  
14 correction<sup>2,11,12</sup>.

15 Samryungbaekchulsan (SRS; Shenlingbaizhu-san in Traditional Chinese Medicine;  
16 Jinryobyakujutsu-san in Kampo Medicine), which was introduced in the famous classical  
17 compendium of herbal formulas “Formulary of Peaceful Benevolent Dispensary,” consists of  
18 10 herbs (*Atractylodes rhizoma Alba*, *Poria sclerotium*, *Dioscoreae rhizoma*, *Glycyrrhizae*  
19 *radix et rhizoma*, *Coicis semen*, *Nelumbinis semen*, *Platycodonis radix*, *Dolichoris semen*,  
20 *Amomi fructus*, and *Ginseng radix*). In traditional Korean and Chinese medicine, this herbal  
21 formula has been used to treat GI disease, and various studies have been published regarding  
22 the treatment of IBS with SRS<sup>13-18</sup>. SRS has been shown to have anti-acetylcholine and anti-  
23 barium chloride effects and to suppress gastric secretion and small intestine motility<sup>13</sup>.  
24 However, no clinical trials have evaluated the efficacy of SRS for IBS when co-administered  
25 with a conventional drug.



1 Otilonium bromide (OB) is widely used for the prevention and reduction of symptoms in  
2 patients with IBS<sup>7 8</sup>. OB has been shown to inhibit L- and T-type calcium channels,  
3 muscarinic receptors, and tachykininergic responses in human cultured smooth muscle cells  
4 and rat colon strips<sup>19-21</sup>. According to a recent randomized controlled trial (RCT), OB (40 and  
5 80 mg) is more effective for treating IBS than placebo, not only for the reduction of bloating  
6 and abdominal pain, but also for protection from relapse owing to its long-lasting effect<sup>22 23</sup>.

7 According to the guidelines of the Korean Society of Gastroenterology, antispasmodic  
8 agents are recommended for the treatment of D-IBS (Grade 1B),<sup>24</sup> and SRS is the preferred  
9 drug for diarrhea treatment in Korean medicine<sup>18</sup>. Recently, several studies have been  
10 conducted to evaluate the therapeutic effect of the co-administration of herbal formulas and  
11 conventional drugs for IBS in China<sup>25 26</sup>. However, there has been no such clinical study in  
12 Korea, even though both herbal medicine and conventional drugs are widely used for IBS  
13 treatment in the clinical field. Therefore, there is a need to evaluate the efficacy and safety of  
14 SRS, OB, and the co-administration of both drugs.

15 In this study, we expect that the combined administration of OB and SRS will result in  
16 synergistic effects that improve D-IBS symptoms, including abdominal pain, discomfort (the  
17 main effect of OB), and diarrhea-like stool patterns (the main effect of SRS).

## 1 METHODS AND ANALYSIS

### 2 *Objectives*

3 The purpose of this study is to evaluate the efficacy and safety of the co-administration of  
4 SRS and OB to patients with D-IBS.

### 6 *Necessity of the trial*

7 Recently, herbal medicines and western drugs have been co-administered for various  
8 medical therapies. This is particularly true in Korea, where approximately 76% of patients  
9 have used the combination of herbal medicines and western drugs<sup>14</sup>. However, only a few  
10 studies have evaluated the interaction between western and herbal medicines. Despite the  
11 need for combined treatment in patients with various diseases, there are no standard clinical  
12 guidelines or scientific evidence regarding co-administration because of a lack of research  
13 and data.

14 D-IBS is a disease that is difficult to cure and many patients require treatment with both  
15 western and herbal drugs to experience an improvement in their symptoms. Therefore, it is  
16 very important to conduct a clinical study regarding the efficacy and safety of the combined  
17 administration of SRS and OB in patients with D-IBS.

### 19 *Basis of drug selection*

20 According to guidelines for IBS treatment, the OB recommendation level is high (i.e., the  
21 level of evidence is moderate and many experts recommend using it) and it is the most  
22 reasonable treatment option<sup>25</sup>. SRS is the herbal formula used most often by clinical Korean  
23 and Chinese medical doctors for abdominal pain, abdominal discomfort, and chronic diarrhea,  
24 which are typical symptoms of D-IBS<sup>15-17 24</sup>. Based on these studies and clinical applications,  
25 OB and SRS were selected for this trial.

1

## 2 *Hypothesis*

3 We hypothesize the following: (1) that co-administration of SRS and OB will have a more  
4 positive effect on D-IBS symptoms than either SRS or OB alone; (2) that after 8 weeks of  
5 treatment with SRS, OB, or both drugs, the Subject's Global Assessment of Relief and  
6 severity of D-IBS symptoms will be more improved than after treatment with placebo; and (3)  
7 that co-administration of SRS and OB will be safe for patients with D-IBS.

## 8 9 *Design*

10 This study is a placebo-controlled, double-blind trial. Eighty patients will be enrolled and  
11 randomly assigned to four separate arms of the trial. The trial will be conducted at Catholic  
12 Kwandong University International St. Mary's Hospital, Incheon, South Korea.

13 The study subjects will be required to participate in a 2-week preparation period (weeks -2  
14 to 0) and an 8-week drug administration period (weeks 0 to 8). The patients will visit four  
15 times, on weeks 0, 4, 8, and 12. The primary outcome measurement will be evaluated at  
16 weeks 2, 4, 6, 8, and 12, and the secondary outcome measurement will be evaluated at weeks  
17 0, 2, 4, 6, 8, and 12. Participants will be assessed for efficacy and safety of the treatment  
18 through visits (0, 4, 8, 12 weeks) and telephone questionnaires (2, 6 weeks). In addition, lab  
19 tests will be conducted at 0, 4, and 8 weeks. According to the intervention protocols, the  
20 clinical research coordinator (CRC) will encourage patients and participants to complete  
21 follow-up at every visit.

22 During the drug administration period, SRS or its placebo will be given as 1 pack of water  
23 extract granules 3 times a day, 30 min before each meal. OB or its placebo will be given as 1  
24 tablet 3 times a day, 30 min before each meal.

25 Participants will be divided into 4 groups: (1) SRS and OB group; (2) SRS and placebo-

1 OB group; (3) placebo-SRS and OB group; and (4) placebo-SRS and placebo-OB group. The  
2 entire flow chart of the study is shown in Figure 1.

3 The protocol of this trial has been approved by the institutional review board (IRB) and  
4 ethics committee of Catholic Kwandong University International St. Mary's Hospital. The  
5 IRB permission number is IS15MISV0033 and CRIS (Clinical Research Information Service,  
6 www.cris.nih.go.kr) protocol identification number is KCT0001621. In addition, this study  
7 received the first approval given by the Korean Ministry of Food and Drug Safety (KMFDS)  
8 for a study of the co-administration of a conventional drug and a Korean traditional herbal  
9 medicine (approval number: 30769).

10 Potential participants will be provided with sufficient information about the study and only  
11 those who agree to the study protocol and sign the consent form will be enrolled. The study  
12 will be implemented according to Good Clinical Practice and the revised version of the  
13 Declaration of Helsinki.

#### 14 ***Sample size calculation***

15 This trial is a study for a new therapeutic regimen of SRS and OB combination treatment.  
16 In a similar study conducted previously by using co-administration of a probiotics mixture  
17 and an herbal medicine (placebo-controlled, double-blind, and randomly 4-arm), each arm  
18 consisted of at least 15 patients and the total sample size was more than 60 participants<sup>27</sup>. In  
19 other similar studies, clinical trials have been conducted with a total of 60–64 participants,  
20 consisting of 12–30 patients per group<sup>28-30</sup>. Based on these previous studies, the minimal  
21 clinical significance of the trial can be obtained when only 16 participants complete the trial.  
22 Because the drop-out rate is expected to be 20%, each trial group will be made up of at least  
23 20 participants. Therefore, the total sample size must be more than 80 participants.

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4 **1** *Inclusion criteria*

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6 The following patients would be included: (1) patients aged 18–75 years; (2) patients  
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8 satisfying the Rome III criteria of IBS (recurrent abdominal pain or discomfort that began at  
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10 least 6 months before the clinical trial, with a rating of more than 3 on a 10-point scale,  
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12 frequency of at least 3 days/month in the last 3 months, and associated with two or more of  
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14 the following: improvement associated with defecation, onset associated with a change in  
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16 frequency of stools, and onset associated with a change in form of stool)<sup>1 9</sup>; (3) patients  
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18 satisfying the Rome III criteria of IBS, whereby D-IBS type is defined as loose/mushy or  
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20 watery stools—Bristol Stool Form (BSF) Scale 6-7  $\geq$  2 times/week<sup>1 30</sup>; (4) patients with a  
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22 negative urine pregnancy test (in women of a childbearing age, within 7 days before the  
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24 clinical trial) and who consent to using contraception during the administration period; (5)  
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26 patients with the ability to read the symptom questionnaire and understand it; and (6) patients  
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28 who agree with the clinical plan and voluntarily sign the IRB-approved documents.  
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35 **15** *Exclusion criteria*

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37 The exclusion criteria are as follows: (1) chronic liver disease (cirrhosis, chronic hepatitis  
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39 B or C); (2) chronic renal failure or renal impairment (serum creatinine  $\geq$  2 times the upper  
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41 limit of normal); (3) liver dysfunction (AST/ALT  $\geq$  3 times the upper limit of normal); (4)  
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43 diabetes (HbA1c > 8% or not controlled by diet or medication), hypertension ( $\geq$  160/100  
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45 mmHg), thyroid dysfunction (exceptions in the following cases: if the disease is controlled by  
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47 drug administration with a stable dose for 12 weeks before the screening, and the drug dose  
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49 remains constant during the trial period), clinically significant hematologic, cardiac,  
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51 pulmonary, neurological disorders, or other severe systemic disorders; (5) abnormal findings  
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53 on colonoscopy or colonography within the last 5 years; (6) history of surgery that affects  
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55 gastrointestinal motility (i.e., gastrectomy, colonic resection, hysterectomy, except for  
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4 1 appendectomy); (7) GI disease characterized by the following symptoms within 6 months  
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6 2 before the clinical trial: inflammation of or ulcer in the esophagus, stomach, or duodenum;  
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8 3 gastroesophageal reflux disease (at the discretion of the examiner, subjects may enroll if the  
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10 4 disease is chronic and not acute); gastrointestinal bleeding; gastrointestinal stenosis or closure;  
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12 5 infectious diarrhea; inflammatory bowel disease (i.e., Crohn's disease, diverticulitis,  
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14 6 ulcerative colitis, infectious enteritis, ischemic colitis); pancreatic insufficiency; biliary  
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16 7 abscess; (8) mental illness or an addiction to drugs or alcohol; (9) severe systemic organ  
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18 8 diseases such as cancer, autoimmune disease, stroke (although patients in remission for more  
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20 9 than 5 years from a cancer unrelated to the GI tract can participate in the trial); (10)  
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22 10 pregnancy, breastfeeding, and unwillingness to use contraception during the trial; (11) a  
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24 11 history of taking the following drugs within 2 weeks before the trial: antibiotics, analgesics,  
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26 12 antidepressants, anti-anxiety agents, anti-inflammatory agents, anti-ulcer agents, anti-gastric  
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28 13 secretion inhibitors, laxatives, antispasmodics, antacid agents, gastrointestinal stimulants,  
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30 14 prostaglandin agents, and corticosteroids; (12) use of medications that do not match the intent  
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32 15 of this trial or have a clinical interaction with SRS or OB; (13) lactose intolerance (not  
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34 16 controlled by food); (14) glaucoma; (15) participation in other clinical studies within 30 days  
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36 17 prior to clinical screening and have received other clinical trial medications (including  
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38 18 placebo); (16) hypersensitivity to clinical trial medicines; and (17) other reasons considered  
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40 19 inappropriate for participation in clinical trials.  
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### 21 ***Recruitment, randomization, blinding, and unblinding***

22 Advertisements for the study will be posted at the Catholic Kwandong University  
23 International St. Mary's Hospital using banner ads and posters. We also plan to post the  
24 advertisements on the hospital homepage, in the monthly hospital magazine, at the internet  
25 café, and on the subway at least five times. All these advertisements will be done with the

1 approval of the IRB.

2 After recruitment, patients will be randomized to one of the four trial arms. Randomization  
3 will be performed using a list of block randomizations made by statisticians, independent of  
4 this clinical trial. A researcher who is not involved in process of drug prescription and  
5 evaluation will execute the randomization process.

6 During the treatment period, the patients and all researchers (investigators and clinical  
7 research coordinators) will be blinded, except the researchers who conducted the  
8 randomization procedure. In addition, the researchers will not know the kind of medication  
9 that is being administered to the patient or any other information that could lead to bias.

10 Allocation concealment will be performed during the process of medication administration.  
11 The management pharmacist, who will not be involved in analyzing the results of the trial,  
12 will use the randomization table to label the medication with the assignment number and  
13 provide the medication. The patients will take the drugs contained in the opaque envelope,  
14 which will be labeled with the assignment number.

15 Unblinding will be performed only in the following situations: (1) if the trial is terminated  
16 and there is a need for statistical analysis; (2) if a serious medical emergency occurs and  
17 information about the medication is needed; and (3) if the chief investigator determines that  
18 unblinding is necessary.

19 The entire process of the study will be directed by the authorized clinical research  
20 organization (CRO), Dream CIS Corporation, Seoul, Korea.

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## 22 ***Intervention***

23 The herbal formula SRS is commonly used by Korean traditional medical doctors for  
24 treatment of diarrhea and related diseases<sup>13-18</sup>. SRS used in this study (Samryungbaekchulsan  
25 granule®, Hankook shin yak, Co., Ltd., Nonsan, Korea) is extracted with water and mixed



1 with starch and lactose in accordance with Korean Good Manufacturing Practice (K-GMP).  
2 Production of SRS is regulated and allowed by the KMFDS. SRS contains 10 herbs, listed in  
3 Table 1. Placebo-SRS is made from cornstarch and has the same taste, shape, color, and  
4 similar scent as SRS. SRS and placebo-SRS will be sealed in identical aluminum bags with  
5 the same labeling. These herbal drug packages will be distributed by an independent  
6 pharmacist in an isolated room. According to the recommended dosing methods of KMFDS,  
7 after SRS or placebo-SRS is dissolved in boiled water, the subjects will take them 30 min  
8 before each meal (5 g/pack, 3 times a day).

9 OB (Menoctyl Tab®, Dong Hwa Pharm Co., LTD., Seoul, Korea) is a tablet containing  
10 otilonium bromide 40 mg. Placebo-OB is a tablet made of Ludipress with the same taste,  
11 shape, and color as OB. Patients will be instructed to swallow one tablet of OB or placebo-  
12 OB 30 min before each meal over the administration period. The drugs used in the trial (SRS,  
13 OB, placebo-SRS, placebo-OB) have been approved by the KMFDS. Patients will be asked at  
14 the end of the study whether the drugs that they have been taking are either real or placebo, to  
15 measure the success of blinding. Compliance will be confirmed by counting returned SRS  
16 packets or OB tablets. Every patient will be instructed to write down any adverse events  
17 during the administration period and these records will be evaluated at the follow-up. At the  
18 patient visits (at 0, 4, and 8 weeks), we will perform a check of vital signs, physical  
19 examination, electrocardiogram, and laboratory tests to evaluate safety for the patients. All  
20 side effects will be reported to the investigator.

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**Table. 1 Ingredients in the herbal formula Samryungbaekchulsan (SRS)**

Scientific name	Part used	Grams/day
Atractylodis Rhizoma Alba	Root	3.0
Poria Sclerotium	Dried core	4.0
Rhizoma Dioscoreae	Root	3.0
Glycyrrhizae Radix et Rhizoma	Root	1.5
Semen Coicis	Seed	8.0
Semen Nelumbinis	Fruit	4.0
Platycodonis Radix	Root	2.5
Dolichoris Semen	Seed	4.0
Amomi Fructus	Fruit	2.0
Ginseng Radix	Root	3.0

### ***Rescue therapy and concomitant medications***

Participants are prohibited from taking any medication that could affect D-IBS during the entire course of the trial. However, if serious side effects occur or symptoms worsen, investigators will provide quick and appropriate treatment (including drug administration), based on their medical judgement. In this case, the direct investigators will record the treatment or drug administration and report to the IRB within 24 h to determine whether the trial should be continued or discontinued.

### ***Outcome Measurements***

#### ***Primary outcome***

The primary outcome will be measured via a questionnaire that confirms subjective

1 symptom improvement. Participants will respond a total of five times during and after the  
2 administration period (at 2 and 6 weeks via telephone, and at 4, 8, and 12 weeks during direct  
3 visits) to the following question: Subject's Global Assessment of Relief; "How much do you  
4 think the symptoms of D-IBS have improved compared to before the clinical trial?"  
5 According to the answers given by the patients to this survey, the improvement is given a  
6 score of 0, 1, 2, 3, or 4.

### 7 8 *Secondary outcomes*

9 At 2, 4, 6, 8, and 12 weeks from the start of the treatment period, patients will be assessed  
10 for severity of D-IBS symptoms (abdominal pain, abdominal discomfort, satisfaction of  
11 defecation, frequency of abdominal pain, quality of life) using a Likert scale ranging from 0  
12 to 10<sup>31</sup>. Patients will also be instructed to record the number of defecations per day, BSF, and  
13 the degree of force used in bowel movements at 0, 2, 4, 6, 8, and 12 weeks<sup>32</sup>.

### 14 15 *Safety assessments*

16 The investigator will record all adverse events that occur during the trial along with any  
17 concomitant medications in the case reports. When an adverse event occurs, the investigator  
18 will record the symptoms and signs of the adverse reaction, the duration (start and end date),  
19 severity, course, outcome, significance, causality by the trial drug, and any action taken in  
20 relation to the adverse event. In the case of concomitant medicines, composition, dosage,  
21 duration of administration, and reason for medication will be recorded in detail. Symptoms  
22 that existed before the start of the clinical trial will not be recorded as adverse events.

### 23 24 *Laboratory tests*

25 The purpose of laboratory tests in this study is to evaluate the safety and pharmacokinetic

1 profiles of SRS and OB. Because of the small number of patients assigned to this study and  
2 the different baseline values for each individual patient, we will not perform a detailed  
3 statistical analysis. However, if significant abnormal results are found in the laboratory tests,  
4 the clinical laboratory results will be described and the connection to the drug will be  
5 considered.

6 Blood tests will be conducted at 0, 2, 4, and 8 weeks and urine tests will be performed at  
7 0 and 4 weeks during the clinical trial. In the case of a participant who drops out or the early  
8 termination of the clinical trial, blood and urine tests will be performed on the last day of the  
9 trial.

10 Using the test results (comprehensive verification of vital signs, laboratory tests,  
11 electrocardiograms, and physical examinations) for each individual patient, the investigator  
12 will determine adverse reactions caused by the drugs and statistical tests will be conducted as  
13 needed on clinically significant parameters.

#### 14 *Test of human derivatives*

15 IBS is known to be closely related to stress<sup>12</sup>. Therefore, we plan to quantify factors  
16 associated with stress or that have been reported to worsen IBS symptoms as follows: 1)  
17 cortisol; 2) corticotropin-releasing hormone (CRH); 3) serotonin; 4) group I cytokines (10  
18 species); 5) group II cytokines (14 species); and 6) growth factors (3 species)<sup>33 34</sup>. Serum will  
19 be separated from blood specimens collected at 0, 4, 8 weeks, stored frozen, and transferred  
20 to the Korea Institute of Oriental Medicine (KIOM) for examination.

#### 21 *Early termination or dropout*

22 The criteria for early termination or dropout are as follows: 1) administration of other  
23 drugs that are expected to affect the safety and efficacy of the clinical trial drugs; 2) request

1 of participants to discontinue the clinical trial, or withdrawal of the trial agreement; 3)  
2 occurrence of significant adverse drug reactions or events that preclude continuing the trial,  
3 according to the judgment of the clinical investigator; 4) new discovery of violations of  
4 significant clinical trial protocol during clinical trial; 5) less than 70% trial drug compliance;  
5 and 6) any other reason that the clinical trial should be discontinued at the discretion of the  
6 clinical trial manager or investigator.

#### *Data collection, access, and management*

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8  
9 The data of this trial will be managed according to the standard work instructions of  
10 Catholic Kwandong University International, St. Mary's Hospital. Other contents not  
11 specified in the trial protocol shall follow the standards of The International Conference on  
12 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human  
13 Use (ICH) Guideline for Good Clinical Practice (GCP) and Korean Good Clinical Practice  
14 (KGCP) guideline.

15 The source document is recorded immediately when the data are collected. After the source  
16 document input is completed, it will be recorded in the case record form (CRF). All the  
17 documents will be kept safe, so that the data can be verified by the relevant government  
18 agencies and the IRB. Only research colleagues and others who have been approved by the  
19 principle investigator will have access to all data obtained from this trial.

#### *Statistical analysis*

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21  
22 The statistical analysis will be conducted by blinded professional statisticians. To evaluate  
23 the efficacy of the study, both an intent-to-treat (ITT) analysis (primary analytical method)  
24 and a per-protocol (PP) analysis (secondary analytical method) will be performed. The ITT  
25 analysis will be conducted for all patients who were followed up at least once after

1 randomization and will be able to be evaluated for effectiveness. The PP analysis will be  
2 performed for patients who complete the 8-week treatment course and meet the inclusion and  
3 exclusion criteria.

4 To analyze the continuous variables in the demographic information and pre-treatment  
5 characteristics between groups, a one-way analysis of variance (ANOVA) and Kruskal-Wallis  
6 test will be conducted. An ANOVA and Kruskal-Wallis test will also be used to test for  
7 symptom improvement compared to baseline (0 week) and the variables for analysis that  
8 include the following: (1) subjective symptom improvement (primary outcomes); and (2)  
9 severity of symptoms related to D-IBS (abdominal pain, abdominal discomfort, satisfaction  
10 of defecation, frequency of abdominal pain, quality of life). All values will be shown as mean  
11  $\pm$  standard error of the mean (SEM). Comparisons of outcome assessments between the four  
12 groups will be performed using the paired t-test or Wilcoxon signed-rank test.

13 If the Subject's Global Assessment of Relief on the Likert scale is "0" or "1" for more than  
14 2 weeks between weeks 8 and 12, then the symptoms will be considered to have improved  
15 sufficiently. Based on this, we will calculate the symptom relief rate by dividing the number  
16 of participants who exhibited sufficient symptom relief by the total number of participants in  
17 the trial and present descriptive statistics. The CATMOD procedure will be used to evaluate  
18 the relief rate improvement of symptoms compared with baseline. Comparisons between the  
19 four groups will be conducted using the chi-square test or Fisher's exact test. These statistical  
20 analyses will also be performed at 2, 4, 6, 8, and 10 weeks from baseline. The Cochran-  
21 Mantel-Haenszel (CMH) test will be used to confirm the difference between the intervention  
22 groups at each time-point.

23 A statistical analysis will also be conducted to evaluate safety. The incidence of adverse  
24 events and abnormality of experimental results will be analyzed statistically according to the  
25 groups and non-parametric methods will be applied as necessary using a paired t-test for

1 continuous data, McNemar's test for categorical data, Fisher's exact test for adverse events,  
2 and a generalized estimating equation for clinically significant changes between groups.

3 All statistical analysis will be conducted using SAS software, version 9.1.3 (SAS institute,  
4 Cary, NC). A P-value < 0.05 will be considered statistically significant.

### 5 6 *Quality control and data monitoring*

7 To ensure the results and quality of the clinical trial, assessments and monitoring will be  
8 performed by the CRO, DreamCIS Corporation (Seoul, Korea), which is independent from  
9 the sponsor and competing interests. During the trial, the CRO will regularly monitor whether  
10 the study is proceeding in accordance with the protocol through the use of all related  
11 documentation, including trial master files, case report forms, informed consent forms, and  
12 adverse event reports.

## 13 14 **DISCUSSION**

15 Herbal medicine is a recognized effective treatment method based on clinical experience  
16 accumulated over thousands of years and more recently gained attention as an alternative  
17 therapy for treating various diseases that are difficult to treat or have unknown causes, such  
18 as IBS<sup>5 7 10 26 35</sup>. SRS is frequently used for abdominal pain and diarrhea in Korean and  
19 Chinese traditional medicine. According to experimental research, SRS has an anti-  
20 cholinergic effect that improves intestinal digestion and absorption and inhibits intestinal  
21 movement, resulting in the prevention of diarrhea and abdominal pain<sup>13</sup>. In addition, clinical  
22 studies have shown that the use of SRS in patients with D-IBS is effective for improving  
23 diarrhea<sup>36 37</sup>. Some studies have reported that co-administration with SRS and trimebutine  
24 maleate or SRS and paroxetine is more effective than trimebutine maleate alone for the  
25 improvement in IBS symptoms<sup>15 16 25</sup>. Other studies have reported that SRS exerted more

1 beneficial effects on IBS patients compared with Smecta or probiotics<sup>17 37</sup>.

2 However, although there is a growing interest in the use of herbal medicines such as SRS  
3 in IBS and related studies are continuously being published, there have been only a few well-  
4 designed RCTs<sup>22 23 26</sup>. To overcome the limitations of the previous studies, this trial was  
5 designed as a double-blind, double-dummy, four-arm, parallel-group RCT. The efficacy of  
6 SRS will be evaluated via the Subject's Global Assessment of Relief and the improvement in  
7 symptoms associated with bowel movements and abdominal pain. The results of these  
8 assessments are expected to provide distinct clinical evidence for the use of SRS in D-IBS  
9 treatment.

10 OB is a representative conventional medicine used for D-IBS treatment<sup>8 21 23 38 39</sup>. It is a  
11 spasmolytic agent that exerts its activity primarily in the distal GI tract through the inhibition  
12 of Ca<sup>++</sup> flux and direct activation of contractile proteins in the smooth muscle<sup>20 21</sup>. OB has  
13 also been shown to reduce hyper-motility and modulate visceral sensation, the effect of which  
14 is to improve D-IBS symptoms<sup>39 40</sup>. RCTs using OB for the treatment of D-IBS have been  
15 conducted. In these studies, treatment with OB resulted in a greater improvement in  
16 symptoms related to D-IBS (defecation frequency, regular intestinal habits, reductions in  
17 frequency of diarrhea, abdominal pain and discomfort, severity of abdominal bloating) and  
18 better protection from symptom relapse compared to placebo<sup>22 23 38</sup>.

19 IBS is a disease with a high rate of progression and frequent recurrence. For this reason,  
20 patients with IBS often require a variety of treatment methods<sup>2 6 10</sup>. Among these methods, the  
21 combination of herbal and conventional drugs is widely used and is more effective for  
22 improving IBS symptoms than conventional drugs alone<sup>2 35</sup>. However, there are several  
23 limitations to the co-administration of herbal and conventional drugs in IBS. Specifically,  
24 there is a high risk of bias in related studies and there are insufficient clinical guidelines  
25 regarding the interaction of herbal and conventional drugs in D-IBS, including SRS and OB.



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4 1 Therefore, it is necessary to perform well-designed RCTs to evaluate the co-administration of  
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6 2 herbal and conventional drugs.  
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9 3 Because only a few studies have evaluated the combination of herbal and conventional  
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11 4 drugs, our proposed study will significantly contribute to overcoming the limitations of  
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13 5 previous studies and provide basic medical evidence for the co-administration of SRS and  
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15 6 OB for D-IBS treatment. Therefore, this RCT has several characteristic features. First, this  
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17 7 trial will be the first to investigate the efficacy of SRS and OB combination therapy for D-  
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19 8 IBS. The results of previous studies suggested that the combination of OB and SRS will  
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21 9 improve two major D-IBS symptoms at the same time: abdominal pain and discomfort (major  
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23 10 effect of OB) and diarrhea (main effect of SRS). This study will assess this hypothesis and  
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25 11 provide a basis for the use of SRS and OB combination therapy for D-IBS. Second, the  
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27 12 participants in this trial will be grouped into four arms, making it possible to compare the  
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29 13 efficacy of combined treatment with the efficacy of each individual treatment. Third, this trial  
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31 14 will evaluate the safety of the subjects using several assessments, including a periodic  
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33 15 assessment of subjective symptoms, physical measurements, and laboratory testing. The  
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35 16 results of the safety analysis may provide evidence for the safety of treatment with the  
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37 17 combination of herbal and conventional drugs in D-IBS. Fourth, this trial was the first clinical  
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39 18 study related to combination treatment with western and traditional herbal medicine in Korea  
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41 19 to receive approval from the KMFDS. Through the systematic management of the trial under  
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43 20 the auspices of the KMFDS, a high quality trial will be performed and the results of this study  
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45 21 will provide information for use in further clinical applications.  
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51 22 Although our trial is designed with a small sample size, it has a creative and systematic  
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53 23 research design and the results will be useful basic clinical evidence in the field of integrated  
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55 24 herbal and conventional drugs for the management of D-IBS.  
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## 1 **Trial status**

2 The research plan and design began in April 2015.

3 The study received the IRB's final approval after two deliberations. The first submission  
4 date was July 01, 2015; the result was a request for revision and supplementation, which was  
5 received on July 13, 2015. We filed an application for re-review on August 06, 2015,  
6 supplemented with the relevant information, and received the IRB's final approval on August  
7 10, 2015. We also requested that the KMFDS review the trial plan on September 14, 2015  
8 and received approval for the clinical research on December 21, 2015.

9 The first participant was randomized on March 29, 2016. Recruitment for the study is  
10 ongoing. The primary completion date for this trial is anticipated to be December 31, 2017,  
11 and the study completion date is expected to be February 28, 2018.

## 13 **Ethics**

### 14 *Research ethics approval*

15 This trial was approved by the IRB and ethics committee of Catholic Kwandong  
16 University International St. Mary's Hospital (approval number IS15MISV0033) and the  
17 KMFDS (approval number 30769).

### 19 *Protocol amendments*

20 An investigator who wishes to change the protocol of the clinical trial plan should first  
21 discuss it with the trial director. Thereafter, the examiner should obtain prior approval from  
22 the IRB for changes to the protocol (except to prevent immediate injury to the patient, in  
23 which case it will be reported to the IRB later). However, when a dangerous situation occurs  
24 and immediate treatment is needed, the investigator may report the protocol change to the  
25 IRB at a later time.

1

## 2 *Consent*

3 Patients recruited through the announcement will receive a full explanation of the details of  
4 the trial in an easy-to-understand manner. The patients and investigators will have a mutual  
5 question and answer time before the patient is asked to sign the clinical trial consent. Through  
6 these processes, if the patient agrees to participate in the trial, a signed consent form will be  
7 obtained.

8

## 9 *Confidentiality*

10 All patient information will be anonymized with initials or symbols and all related  
11 investigators will keep the trial results confidential. The trial director will keep the signed  
12 consent forms and prepare a list that will be used to confirm the patient identities.

13

## 14 *Post-trial care*

15 If the patients experience unexpected accidents or injuries, appropriate compensation will  
16 be made by the Federal Insurance Company Korea (12th Floor Ferrum Tower 66 Suha-Dong  
17 Jung-gu Seoul, 100210, South Korea), according to the patient compensation rules of the trial.  
18 Additionally, in the case of an emergency, the patients will receive appropriate medical care  
19 at the Catholic Kwandong University International, St. Mary's Hospital.

20

## 21 **Dissemination**

22 The results of the trial will be disseminated through a peer-reviewed journal and/or  
23 conference presentations.

24

## 25 **Contributors**

1 Joong Il Kim, Pumsoo Kim, Jin-Hyun Lee, and Jung-Han Lee contributed to the protocol  
2 design and writing of the manuscript. Hyekyung Ha is responsible for monitoring the process  
3 of the trial. Na-rae Yang, Yoo-Jin Kim, Myong Ki Baeg, Ja Sung Choi, Hye-Jung Kim, Ja-  
4 Young Kim and Yun-Young Sunwoo provide advice on the process of the trial. Tae-Yong  
5 Park is responsible for writing the manuscript and also managing and supervising the clinical  
6 research. All authors approved the final manuscript.

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10 Formulas (K15250)” grant from the Korea Institute of Oriental Medicine (KIOM).  
11 (Telephone: +82-42-868-9513)

### 13 **Competing interests**

14 The authors have no competing interests to declare.

### 16 **Ethics approval**

17 This trial has been approved by the IRB and ethics committee of Catholic Kwandong  
18 University International St. Mary’s Hospital (approval number IS15MISV0033).

### 20 **Provenance and peer review**

21 Not commissioned; externally peer reviewed.

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## 8 REFERENCES

- 9 1. Drossman DA. Introduction. The Rome Foundation and Rome III. *Neurogastroenterol*  
10 *Motil* 2007;19(10):783-6. doi: 10.1111/j.1365-2982.2007.01001.x
- 11 2. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment:  
12 an update for health-care practitioners. *J Gastroenterol Hepatol* 2010;25(4):691-9. doi:  
13 10.1111/j.1440-1746.2009.06120.x
- 14 3. Maxison-Bergemann S, Thielecke F, Abel F, et al. Costs of irritable bowel syndrome in the  
15 UK and US. *Pharmacoeconomics* 2006;24(1):21-37.
- 16 4. Soares RL. Irritable bowel syndrome: a clinical review. *World J Gastroenterol*  
17 2014;20(34):12144-60. doi: 10.3748/wjg.v20.i34.12144
- 18 5. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based  
19 medicine. *World J Gastroenterol* 2014;20(22):6759-73. doi:  
20 10.3748/wjg.v20.i22.6759
- 21 6. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*  
22 2015;313(9):949-58. doi: 10.1001/jama.2015.0954
- 23 7. Boeckxstaens G, Corazziari ES, Mearin F, et al. IBS and the role of otilonium bromide. *Int*  
24 *J Colorectal Dis* 2013;28(3):295-304. doi: 10.1007/s00384-012-1598-0
- 25 8. Boeckxstaens G, Clave P, Corazziari ES, et al. Irritable bowel syndrome: focus on

- 1  
2  
3  
4 1 otilonium bromide. *Expert Rev Gastroenterol Hepatol* 2014;8(2):131-7. doi:  
5  
6 2 10.1586/17474124.2014.869477  
7  
8  
9 3 9. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders.  
10  
11 4 *Gastroenterology* 2006;130(5):1480-91. doi: 10.1053/j.gastro.2005.11.061  
12  
13 5 10. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel  
14  
15 6 syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med*  
16  
17 7 2000;133(2):136-47.  
18  
19 8 11. Liu JP, Yang M, Liu YX, et al. Herbal medicines for treatment of irritable bowel  
20  
21 9 syndrome. *Cochrane Database Syst Rev* 2006(1):CD004116. doi:  
22  
23 10 10.1002/14651858.CD004116.pub2  
24  
25 11 12. Palsson OS, Drossman DA. Psychiatric and psychological dysfunction in irritable bowel  
26  
27 12 syndrome and the role of psychological treatments. *Gastroenterol Clin North Am*  
28  
29 13 2005;34(2):281-303. doi: 10.1016/j.gtc.2005.02.004  
30  
31 14 13. Song DS, Ryu BH, Park DW, et al. Experimental studies on the efficacy of  
32  
33 15 Samryungbaekchulsan. *J Korean Med* 1993;14(1):179-95.  
34  
35 16 14. Park JK, Choi SY, Koh KW, et al. Combined utilization with herbal products and  
36  
37 17 prescribed drugs: A result from health examinee-based national survey. *Korean J*  
38  
39 18 *Health Policy Adm* 2006;16(1):1-16.  
40  
41 19 15. Duan W. Observation of sixty-five cases on Irritable Bowel Syndrome treated by  
42  
43 20 Trimebutine and Shenlingbaizhu-san granule [Chinese]. *Journal of Practical*  
44  
45 21 *Traditional Chinese Medicine* 2010;26(5):320.  
46  
47 22 16. Chen Y. Clinical observation of irritable bowel syndrome treated by shenlingbaizhu-san  
48  
49 23 granule and trimebutine [Chinese]. *Journal of Practical Traditional Chinese Medicine*  
50  
51 24 2011;27(5):318-9.  
52  
53 25 17. Li Z, Jiang J. Clinical observation of 80 cases on diarrhea - predominant irritable bowel  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 1 syndrome treated by Shenlingbaizhu-san granule [Chinese]. *Guiding Journal of*  
5  
6 2 *Traditional Chinese Medicine and Pharmacy* 2013;20(5):41-2.  
7  
8  
9 3 18. Shin B, Lee B. Frequency Analysis of Clinical Prescriptions in the Korean Medicine  
10  
11 4 Hospital, Pusan National University based on Herb Weight Ratio(2) - Focusing on  
12  
13 5 Prescriptions of Herbal Formula Study Textbook[Korean]. *Herbal Formula Science*  
14  
15 6 2015;23(1):77-89. doi: dx.doi.org/10.14374/HFS.2015.23.1.077  
16  
17 7 19. Martinez-Cutillas M, Gil V, Gallego D, et al. Mechanisms of action of otilonium bromide  
18  
19 8 (OB) in human cultured smooth muscle cells and rat colonic strips.  
20  
21 9 *Neurogastroenterol Motil* 2013;25(12):e803-12. doi: 10.1111/nmo.12206  
22  
23  
24 10 20. Traini C, Cipriani G, Evangelista S, et al. Chronic treatment with otilonium bromide  
25  
26 11 induces changes in L-type Ca(2)(+) channel, tachykinins, and nitric oxide synthase  
27  
28 12 expression in rat colon muscle coat. *Neurogastroenterol Motil* 2013;25(11):e728-39.  
29  
30 13 doi: 10.1111/nmo.12197  
31  
32  
33 14 21. Traini C, Evangelista S, Girod V, et al. Repeated otilonium bromide administration  
34  
35 15 prevents neurotransmitter changes in colon of rats underwent to wrap restraint stress.  
36  
37 16 *J Cell Mol Med* 2017;21(4):735-45. doi: 10.1111/jcmm.13016  
38  
39  
40 17 22. Chmielewska-Wilkon D, Reggiardo G, Egan CG. Otilonium bromide in irritable bowel  
41  
42 18 syndrome: a dose-ranging randomized double-blind placebo-controlled trial. *World J*  
43  
44 19 *Gastroenterol* 2014;20(34):12283-91. doi: 10.3748/wjg.v20.i34.12283  
45  
46 20 23. Clave P, Acalovschi M, Triantafillidis JK, et al. Randomised clinical trial: otilonium  
47  
48 21 bromide improves frequency of abdominal pain, severity of distention and time to  
49  
50 22 relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*  
51  
52 23 2011;34(4):432-42. doi: 10.1111/j.1365-2036.2011.04730.x  
53  
54  
55 24 24. Kwon JG, Park KS, Park JH, et al. [Guidelines for the treatment of irritable bowel  
56  
57 25 syndrome]. *Korean J Gastroenterol* 2011;57(2):82-99.  
58  
59  
60

- 1  
2  
3  
4 1 25. Li C, Zuo M, Wang L, et al. Clinical observation of diarrhea - predominant irritable bowel  
5  
6 2 syndrome treated by Shenlingbaizhu-san and Paroxetine [Chinese]. *Chinese Journal*  
7  
8 3 *of Traditional Medical Science and Technology* 2010;17(2):154-5.  
9  
10  
11 4 26. Leung WK, Wu JC, Liang SM, et al. Treatment of diarrhea-predominant irritable bowel  
12  
13 5 syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled  
14  
15 6 trial. *Am J Gastroenterol* 2006;101(7):1574-80. doi: 10.1111/j.1572-  
16  
17 7 0241.2006.00576.x  
18  
19  
20 8 27. Ko SJ, Han G, Kim SK, et al. Effect of korean herbal medicine combined with a probiotic  
21  
22 9 mixture on diarrhea-dominant irritable bowel syndrome: a double-blind, randomized,  
23  
24 10 placebo-controlled trial. *Evid Based Complement Alternat Med* 2013;2013:824605.  
25  
26 11 doi: 10.1155/2013/824605  
27  
28  
29 12 28. Whitehead AL, Julious SA, Cooper CL, et al. Estimating the sample size for a pilot  
30  
31 13 randomised trial to minimise the overall trial sample size for the external pilot and  
32  
33 14 main trial for a continuous outcome variable. *Stat Methods Med Res* 2016;25(3):1057-  
34  
35 15 73. doi: 10.1177/0962280215588241  
36  
37  
38 16 29. Cha BK, Jung MS, Choi CH, et al. The effect of a multispecies probiotic mixture on the  
39  
40 17 symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a  
41  
42 18 randomized, double-blind, placebo-controlled trial. *J Clin Gastroenterol*  
43  
44 19 2012;46(3):220-7. doi: 10.1097/MCG.0b013e31823712b1  
45  
46  
47 20 30. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a  
48  
49 21 probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating.  
50  
51 22 *Neurogastroenterol Motil* 2005;17(5):687-96. doi: 10.1111/j.1365-2982.2005.00695.x  
52  
53  
54 23 31. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a  
55  
56 24 disease-specific quality-of-life questionnaire. *Am J Gastroenterol* 2000;95(4):999-  
57  
58 25 1007. doi: 10.1111/j.1572-0241.2000.01941.x  
59  
60



- 1  
2  
3  
4 1 32. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand*  
5  
6 2 *J Gastroenterol* 1997;32(9):920-4. doi: 10.3109/00365529709011203  
7  
8  
9 3 33. Sugaya N, Izawa S, Saito K, et al. Effect of prolonged stress on the adrenal hormones of  
10  
11 4 individuals with irritable bowel syndrome. *Biopsychosoc Med* 2015;9(1):4. doi:  
12  
13 5 10.1186/s13030-015-0031-7  
14  
15 6 34. Fadgyas-Stanculete M, Buga AM, Popa-Wagner A, et al. The relationship between  
16  
17 7 irritable bowel syndrome and psychiatric disorders: from molecular changes to  
18  
19 8 clinical manifestations. *J Mol Psychiatry* 2014;2(1):4. doi: 10.1186/2049-9256-2-4  
20  
21 9 35. Shi J, Tong Y, Shen JG, et al. Effectiveness and safety of herbal medicines in the  
22  
23 10 treatment of irritable bowel syndrome: a systematic review. *World J Gastroenterol*  
24  
25 11 2008;14(3):454-62.  
26  
27  
28 12 36. Zhong Y, Wu Y. Forty cases of diarrhea - predominant irritable bowel syndrome treated  
29  
30 13 by Shenlingbaizhu-san granule and Montmorillonite powder [Chinese]. *Jiangxi*  
31  
32 14 *Journal of Traditional Chinese Medicine* 2013;44(7):45-6.  
33  
34  
35 15 37. Xiong B. Thirty cases of irritable bowel syndrome treated by Shenlingbaizhu-san granule  
36  
37 16 and Probiotics [Chinese]. *Jiangxi Journal of Traditional Chinese Medicine*  
38  
39 17 2011;42(5):22-3.  
40  
41  
42 18 38. Battaglia G, Morselli-Labate AM, Camarri E, et al. Otilonium bromide in irritable bowel  
43  
44 19 syndrome: a double-blind, placebo-controlled, 15-week study. *Aliment Pharmacol*  
45  
46 20 *Ther* 1998;12(10):1003-10.  
47  
48  
49 21 39. Evangelista S. Otilonium bromide: a selective spasmolytic for the gastrointestinal tract. *J*  
50  
51 22 *Int Med Res* 1999;27(5):207-22. doi: 10.1177/030006059902700501  
52  
53 23 40. Giachetti A. Pharmacological studies on otilonium bromide. *Ital J Gastroenterol*  
54  
55 24 1991;23(8 Suppl 1):56-9.  
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4 **1 Figure legend**

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6 **2 Figure 1.** Flow chart of Trial. GIIM: Gastrointestinal internal medicine, FM: Family  
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8 medicine, D-IBS: diarrhea-irritable bowel syndrome, P: placebo, OB: otilonium bromide,  
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11 **4 SRS:** Samryungbaekchulsan  
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For peer review only

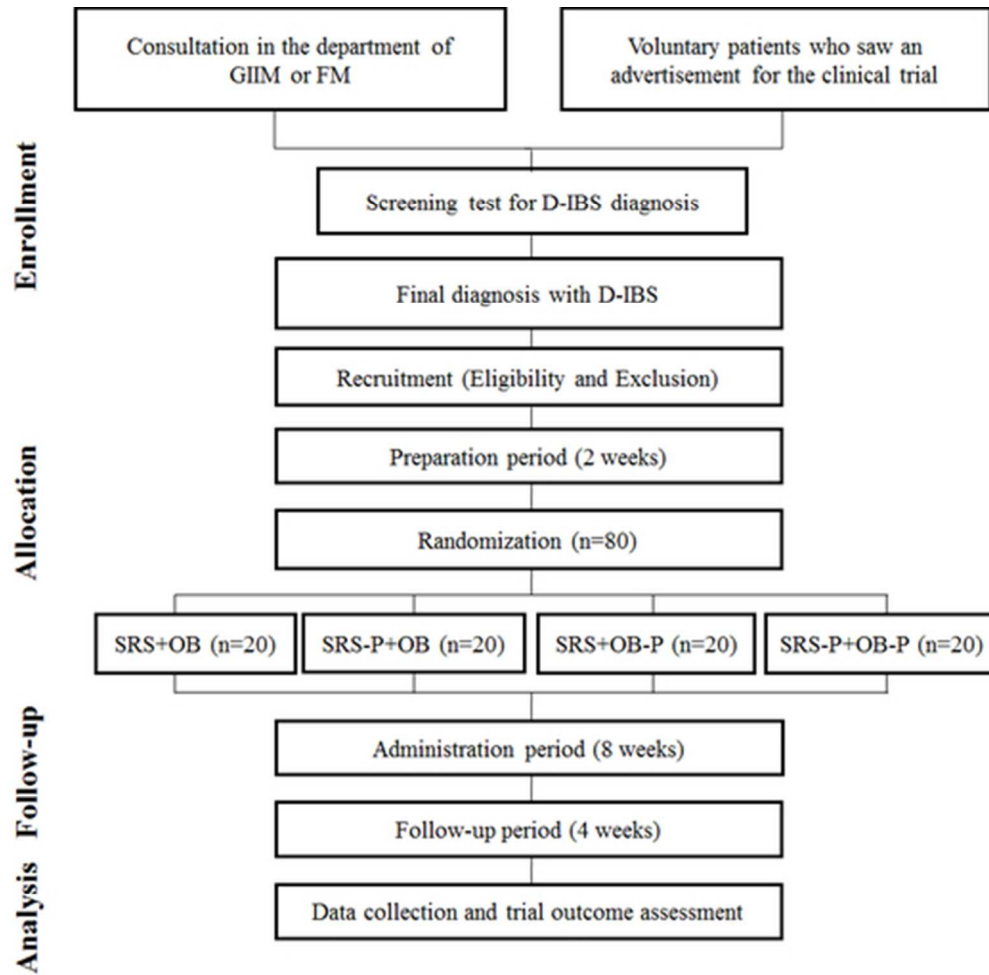


Figure 1. Flow chart of Trial. GIIM: Gastrointestinal internal medicine, FM: Family medicine, D-IBS: diarrhea-irritable bowel syndrome, P: placebo, OB: otilonium bromide, SRS: Samryungbaekchulsan

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>P1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>P4</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Attachment</u>
Protocol version	3	Date and version identifier	<u>P4</u>
Funding	4	Sources and types of financial, material, and other support	<u>P1, P24</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>P1, P23</u>
	5b	Name and contact information for the trial sponsor	<u>P1, P24</u>
	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	<u>N/A</u>
	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)	<u>P8-9, P11-13, P17-19</u>

## 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	<u>P5-6</u>
	6b	Explanation for choice of comparators	<u>P6</u>
Objectives	7	Specific objectives or hypotheses	<u>P7-8</u>
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)	<u>P8-9</u>

## 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	<u>P8</u>
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)	<u>P9-12</u>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>P12-14</u>
	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)	<u>P14-17</u>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>P14-17,19</u>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>P14</u>
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	<u>P14-16</u>
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)	<u>P8-9, Figure1</u>

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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 P9

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size P11-12

**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 P11-12

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 P12

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P11-12

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P11-12

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial P11-12

**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 P17-19

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 P8-9

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3	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	<u>P17,19</u>
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7	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	<u>P17-19</u>
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>P17-19</u>
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12		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)	<u>P17-19</u>
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16	<b>Methods: Monitoring</b>			
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18	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	<u>P19</u>
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23		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	<u>P17,19</u>
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26	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	<u>P15-17</u>
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>P19</u>
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33	<b>Ethics and dissemination</b>			
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35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>P3, P22</u>
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38	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)	<u>P22</u>
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>P22-23</u>
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>N/A</u>
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9	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	<u>P23</u>
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>P24</u>
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15	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	<u>P17</u>
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18	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	<u>P23</u>
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21	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	<u>P3, 23</u>
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
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28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
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30	<b>Appendices</b>			
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32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>Attachment</u>
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35	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	<u>P15-16</u>
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.