A placebo-controlled, crossover trial to investigate the efficacy of Tiotropium Bromide or Placebo added to usual care in stable symptomatic post-Hematopoietic Stem Cell Transplantation (HSCT) Bronchiolitis Obliterans Syndrome (BOS)

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Abstract

Background:

Despite the fundamental progress in Hematopoietic stem cell transplant, this treatment is also associated with complications. Graft versus Host Disease is a possible complication of HSCT. Bronchiolitis obliterans syndrome (BOS) is the pulmonary form of this syndrome. Due to the high morbidity and morbidity rate of BOS, various studies have been conducted in the field of drug therapy for this syndrome, although no standard treatment has yet been proposed. According to the hypotheses about the similarities between BOS and chronic obstructive pulmonary disease, the idea of using tiotropium bromide as a bronchodilator has been proposed.

Method/design:

A randomized, double-blind, placebo-controlled, and crossover clinical trial is being conducted to evaluate the efficacy of tiotropium in patients with BOS. A total of 20 patients with BOS, were randomly assigned (1:1) to receive a once-daily inhaled capsule of either Tiotropium bromide (KP-Tiova Rotacaps 18 mcg; Cipla; India) or placebo for 1 month. Patients will receive Tiotropium Bromide or placebo Revolizer added to usual standard care. Measurements will include spirometry, six-minute walking test.

Ethics/dissemination:

This study was approved by the Research Ethics Committees of Imam Khomeini Hospital Complex, Tehran University of Medical science. Recruitment started in September 2022, with 20 patients randomized. The treatment follow-up of participants with Tiotropium is currently ongoing and is due to finish in December 2023. The authors will disseminate the findings in peer-reviewed publications, conferences and seminar presentations.

Trial registration: Iranian registry of clinical trial

IRCT registration number: IRCT20200415047080N3

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Background

Pulmonary complications account for more than 90% of mortality after Bone Marrow Transplant (BMT). Bronchiolitis obliterans syndrome (BOS) is one of them, which is defined as the pulmonary form of Graft versus Host Disease (GVHD). Due to Post Bone Marrow Transplant BOS (PBMTBOS), high morbidity and morbidity rate, various studies have been conducted in the field of drug therapy (1), although no standard treatment has yet been proposed (2, 3).

Different treatments have been investigated for this disease, but if new bronchiolitis obliterans has been diagnosed, azithromycin along with immunosuppressant and adjustment of the immunosuppressant regimen, is one of the therapeutic strategies (2–9).

Systemic corticosteroids, along with other immunosuppressive drugs, are known as the core of treatment in BOS (2). Clinical studies conducted so far have not seen a significant effect on the treatment of patients by adding azathioprine, mycophenolate, thalidomide, and hydroxychloroquine (11–13). On the other hand, in a 2002 study of Koc et al, concluded the use of cyclosporine as corticosteroid sparing can be considered (14).

Bergeron et al., in 2014, in a randomized double-blind clinical trial on PBMTBOS, evaluated the possible effect of budesonide/formoterol in these patients. In this study of, the FEV1 saw an increase in the treatment group (15).

In another study conducted in 2005 by Khalid et al., the effect of azithromycin on PBMTBOS was evaluated. Based on the results of this study, patients showed an increase in forced vital capacity and FEV1 compared to baseline (16). Also, in another study conducted by Vos et al., in Post Lung Transplant BOS (PLTBOS), the results showed that long-term use of azithromycin can reduce the rate of drop in FEV1 in patients (17).

Williams and colleagues evaluated the effect of fluticasone/azithromycin/montelukast regimens in a 2016 study on patients with PBMTBOS. The study reported significant improvements in FEV1, functional status and life satisfaction in patients (18).

Due to the different possible processes in disease pathogenesis, several studies have investigated the role of TNF-alpha inhibitors as well as drugs such as Imatinib and Ruxolitinib (2). In a study conducted by Zeiser et al. on 41 patients with chronic GVHD on the efficacy of Ruxolitinib, the results of the study showed an improvement in respiratory symptoms in 4 patients with respiratory GVHD in this study (19). In another study by Olivieri and colleagues on the possible benefits of Imatinib on the treatment of 19 patients with chronic GVHD, 7 out of 11 patients with pulmonary involvement showed improvement in respiratory function. (20).

Few studies evaluated the effect of tiotropium in the treatment of BOS. In 2014, Kawassaki and colleagues investigated the possible impact of tiotropium bromide on the treatment of patients with secondary constrictive bronchiolitis due to various causes. In this study, 11 patients with constrictive bronchiolitis were treated with tiotropium bromide for an average of 21 days (with a minimum treatment period of 14 days) and spirometry tests were evaluated before and after treatment in the patients. According to the results of this study, FEV1 saw a rise. Also, FVC levels increased, although no significant difference was observed in FEV1/FVC levels. This study was conducted without a control group and the results were only compared before and after the intervention (21).

Bronchiolitis obliterans (BO) is believed to be caused for a myriad of reasons like infection, post-toxin exposure, post HSCT and post lung transplant. Following the data, however, somehow in PLTBOS, fibrosis might be made and the treatment might be different. But general speaking, BO refers to the small-airway epithelial cells and subepithelial structures changes which cause excessive fibroproliferation due to aberrant tissue repair. The disease is mentioned to cause air trapping, mosaic attenuation, and hyperinflation and defined as an obstructive pulmonary function. The disease is pure obliteration of the small airways (< 2 mm) (5, 22).

All in all, for patients with bronchiolitis obliterans who have undergone HSCT or lung transplantation, several immunosuppressive medications and immune-modulating treatments have been reported to stabilize pulmonary function in BOS patients in some trials. Low-dose macrolide antibiotics (azithromycin), leukotriene-receptor antagonists (montelukast), and combinations of inhaled bronchodilators and glucocorticoids is believed to help BOS symptoms and halt the decrease in pulmonary function tests (22), but more studies are needed to find the best protocol for disease management.

Tiotropium is an anticholinergic drug which is used in the management of chronic obstructive pulmonary disease (COPD) and is believed to have anti-inflammatory effects as well (10). It has been studied in post infectious and post HSCT BOS and a decrease in airway obstruction and improvement in lung function was reported (24, 25). According to the hypotheses about the similarities between BOS and COPD, the idea of using Tiotropium bromide as a bronchodilator has been proposed. This is to observe and evaluate the changes of FEV1 with the tiotropium add-on therapy.

Methods/design

Study design

This is a, randomized, double blind, placebo-controlled, crossover trial of maintenance treatment with once daily tiotropium for patients with BOS. The study will be conducted in two general educational hospital. This paper presents the design and protocol for the trial according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (26). An overview of the study design and timeline for participants is provided in Fig. 1.

The crossover design will consist of two sequences with two treatment periods (AB/BA or BA/AB) each lasting one month and separated with a one-week wash-out period. In treatment period A or B, patients will receive Tiotropium Bromide or placebo Revolizer added to usual standard care. Patients will be screened for eligibility, and once confirmed, will be randomized (1:1) to each treatment sequence. After completing the first treatment period in the sequence, patients will undergo a one-week wash-out period in which they receive only usual standard care. Then, they will receive the alternative treatment period which they have not received yet. Patients allocated to treatment sequence 1 will receive treatment period A,

then wash-out period, and then treatment period B; patients randomized to treatment sequence 2, will receive treatment period B, then wash-out period, and then treatment period A.

Consecutive patients who are referred to pulmonary clinics will be screened for eligibility criteria. Baseline data must be collected before enrollment. Baseline data include age, gender, time from transplantation, time from diagnosis of BOS, prior and current immunosuppressive and topical respiratory medication history, NIH lung symptom score, and chronic GVHD activity in other organs. Spirometry, six-minute walking test (6MWT) must be performed before enrollment. All patients are required to complete 36-Item Short Form Survey (SF-36), Cough Quality-of-Life Questionnaire (CQLQ) and St. George's Respiratory Questionnaire (SGRQ) before enrollment.

A total of 20 eligible patients will be enrolled in the trial. Central computerized permuted blocked randomization will be performed using a 1:1 allocation schedule with random block sizes of 4. Randomization process is performed by investigators who are not involved in participant recruitment. The allocation sequence will be concealed from the researchers using sequentially numbered, opaque and sealed envelopes.

During the treatment period A, patients will receive inhaled Tiotropium Bromide (KP-Tiova) at a dose of 18 micrograms once daily in the morning plus usual standard care. Standard usual care consists of inhaled corticosteroid and long-acting beta-2 agonist in a fixed combination in the formulation and dosage which were prescribed to the patient before study enrollment. Other immunosuppressive or GVHD modifying agents must be administered through the study at the dose similar to study onset. All the patients must be instructed regarding the self-administration of study treatment at the onset of trial.

During the treatment period B, patients will receive Tiotropium Bromide Placebo Revolizer plus standard usual care. The placebo Revolizer is identical to the experimental Revolizer in appearance, smell, taste, and texture and is administered in the same schedule as experimental treatment.

In the wash-out period, patients receive only standard usual care as above. The wash-out period is supposed to last one week.

Patients will continue to receive study schedules until completion of trial, occurrence of unacceptable adverse events, progressive pulmonary disease, change in immunosuppressive agents due to alterations in GVHD activity in other organs, malignancy relapse or graft failure, and withdrawal of consent.

Assessments will be performed at the end of the first treatment period, at the end of wash-out period, at the end of the second treatment period. Assessments include: Spirometry, 6MWT, NIH lung symptom score, GVHD activity in other organs, SF-36 score, SGRQ score, CQLQ score, VAS score, and monitoring of adverse events.

Eligible participants

The outpatient BOS cases of pulmonology clinic of Shariati Hospital and Taleghani Hospital were selected. Patients to be enrolled require meet all inclusion criteria listed in Table 1 and not meet any of the exclusion criteria. Those with BOS patients with baseline 20%≤%FEV1 < 70% will be selected and contacted by telephone. The acceptors will be asked to visit the research center.

Follow-up and duration of the study

There will be 4 visits, one baseline, one after 1 month of being included, another one after passing the washout period which is the time of being included in the next period and the last one is going to be 1 month after. An overview of the measures used at each of the four time points is illustrated in Table 2. By means of improving the compliance of patients; the strategies are as follows: adhere to the principle of voluntary participation and explain the benefits of this study to the participants and the importance of treatment and adherence to the treatment. Health education process could increase the related knowledge, change the behavior, and enhance the compliance of patient, but they were excluded if they did not have enough adherence and did not use more than 25% of their drug in the previous period. Written informed consent will be obtained from each patient before they begin the trial. All participants will fill in informed consents.

Sample size

The sample size calculation for this trial was performed using the PASS 15 [Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA.]. The primary end point of the main study was the surge in %FEV1, a rise from 45%±13–47%±14.5% was seen in the study of Jeong Uk Lim (24). Based on existing data, a 2% change in %FEV1 in the control group was assumed as negligible and zero, based on a power of 80% and an alpha value of 5%, it was calculated that a rounded sample size of 20 patients would be sufficient to detect a difference.

Randomization process

A total of 20 eligible patients will be enrolled in the trial. Central computerized permuted blocked randomization will be performed using a 1:1 allocation schedule with random block sizes of 4. Randomization process is performed by investigators who are not involved in participant recruitment. The allocation sequence will be concealed from the researchers using sequentially numbered, opaque and sealed envelopes.

Study drug

Patients will receive inhaled Tiotropium Bromide (KP-Tiova Rotacaps 18 mcg; Cipla; India) or Placebo (KP-Tiova Placebo with lactulose; Cipla; India) which was produced by the same manufacture. Tiotropium Bromide Revolizer or Placebo is added to usual standard care and in treatment period. Standard usual care consists of inhaled corticosteroid and long-acting beta-2 agonist in a fixed combination in the formulation and dosage which were prescribed to the patient before study enrollment. Other immunosuppressive or GVHD modifying agents must be administered through the study at the dose similar to study onset. All the patients must be instructed regarding the self-administration of study

treatment at the onset of trial. Subjects will be advised to take the study drug at the same time everyday according to approved instructions.

Table 1
Inclusion and exclusion criteria

Exclusion Criteria	Inclusion Criteria
1) Life expectancy < 6 months at the time of enrollment as judged by the enrolling investigator	1) Subjects able to sign the Informed Consent
2) The need for chronic oxygen therapy	2) 18 years of age or older
3) Baseline %FEV1 ≤ 20%	3) Diagnosis of post-HSCT-BOS according to NIH 2014 criteria
4) History of thoracic air leak syndrome	4) Baseline %FEV1 < 70%
5) Documented respiratory infection	5) Must be symptomatic, defined as NIH Lung Score 1–3, and no other contributing etiology (including cardiac diseases, infection, anemia or extrinsic thoracic compression) is present for respiratory symptoms
6) Active malignancy	6) Stable disease defined as less than 10% change in %FEV1 during the past 3 months while having no change in immunosuppressive and topical respiratory medications in the past 3 months
7) Graft failure	7) Must have received a combination of inhaled corticosteroid and inhaled long-acting beta-2 agonist during the past 3 month
8) Known history of asthma or chronic obstructive lung disease (COPD)	8) No new or supplemental immunosuppressive therapy for extra-thoracic GVHD during the past 3 month
9) Active smoking during the past 12 month	9) Patients with prior exposure to short-acting or long-acting inhaled anti-cholinergic drugs are eligible unless they have been received within the past 3 months
10) Substance abuse or uncontrolled psychiatric disorder	10) Ability to use Revolizer
11) Pregnant or nursing women	
12) Daily corticosteroid more than 1 mg/kg prednisone equivalent	
13) Known intolerance or allergy to anticholinergic drugs	
14) History of urinary retention, angle-closure glaucoma, CrCl ≤ 30ml/min	
15) History of arrhythmia in past years, MI in past 6 months or hospital admission due to heart failure in past year	

Exclusion Criteria	Inclusion Criteria
16) Ongoing participation in any other clinical trial (more typical would be using an investigational agent within 28 days of enrollment)	
17) Any condition that, in the opinion of the enrolling investigator, would interfere with the subject's ability to comply with the study requirements	
18) Inability to perform pulmonary function tests (PFT) reliably, as determined by the enrolling investigator or PFT lab	
19) No compliance	

Outcomes

Primary Outcome

The change from baseline in the mean Forced Expiratory Volume in 1 second (FEV1) (mL) one month after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS.

Secondary Outcomes

1. The changes from baseline in the mean percent predicted FEV1 (%FEV1) (%), and FVC after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
2. The change from baseline in the mean NIH Lung Symptom Score after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
3. The proportion of complete or partial response rate after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
4. The change from baseline in 6-minute walk test distance after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
5. The change from baseline in SF-36 score after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
6. The change from baseline in SGRQ score after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
7. The change from baseline in CQLQ score after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS

8. The change from baseline in VAS score after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
9. The change in admission rates due to respiratory, mediastinal and thoracic disease after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS
10. The rate of adverse event rates after treatment with Tiotropium Bromide Revolizer or Placebo added to usual care in stable symptomatic post-HSCT-BOS.

Adverse events

The adverse events will be examined by open questions, as well as symptoms, and by precise questions about potentially related adverse effect of the tiotropium which was used in the trial, as xerostomia, pharyngitis, cardiovascular event like hypertension, edema and chest pain, etc. The rate of adverse effects will be determined by linking the frequency of adverse events in the experimental drug and placebo with calculating the NARAJNJO scale.

Data entry and management of data files

Data will be entered into computerized database with the Excel software. All participants' data and patient health information will be confidential and protected during and after the trial. A code will be used to identify study participants, that will not be given to anybody outside of the study staff except when required by law. Records will be stored in an area with two locked doors. Only the study staff will have access to the locks.

Ethics approval and Dissemination

Participants will be asked to sign the approved informed consent form prior to participation in the study. The study protocol (protocol version 1.0, issue date:1 DEC 2021) was approved by the Ethics Committee of the Imam Khomeini Hospital Complex, Tehran University of Medical science under the number IR.TUMS.IKHC.REC.1400.361. The trial is conducted in keeping with Good Clinical Practice Guidelines, the ethics drawn in the Declaration of Helsinki, and applicable local laws and regulations. The trial is registered at www.irct.ir under the identification number IRCT20200415047080N3. Informed consent will be signed. Clinical results will be available in a medical journal and presented at national or international conferences. De-identified data can be supplied upon request with data usage agreements to ensure the scientific dissemination and transparency.

Statistical methods

Analysis will be done by intention-to-treat and per-protocol. Non- normally and normally distributed data will be presented as median, interquartile range and means, standard deviation, respectively. The significance of the differences between two groups will be tested by chi-squared test for categorical variables and t test for measurement data. Results with a P value lower than 0.05 will be considered

statistically significant. Statistical analyses will be performed using the STATA 14 software (STATA Inc., Texas, US).

Discussion

Increasing data, shows negligible effect of some immunosuppressants in the pulmonary function of BOS patients, also there is little available evidence on the impact of inhalation medication influence on the prognosis and the relief of lung function decline. As far as we are considered this study will be the first crossover trial to investigate the efficacy of tiotropium bromide in stable symptomatic post HSCT, BOS adult patients.

We are all aware of the effect of HSCT on the lives of cancer patients but this comes with indisputable side effects to the lungs, like: infection, pulmonary edema and of course pulmonary GVHD. Generally, GVHD lies in two categories: Acute and Chronic. The pulmonary GVHD which is a form of chronic GVHD, is called Bronchiolitis obliterans and diagnosed with lung biopsy. The term bronchiolitis obliterans syndrome (BOS) is used when a patient has airflow limitation in the absence of other etiologies, but histopathology to document BO is not available (1–3, 22).

Currently, there is no precise treatment protocol for BOS (1–13). Based on, Kirsten M. Williams et al study, inhaled fluticasone, azithromycin, and montelukast (FAM) and steroid pulse may halt pulmonary deterioration in new-onset BOS in the majority of patients, therefore the steroid dose could be reduced (18).

As steroids and other immunosuppressants have long term adverse effect, we believed that with the somehow same pathophysiology of COPD and BOS and the previous study of the tiotropium, it could be a promising drug and may become a great hand.

Little is known about tiotropium effect on BOS. Jeong Uk Lim et al, disclosed inhaled tiotropium add-on to combination budesonide/formoterol can significantly improve lung function, but not respiratory symptoms, in patients with post-HSCT BOS (24).

Mariângela F C Teixeira et al, conducted a randomized, double-blind, placebo-controlled, crossover, prospective study in patients with stable PIBO, 6 to 16 years of age. They concluded tiotropium acutely decreased airway obstruction and air trapping for up to 24 h in children with postinfectious bronchiolitis obliterans (25).

This study is designed to determine tiotropium effects on lung function in patients with BOS. Our hypothesis is that tiotropium significantly will improve the FEV1 and symptoms of BOS patients.

A limitation of this study is the sample size is not large enough, and the follow-up time is 1 month. Another limitation is the heterogenicity of bronchodilators and immunosuppressants used by patients.

In summary, our RCT will afford data for analyses of the relationship between BOS and tiotropium, which may be a potential treatment for BOS.

Declarations

Trial status

At the time of trial protocol submission, the enrollment of volunteers is ongoing. The study has been ongoing from September 2022. The treatment follow-up of participants with Tiotropium is currently ongoing and is due to finish in December 2023. The protocol version is 1.0.

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Contributors

A.S. and A.R. conceived the original idea for the study. B.H. will perform the analysis. D.N. and A.K wrote the draft of the manuscript and performed the experiment. The final content was developed in collaboration with all authors. All authors saw and approved the final version of the manuscript.

Availability of data and materials

Data and materials can be obtained from the corresponding author after the trial.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table 2

Table 2 is available in the Supplementary Files section.

Figures

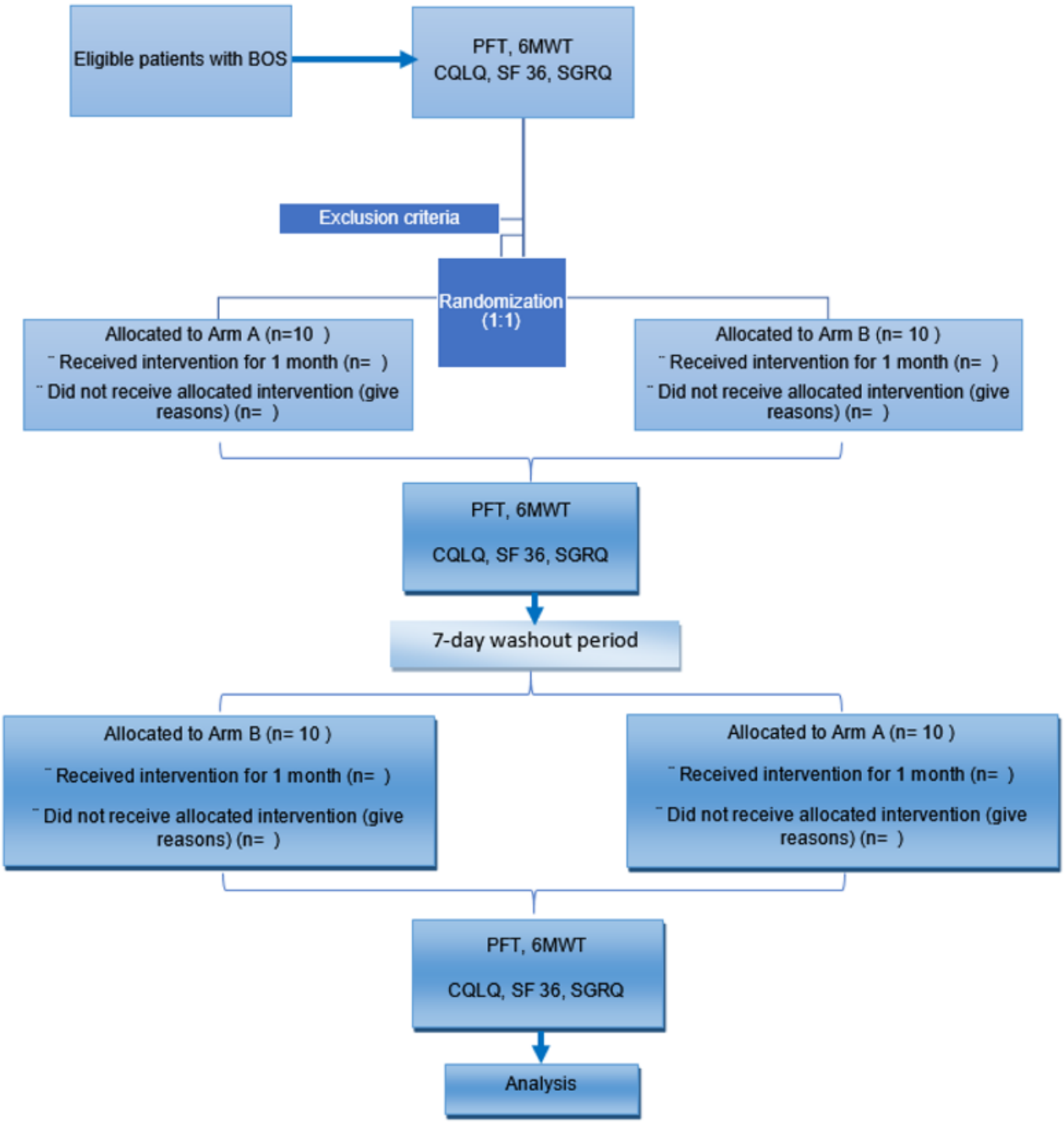

Figure 1

Study design overview

Supplementary Files

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- SPIRITchecklistforBMC.docx
- Table2Scheduleofenrolment.docx