The Effect of Synbiotic Supplementation on Fatigue and Sleep Quality in End-Stage Renal Disease Patients Undergoing Hemodialysis : Study Protocol for a Double-Blind Controlled Randomized Clinical Trial

Ali Asghar Jesmi
Sabzevar University of Medical Sciences
Mina Jangpoor (mina.jangpoor@gmail.com)
Sabzevar University of Medical Sciences https://orcid.org/0000-0002-6353-0514
Neda Mahdavifar
Sabzevar University of Medical Sciences

Study protocol

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Abstract

Background: Chronic kidney disease is one of the public health issues in the world. Imbalances in the gut microbiome have been revealed to contribute to the progression of multiple diseases including Chronic Kidney disease. The consumption of probiotics and synbiotics in the treatment of various diseases has a significant progression. The present study will investigate the effects of synbiotics supplement on intestinal microbiome through monitoring of inflammatory factor C Reactive Protein and Hemoglobin and ultimately its effect on fatigue and sleep quality of End Stage Renal Disease patients undergoing hemodialysis.

Design and Methods: Sixty patients with End Stage Renal Disease who undergoing haemodialysis will be recruited in this double-blind randomized controlled trial. Participants will be randomly assigned via permuted block randomization to intervention and control group. The intervention group received 500 mg of synbiotic (lactoker) twice a day for eight weeks and the control group received placebo for the same period. The "Chalder Fatigue" and "Pittsburgh Sleep Quality" questionnaires, Hemoglobin and C Reactive Protein level will be assessed at the beginning, week four and at the end of the study.

Discussion: To our best knowledge**,** this is the first randomized controlled trial that will determine the effect of symbiotic supplement on the intestine microbiota and its probable impacts on Hemoglobin and C Reactive Protein as an inflammatory factor level and consequently its effect on fatigue and sleep quality of End Stage Renal Disease patients undergoing hemodialysis.

Trial registration: IRCT20210117050055N1. Registered on 2021-02-21. https://www.irct.ir/trial/53770

1. Background

Chronic kidney disease is one of the public health issues in the world. It is a progressive and irreversible renal disorder in which the kidneys are unable to maintain homeostasis and lead to azotemia or uremia. When the kidney function decline to less than 10–15% of its normal level, the end stage renal disease has occurred [1]. The prevalence of chronic kidney disease is estimated to be 8–16% worldwide [2]. In most developed countries, Hemodialysis is the most common strategy for treatment at the beginning of ESRD(End Stage Renal Nutrition) treatment and patients over 65 years [3].

ESRD leads to the accumulation of uremic toxins in body and has various complications [4]. Fatigue is one of the most common complications experienced by hemodialysis patients. At least half of the patients complain of persistent fatigue and about 86% of the patients report fatigue after dialysis [3–4]. Also, about 50 to 83% of these patients suffer from poor sleep quality [5]. The onset of chronic kidney disease and hemodialysis followed by complications such as fatigue and decreased sleep quality significantly affect quality of life [6]. In a study conducted by Bossola et al. On fatigue in patients undergoing hemodialysis; Fatigue unrelated to depression alone can increase the risk of mortality in these patients [7].

The pathophysiology of fatigue and poor sleep quality in ESRD patients remains unknown [3–5]. A hypothetical model of the fatigue cycle was proposed in 1998 by Wessely et al. Which showed that factors such as anemia, inflammation, and hemodialysis treatment may trigger the onset of the fatigue cycle and then patients' cognitive, behavioral, and emotional responses to early symptoms such as negative beliefs, depression, anxiety, and maladaptive behaviors. Gradually, this cycle leads to physiological complications such as systemic inflammation, central nervous system and endocrine disorders, and poor sleep quality. Finally, the fatigue cycle can lead to poor clinical outcomes in the patient [3].

Recently, the role of inflammatory factors as a primary agents in the fatigue cycle has become more prominent [8]. Inflammatory factors have a direct effect on the central nervous system, pituitary gland, hypothalamus and adrenal glands and also indirectly lead to poor sleep quality and physiological disorders such as fatigue [4]. On the other hand, the increase of uremic toxins in ESRD can also accelerate the fatigue cycle in patients by affecting different systems [9]. Therefore, it has been suggested that reducing systemic inflammation can be an effective strategy to reduce fatigue and improve sleep quality and ultimately improve the quality of life [9–10].

Scheper et al, in 2010; declare Intestine was introduced as a neglected organ in chronic kidney disease and its associated uremia [11]. Recent studies have shown that imbalances and quantitative and qualitative changes in the composition and activity of intestinal microbiota in ESRD patients accelerates the progression of the disease, uremia and its complications such as fatigue and poor sleep quality [12]. The increase in uremic toxins in patients with chronic kidney disease may be due to increased production of these toxins due to intestinal dysbiosis or decreased renal function for eliminating these toxins [13]. High levels of potassium and phosphate in patients undergoing hemodialysis caused avoiding the source of this elements consequently, patients are deprived of a rich source of indigestible complex carbohydrates, which are in fact the main nutrients for intestinal bacteria [14]. The "brain-intestine-kidney" axis plays an important role in the normal homeostasis of the body, and disturbance in the regulation of this axis can lead to exacerbation of chronic kidney disease and its complications [15]. Due to the effects of intestinal microbiota on ESRD and other chronic diseases, a wide range of therapeutic approaches aimed at modulating the intestinal microbiome have recently been studied. These include probiotic and prebiotic interventions, which are relatively safe and non-invasive measures in modulating intestinal microbiota.

Probiotics are defined as "living microorganisms that, if taken in optimum level, have benefits. Prebiotics are also defined as dietary supplements (such as inulin) that support the growth of probiotics. Synbiotics are a combination of probiotics and prebiotics together that may have a greater effect on gastrointestinal health and systemic inflammation in hemodialysis patients due to their synergistic effect [9–14].

Therefore, it is hypothesized that changes in intestinal microbiota following the use of synbiotic supplements can improve metabolic health by reducing inflammatory factors. According to the results of the study published by Koushki et al. In 2019, taking 8 weeks of synbiotic dietary supplement in

hemodialysis patients compared to the control group can reduce inflammatory factors CRP(C Reactive Protien), MDA(Malondialdehyde) and also reduce total cholesterol and LDL(Low Density Lipoprotein) [16]. Also, considering the important role that anemia plays in fatigue caused by chronic diseases, in a systematic review conducted by Vonderheid et al. in 2019, which investigate 12 clinical trials in patients diagnosed with iron deficiency anemia, the results showed increasing absorption of Iron with consumption of probiotics [17].

Considering that several studies have investigated the effect of synbiotic supplementation on inflammatory and anemic factors and improving the immune system of patients undergoing hemodialysis; however, to our best knowledge, this is the first clinical trial that evaluates the effects of synbiotic supplement therapy on improving sleep quality and fatigue in ESRD patients undergoing hemodialysis.

1.2. Objectives

The primary objective of this randomized clinical trial is to evaluate the effects of synbiotic supplementation on fatigue and sleep quality in patients with hemodialysis treated with ESRD.

The secondary objectives of this experiment is to compare the inflammatory factor changes of CRP and Hb(Hemoglobin) between the control and intervention groups.

2. Materials And Methods

2.1. Study design

This study is a 8-weeks randomized, double-blind clinical trial with a control group in the dialysis ward of Musabn Jafar Hospital in Quchan. Patients with ESRD undergoing hemodialysis will randomly be assigned using a permuted block randomization method to intervention and control group (30 patients in each group). In the intervention group patients receive two synthetic supplements of lactoker (500 mg) daily with lunch and dinner for 8 weeks. In the control group, patients received placebo capsules containing 500 mg of cornstarch twice a day for 8 weeks, with the same size, shape and color of synbiotic capsules.

2.2. Inclusion criteria

Participants will be eligible for this study if they meet the following criteria:

1) Having informed consent to participate in the study, 2) Age between 18, to 65 years, 3) patient with a diagnosis of chronic renal failure who undergoing hemodialysis for at least 3 months, 4) Patient with arterial fistula, permanent catheter or venous artery graft, 5) patient undergoing hemodialysis 3 times a week for 4 hours each time, 6) Patient with KT / V>1, 7) Do not suffer from hearing and visual disorders, 8) Not suffering from neurological disorders and history of hospitalization in the psychiatric ward.

2.3. Exclusion criteria

The following people will be excluded from the study:

1) Active infection during the last 30 days, 2) Pregnant or lactating mothers, 3) Taking antibiotics, prebiotics, probiotics, synbiotics, vitamin supplements or antioxidants during the last 30 days, 4) Suffering from autoimmune diseases or connective tissue disorders, 5) History of cardiovascular diseases, 6) Diabetic foot infection, 7) Gastrointestinal diseases (inflammatory bowel disease, ulcerative colitis, Crohn's disease, celiac disease, lactose intolerance or allergy, irritable bowel syndrome), 8) Liver disease (hepatitis B, hepatitis C), 9) Infection with various cancers and malignancies, 10) Smoking more than 10 cigarettes a day, 11) Participate in other drug interventions, 12) Having Hb less than 8 mg/dl, 13) PSQI(Pittsburgh Sleep Quality Index) score less than 6 (good sleep quality), 14) CFS(Chalder Fatigue Scale) score less than 18

2.4. Setting

After receiving ethics code from the committee of research and technology, the researcher referred to the "Dialysis Department of the Educational Center of Musabn-Jafar Hospital in Quchan and provided the necessary explanations about the research objectives and benefits of Synbiotics supplements, method and rights of research samples such as confidentiality of patient information, etc. written consent will be received. First, the demographic information will received. The Pittsburgh Sleep Quality and Chalder Fatigue Questionnaires complete by research samples after that they will randomly assigned by permutation block randomization method to intervention and control groups. Patients in the intervention group receive synbiotic supplement and the control group receive placebo for eight weeks. Pittsburgh Chalder Fatigue and Sleep Quality Questionnaire is completed by patients at the end of the fourth week and at the end of the eighth week after the intervention. The choice of study duration is based on the results of studies performed so that the positive results of the interventions have been proven during 6 weeks or more [9–16–18–19]. All subjects, researchers, statistical analyst and dialysis staff will be blind to the intervention.

Synbiotic and placebo capsules are packed in the same shape and size in boxes with the same appearance. The capsule will be labelled "A" and "B" by a third colleague who will not be involved in the study method. Subjects, researchers, statistical analysts, and dialysis staff will be blind to the analysis of data on box contents, allocation, and treatment.

2.5. Sample size

The sample size required for the present study was based on the data of Soleimani et al. who investigated the effect of probiotics supplementation on metabolic factors in diabetic hemodialysis patients. The sample size for each group was 26 individuals. Considering the 20% probability of falling for each group of 30 subjects was calculated ($\alpha = 0.05$ and $\beta = 20\%$). Equation (1).

$$n_1 = n_2 = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2(\sqrt{(S_1)^2 + (S_2)^2})}{(\mu_1 - \mu_2)^2} = \frac{(20.61 * 28.3)}{4.74^2} = 26 \quad (1)$$

The probable start date of sampling for this study is from the beginning of August and it is predicted that the sampling will end by the end of November 2021. A period of one month is also predicted for statistical analysis of data.

2.6. Intervention

The intervention group take two synbiotic capsules daily (one after lunch and the other after dinner) and the control group take two placebo capsules (containing 500 mg of cornstarch) daily at the same time for 8 weeks. Synbiotic and placebo capsules are similar in appearance and are marked only with the label "A" or "B" on the box. Boxes are tagged by a third party not directly involved in this study. Each Lactoker Synbiotic Capsule (500 mg), produced by Bio Fermentation Company of Iran, contains high amounts of 12 beneficial and safe bacterial strains along with fructooligosacharide as a probiotic. The strains used in this product includes: (Lactobacillus rhamnosus, Lactobacillus Hlvtykvs, Lactobacillus casei, Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium Barwa, Lactobacillus bulgaricus, Bifidobacterium Langvm, Lactobacillus plantarum, Bifidobacterium bifidum, Lactobacillus Gsry, Streptococcus thermophilus). Each box contains 30 capsules. Participants are given four boxes for the entire 2-month intervention (two boxes at the beginning of each month). In addition, patients continue to take their daily medications throughout the study. The Ethics Committee of Sabzevar University of Medical Sciences will be responsible for following up on reports from participants regarding any possible related issues and side effects. Any possible side effects will be reported to the Medical Ethics Committee during the study. At the beginning of the study, subjects are informed consent take from the study subjects. Written and oral instructions on how to use the capsules are provided at the first visit and at subsequent visits. Patients followed for Adherence to the intervention twice a week by telephone. People are asked to take one capsule after lunch and another after dinner, which also improves their adherence to the intervention. In addition, subjects ask to record the daily intake of supplements or placebo in the delivered booklet. All subjects ask to return the capsules left in the boxes at the next visit. At the end of the 8 weeks if the number of capsules remaining for each participant is more than 10% of the total capsules prescribed, that participant will be excluded from the intervention.

2.7. Outcomes

Primary outcomes include evaluation of fatigue status and sleep quality in patients with ESRD undergoing hemodialysis. The feeling of reduced capacity for physical and mental work at the usual level is called fatigue [1]. The patient's fatigue rate is assessed based on the Chalder fatigue scale. This scale has a total score between 0 and 33 and if the patient scores above 18 according to this questionnaire, it will be considered tired. The higher the score, the more severe fatigue the patient experiences [20]. Sleep

disturbances are typically known as difficulty in initiating or maintaining sleep or as excessive or uncontrollable drowsiness. Sleep disorders occur in the form of partial awakening in sleep [1]. Sleep quality is calculated based on the Pittsburgh Sleep Quality Questionnaire. This scale has a total score between 0 and 21 and a score between 0 and 5 means good sleep quality and a higher score means poor sleep quality [21]. Secondary outcomes include evaluation of the CRP and evaluation of patients' Hb level. All measurements will be done at the beginning, the end of the fourth week ,and at the end of the intervention.

2.8. Fatigue and sleep quality assessment

Chalder fatigue and Pittsburgh sleep quality questionnaire use to measure patients' fatigue and sleep quality score respectively.

The Chalder Fatigue Scale to assess fatigue disability was first published by Chalder et al. in 1993 and then in 2010 with further psychometric evaluation. This questionnaire contains 11 questions and two general areas for examining physical and emotional fatigue and examines fatigue during the last month. How to answer the questions is fourfold (much less than usual, less than usual, more than usual, much more than usual). The scoring system on this scale is such that each question is assigned a score between 0 and 3, which in total, the result is between 0 and 33. If the patient scores above 18 according to this questionnaire, he / she will be considered tired; the patient suffers from more fatigue with a higher score. The validity of this scale has been examined by Chalder et al. And by using the list of symptoms and clinical interview, the sensitivity was 75.5% and the specificity was 74.5%. The internal consistency coefficient was 0.85 for physical fatigue questions and 0.82 for mental questions. The reliability of this scale was calculated by Chalder et al. 0.92 [20].

In Iran, for the first time Nasri et al. evaluated the validity of this questionnaire, a group of patients with symptoms of fatigue were compared with a group of healthy individuals using this scale, and the results showed that this scale is valuable for measuring fatigue. Test-retest coefficient and internal consistency calculated in the study were reported to be 0.85 and 0.91, respectively, indicating the high validity and reliability of this questionnaire [22].

The Pittsburgh Sleep Quality Index is used to measure sleep quality, which is a validated standardized tool for assessing sleep quality. This self-monitoring questionnaire was designed in 1989 by Boris et al. And assesses sleep quality over the past month. The questionnaire includes 19 questions about 7 important components of sleep (mental quality of sleep, duration of sleep, duration of sleep, sleep efficiency, sleep disorders, use of sleeping pills, and inefficiency during the day). Each component is assigned a score between 0 and 3, so the overall PSQI score is between 0 and 21. A score between 0 and 5 means good sleep quality, while a score between 6 and 21 means poor sleep quality. The sensitivity and specificity of this questionnaire were reported by Boris et al. 89.6% and 86.9%, respectively [21].

Based on the study of Farhi Moghadam et al. Who first validated this questionnaire; based on cut-off point 6 for this questionnaire, sensitivity and specificity, scores of 94% and 72% were obtained,

respectively [23].

2.9. Anthropometric assessment

Anthropometric indices will be accurately measured at the beginning. At the beginning of the study, the height of each participant standing on the wall without shoes will be measured with an accuracy of 0.1 cm with a stadiometer (seca, Hamburg, Germany). Waist and pelvis will be measured with an accuracy of 0.1 cm in the area with the smallest diameter with a non-stretching tape. Waist-to-height and waist-to-hip ratios are calculated using standard equations. The weight of the subjects in the fasting state, without shoes, and only by wearing light clothes, will be measured using a scale (seca, Hamburg, Germany) with an accuracy of 0.1 kg. Body mass index will be calculated by dividing body weight by kilograms by height per square meter.

2.10. Blood sampling, biochemical assessment

A 5 ml venous blood sample is collected from each participant at the beginning and end of the test. 3 ml of it is collected in a test tube containing clot activator and centrifuged at room temperature at 3000 rpm for 10 minutes (Eppendorf AG, Hamburg, Germany) to separate serum. Serum samples are stored at 70 ° C. Residual blood samples are collected in a tube containing ethylene diamine tetraacetic acid (EDTA) to measure Hb. To maintain patient confidentiality, all laboratory information is stored using an ID number.

2.11. Statistical analysis

Statistical analyses will be performed with SPSS software V.23.0 (SPSS Inc. Chicago, IL, USA). Normality of distribution of data will be assessed by the Shapiro-wilk test. At first, the primary information of the intervention and control groups will be compared. Continuous data will be presented as means ± standard deviation (SD), and categorical data will be expressed as numbers and percentages. The independent samples t test and the Mann-Whitney U test will be used for analysing the differences in parametric continuous and asymmetric variables between the two groups, respectively. Pearson correlation test is also used to analyse the correlation between quantitative variables. The repeated measure is used to examine the dependent variables that are measured in three turns. P values < 0.05 will be considered as statistically significant. The significance level is 95% and the confidence interval is 95%.

Because dialysis patients come for dialysis three times a week and the questionnaires are completed by the patients in the presence of the researcher's help, there will be no missing data. The results of the aforementioned analyses will be compared with each other.

3. Discussion

Chronic kidney disease is one of the public health problems in the world. When the kidney function decline less than 50% of its normal level, it is called chronic kidney disease, and if this rate reaches less than 10 to 15%, the final stage of kidney disease has occurred [24]. The prevalence of chronic kidney disease is estimated to be between 8% and 16% worldwide [2]. In most developed countries of the world,

the most common method of renal replacement at the beginning of ESRD treatment is Hemodialysis; especially at patients over 65 years [3]. Increased toxins in uremic patients with chronic kidney disease may be related to increased production of toxins caused by changes in the composition of the gut microbiome or due to loss of kidney function to excrete these toxins and lead to various complications such as fatigue and poor sleep quality [12–13]. The "brain-intestine-kidney" axis plays an important role in the normal homeostasis of the body, and disturbance in the regulation of this axis can lead to exacerbation of chronic kidney disease and its complications [15]. Recent studies have shown that balancing the quantitative and qualitative composition of the intestinal microbiome may be a stimulus for improving the inflammatory and anemic status of hemodialysis patients as factors contributing to fatigue and reduced sleep quality [12]. Synbiotics are a combination of prebiotics and probiotics that can have a profound effect on the gut microbiome [9, 14]. However, until now, the indirect effects of synbiotics on fatigue and sleep quality in hemodialysis patients have not been investigated.

Therefore, the present study will investigate the indirect effects of synbiotics on the intestinal microbiome through monitoring of inflammatory factor CRP and Hb and ultimately its effect on fatigue and sleep quality of ESRD patients undergoing hemodialysis. The results of this study provide clinical evidence for the effectiveness of synbiotic supplementation in reducing inflammation and anemia, and ultimately sleep quality and fatigue status in patients with hemodialysis-treated ESRD. One of the strengths of this study is that it is a double-blind randomized controlled clinical trial. If the results of this test are valid, a new approach will be made to improve the debilitating effects of fatigue and poor sleep quality of ESRD patients undergoing hemodialysis.

Abbreviations

ESRD
End Stage Renal Disease
CRP
C Reactive Protien
MDA
Malondialdehyde
LDH
Low Density Lipoprotein
HB
Hemoglobin
PSQI
Pittsburgh Sleep Quality Index
CFS
Chalder Fatigue Scale

Declarations

Ethics approval and consent to participate

This study will be done in accordance with the ethical standards as laidbdown in the 1964 Declaration of Helsinki. This clinical trial is approved by the Ethics Committee of the Sabzevar University of Medical Sciences 163.1399.REC.MEDSAB.IR .All participants will provide a signed written consent form before the study initiation. The intervention will not interfere with the routine treatment of patients. This study is registered at the Iranian Registry of Clinical Trials IRCT20210117050055N1. Registered on 2021-02-21.

Consent for publication

The informed written consent obtained from the individuals involved in the research includes the consent to publish the information obtained from the research. The published information is without the name and identity of the participants.

Availability of data and materials

The datasets generated during the current study will be available via the corresponding author on reasonable request.

Competing interests

None of the authors have any interest in competing.

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Authors' contributions

*Mina Jangpoor. M.A. student in critical care nursing. Iran. Sabzevar University of Medical Sciences

Mina.jangpoor@gmail.com

*Dr. Ali Asghar Jesmi .Assistant Professor in nursing.Iran.Sabzevar University of Medical Sciences

jesmia@medsab.ac.ir

*Neda Mahdavifar. M.A. in Epidemiology. Iran . Sabzevar University of Medical sciences

n.mahdavifar90@gmail.com

MJ and AJ conceived the study. MJ undertook a literature review, extracted the data, analysed and drafted the manuscript. AJ assisted in analysis, drafting and revision of the manuscript. NM was responsible for calculating the sample size required for this clinical trial.MJ and AJ were involved in the critical revision of the manuscript. All authors read and approved the final manuscript.

Corresponding author

Mina Jangpoor

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Authors' information

Mina Jangpoor. M.A. student in nursing. Iran. Sabzevar University of Medical Sciences

Dr. Ali Asghar Jesmi . Assistant Professor in nursing. Iran. Sabzevar University of Medical Sciences

Neda Mahdavifar. M.A.in Epidemiology. Iran. Sabzevar University of Medical Sciences

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Figures

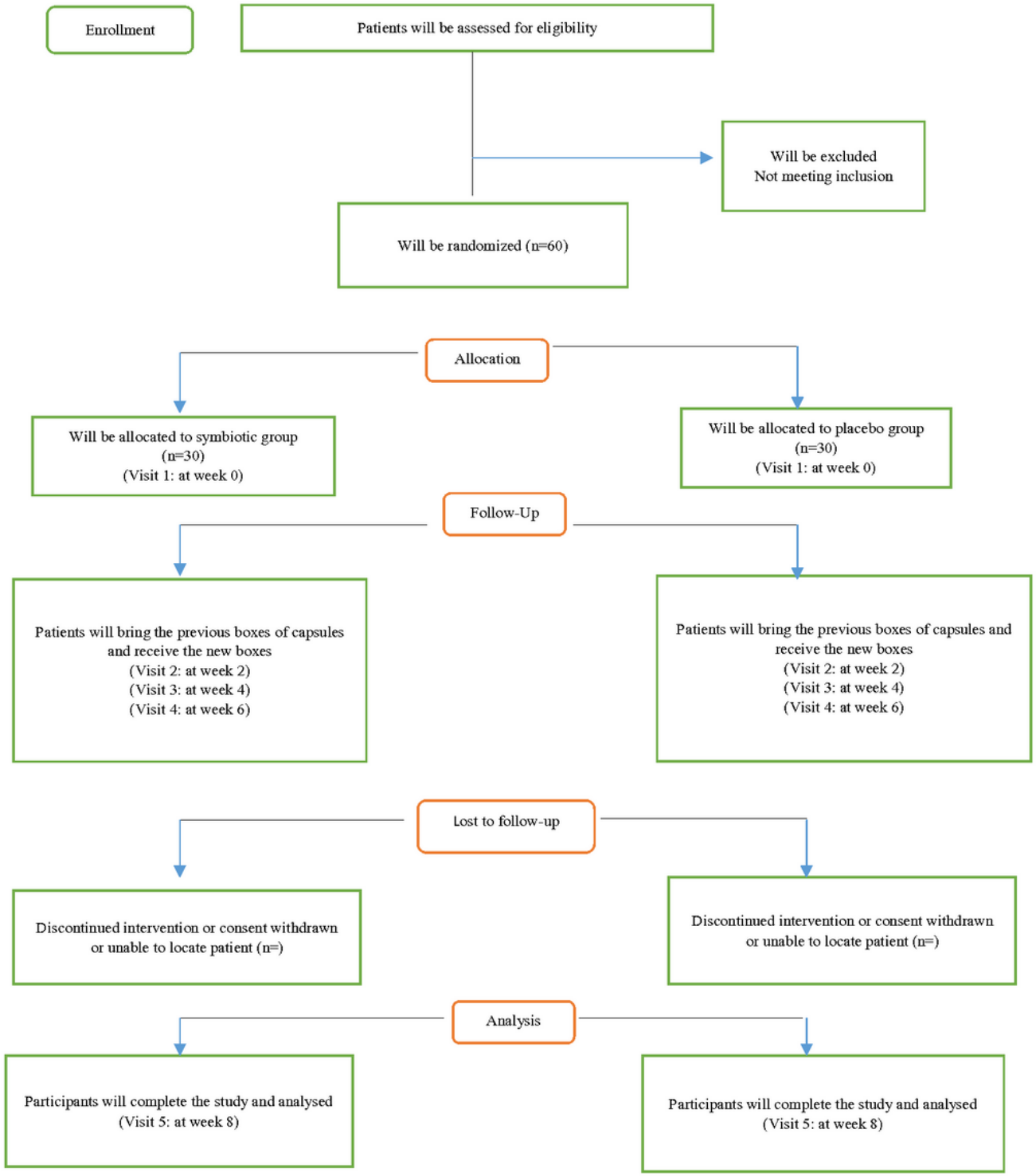

Figure 1

Overview of the study

Supplementary Files

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