Study protocol: «Comparative assessment of the efficacy and safety of venoactive drug treatment of pelvic venous disorders: results of a single-center randomized open trial»

ID: NCT06584799

Date: 09/04/2024

Project Summary

Venoactive drug (VAD) therapy is one of the most effective methods of treating chronic venous diseases (CVD) [1-3]. Numerous studies have proven its high efficacy in relieving symptoms of CVD, such as leg pain and swelling, leg heaviness and fatigue, as well as an association between the VAD intake and acceleration of venous ulcer healing [4-8]. Pelvic venous disorders (PeVDs) represent a group of pathological conditions including varicose veins of the pelvis and vulva, and compression stenoses of the left renal and common iliac veins. Although PeVDs are associated with venous lesions of the pelvis and retroperitoneum and have specific clinical manifestations, they are one of the forms of CVD and constitute a separate cohort [9,10]. A number of studies on the VAD usage in PeVD indicate the wide possibilities of this type of treatment in eliminating chronic pelvic pain (CPP), the most dramatic symptom of PeVD, which is the main cause of disability and decreased quality of life, social and daily activity in women with PeVD. The healthcare systems of industrialized countries are known to spend annually more than 2 billion US dollars on the treatment of patients with PeVD and CPP, and the cost of treating one patient with PeVD ranges from 3,600 to 27,000 US dollars per year [11-13].

Currently, a variety of VADs are presented on the pharmaceutical market, which, according to the product labels, provide effects not only on the venous outflow from the lower extremities, but also on venous hemodynamics in the pelvis [14]. At the same time, a literature analysis shows that micronized purified flavonoid fraction (MPFF, Detralex, Daflon) has the greatest evidence base obtained in the efficacy and safety studies of VADs in PeVD [15-19]. Nevertheless, patients are rarely interested in the scientific dossier of drugs, and in the real practice the patients with PeVD and CPP most often ask: “What is the best drug to use for the CPP relief?” This is quite understandable, as it is CPP in PeVD that results not only in disability, but also in family conflicts, psycho-emotional stress and depressive states [20,21]. In this regard, patients seek to get rid of pain as soon as possible and strive to use the most effective drug.

An extensive scientific base of comparative studies on the use of various VADs in patients with CVD and PeVD has been accumulated to date [15-19, 22-26]. However, the literature is lack of any data on the comparative efficacy and safety of VADs in the treatment of patients with PeVD.

This, in turn, makes not possible for doctors and patients to choose the optimal and most effective drug based on the objective research data. All the above has predetermined the purpose of the planned study as evaluating the efficacy and safety of different VADs in the treatment of female patients with PeVD.

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Study objectives:

- To evaluate the efficacy of diosmin-containing VADs in the CPP relief in female patients with PeVD;
- To evaluate the safety (by the number of side effects and adverse events) of diosmin-containing VADs in female patients with PeVD;
- To compare the efficacy and safety of treatment with different diosmin-containing VADs;
- To evaluate the patients' adherence to the different recommended diosmin-containing VADs in female patients with PeVD.

Patients and methods: A total of 150 female patients of reproductive age with symptomatic PeVD and without any other diseases accompanied by CPP are planned for the inclusion in the study.

Clinical study: All patients will be examined by an investigating physician. Complaints, medical history, and physical examination results will be recorded in the individual patient's case report form (CRF). The severity of CPP will be assessed using a 10-score visual analogue scale (VAS) before treatment and then weekly for 2 months of treatment with VAD.

Diagnostic methods:

All patients will undergo transabdominal and transvaginal duplex ultrasound scanning (DUS) of the pelvic veins.

Treatment methods: the following VADs will be used as the study drugs.

1. ***Micronized purified flavonoid fraction 1000.*** Manufacturer: SERVIER RUS, LLC (Russia). Active substance: micronized purified flavonoid fraction (diosmin+flavonoids expressed as hesperidin).

   Micronized purified flavonoid fraction (MPFF) is a venotonic agent that also has angioprotective properties. It reduces venous distensibility and blood stasis, capillary permeability, and increases capillary resistance. The results of clinical studies confirm the pharmacological activity of drugs containing this active substance in relation to the parameters of venous hemodynamics. MPFF improves venous tone: a reduction in venous emptying time has been shown by venous occlusion plethysmography. In patients with signs of severe microcirculatory disorders the treatment with drugs containing this active substance is associated with a statistically significant (as compared to placebo) improvement in the capillary resistance, as has been shown by angiostereometry. The drug also has a proven efficacy in the treatment of CVD of the lower extremities (Source: https://www.vidal.ru/drugs/detralex__38634; accessed: September 4, 2023).

   MPFF 1000 dosing regimen is 1000 mg once daily for 2 months.

2. ***Diosmin 600.*** Manufacturer: INNOTHERA CHOUZY (France). Active substance: diosmin.

   Venotonic action: the drug reduces venous distensibility, increases venous tone, reduces blood stasis, and enhances the vasoconstrictor effect of epinephrine and norepinephrine. The optimal daily dose of diosmin for obtaining venotonic effect is 600 mg.

   Angioprotective action: the drug improves microcirculation, increases capillary resistance, and reduces capillary permeability. Effect on the lymphatic system: the drug improves lymphatic drainage, increases the tone and frequency of contraction of lymphatic capillaries, increases their functional density, and reduces lymphatic pressure. It has an anti-edematous effect, reduces symptoms of inflammation (dose-dependent effect), reduces adhesion of leukocytes to the venous wall and their migration into paravasal tissues, and improves oxygen diffusion and perfusion in tissues. The drug hinders the production of free radicals and synthesis of prostaglandins and thromboxane. A double-blind, placebo-controlled study using Duplex ultrasound has confirmed that the drug reduces the mean venous pressure in the system of superficial and deep veins of the lower extremities (Source: https://www.vidal.ru/drugs/phlebodia_600__4622; accessed: September 4, 2023).

   Diosmin 600 dosing regimen is 600 mg once daily for 2 months.

3. ***Hesperidin + Diosmin 1000.*** Manufacturer: ALLIUM (Russia). Active substance: diosmin and hesperidin.

   A venotonic agent that also has angioprotective properties. It reduces venous distensibility and blood stasis, reduces capillary permeability and increases their resistance. The results of clinical studies confirm the pharmacological activity of drugs containing this active substance in relation to the parameters of venous hemodynamics. It increases venous tone: a reduction in the time of venous emptying has been demonstrated in studies with venous occlusion plethysmography. In patients with signs of severe microcirculatory disorders the treatment with drugs containing this active substance is associated with a statistically significant (as compared to placebo) improvement in the capillary resistance, which has been proven by angiostereometry. The drug has a proven efficacy in the treatment of CVD of the lower extremities (Source: https://www.vidal.ru/drugs/gesperidin-diosmin; accessed: September 4, 2023).

   Hesperidin + Diosmin 1000 dosing regimen is 1000 mg once daily for 2 months.

All three of these drugs are venotonic and venoprotective drugs used in the CVD treatment. They are comparable in their pharmacological properties, product labels, profile of side effects and adverse events, and the cost per package of 30 tablets, according to the Moscow chain of

pharmacies (Source: https://gorzdrav.org/p/detraleks-tabl-p-o-1000mg-n30-62440/; https://gorzdrav.org/p/flebodia-600-tabl-p-o-600mg-n30-17602/; https://gorzdrav.org/p/venarus-tabl-p-o-900mg-100mg-n30-64844/; accessed: September 4, 2023).

Patients will take these VADs at the same time every morning, during breakfast. Patients will be warned in advance about possible side effects and adverse events. In a case of their occurrence, the patients shall immediately notify the principal investigator or investigators using one or more mobile phone numbers provided to them in advance.

General information

Study title: «Comparative assessment of the efficacy and safety of venoactive drug treatment of pelvic venous disorder: results of a single-center prospective randomized trial»

Protocol ID: NCT06584799.

Protocol of the study: The study was approved by the local ethical committee of the Pirogov Russian National Research Medical University (Protocol No. 20452024)

Responsible for the study: Gavrilov Sergey Gennadievich, Doctor of Medical Sciences, Professor, Pirogov Russian National Research Medical University, 1Ostrovityanova str., Moscow 117997; phone: 8 (495) 434-30-83.

Department: University Surgical Clinic named after V.S. Savelyev, Room 0076, 10/5 Leninsky prospect, Moscow 119049.

Rationale

Pelvic varicose veins with blood reflux, described as “Pelvic varicose disease” (PVD) or “Pelvic venous insufficiency” (PVI), represent one of the nosological entities of PeVD [1]. PVD and PVI develop in about 15% of women of reproductive age and 30% of female patients seeking medical help for CPP [2,3]. Two third of patients with PVI have no indications for surgical or endovascular interventions and require only medical treatment, which is based on VAD. The purpose of VAD treatment is to relieve PVI symptoms, primarily CPP, improve venous outflow from the pelvic organs, and reduce venous stasis in the pelvis [4,5]. A variety of diosmin-containing VADs are successfully used nowadays in the treatment of CVD, including PVI. Many studies have proven that their use is associated with the reduction or relief of leg pain, heaviness and swelling, as well as a faster healing of the venous ulcers [6,7]. Moreover, a number of studies have demonstrated a high efficacy of MPFF in relieving PVI symptoms and pelvic pain [8-12]. CPP significantly reduces the quality of life of patients with PVI, their social and household activity, and it is quite natural that patients seek to get rid of this suffering as soon as possible, using the most effective

drug in this regard. One of the most frequently asked questions by patients with PVI is: “What venoactive drug is best to take in order to relief or alleviate CPP?”

This is an absolutely natural question, because today the pharmacy chain offers a wide range of VADs. Based on an analysis of literature data, the most often used diosmin-containing VADs are MPFF (micronized purified flavonoid fraction), Diosmin 600, and the combination of hesperidin and diosmin. In the product labels for these VADs, the manufacturers claim about almost identical therapeutic effects in relation to the CVD treatment, and advertising campaigns in the media assure patients that each of them will provide an excellent effect in the treatment of venous diseases. However, there are no studies in the available medical literature comparing the efficacy and safety of various VADs in the treatment of PeVD. Moreover, the vast majority of studies on the treatment with VADs for PeVD were performed using MPFF 1000 [8-11]. This, in turn, creates the impression that the authors of these studies are biased by the manufacturer, i.e. have a conflict of interest that promotes the choice of MPFF 1000 for the treatment of PeVD.

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Aim and objectives of the study

Study aim: to evaluate the efficacy and safety of using various diosmin-containing VADs in the treatment of patients with PeVD.

Study objectives:

1. To evaluate the efficacy of MPFF 1000 in relieving CPP in female patients with PeVD;
2. To evaluate the efficacy of Diosmin 600 in relieving CPP in female patients with PeVD;
3. To evaluate the efficacy of Hesperidin + Diosmin 1000 in relieving CPP in female patients with PeVD;
4. To evaluate the safety (the number of side effects and adverse events) of MPFF 1000, Diosmin 600 and Hesperidin + Diosmin 1000 in the treatment of female patients with PeVD;
5. To compare the efficacy of MPFF 1000, Diosmin 600 and Hesperidin + Diosmin 1000 relieving CPP in female patients with PeVD;
6. To evaluate the patients' adherence to the recommended treatment with VADs using MPFF 1000, Diosmin 600 and Hesperidin + Diosmin 1000 in female patients with PeVD.

Study design

This will be a single-center randomized study. The period of the study will be from 2023 to 2024. The study will include 150 female patients with symptomatic PeVD.

Inclusion criteria:

- Age from 18 to 45 years;
- The presence of PeVD symptoms (CPP, dyspareunia, discomfort in the hypogastrium, dysuria, vulvar varicose veins);
- The presence of pelvic varicose veins with reflux in them, according to DUS;
- Pelvic venous reflux (PVR) lasting for greater than 1 s, according to DUS;
- Isolated dilation and reflux in the parametrial and uterine veins, according to DUS;
- Absence of competing abnormalities, accompanied by CPP.

Exclusion criteria:

- Asymptomatic form of the disease;
- Menopause;
- Pregnancy;
- Post-thrombotic disease;
- Neoplasms;
- Competing diseases with CPP;
- Known hypersensitivity to any of the components of the used VAD.

Each patient will sign a voluntary informed consent prior to the inclusion in the study.

Methodology

The study will include 150 consecutive female patients with symptomatic PeVD, according to the inclusion/exclusion criteria. All patients will undergo a clinical examination, transabdominal and transvaginal DUS of the pelvic veins to verify the diagnosis and to determine the diameters of the pelvic veins and the duration of reflux in them. The study will include patients with PeVD and isolated dilation and reflux in the parametrial and uterine veins. Previous studies have shown that the use of VADs in patients with a combination of reflux in the ovarian, parametrial and uterine veins is ineffective [4,14]. The CPP intensity will be assessed using a visual analogue scale (VAS), which is a 10-cm horizontal line ranged from 0 to 10 scores (1 cm equals 1 score). The CPP intensity will be assessed by VAS scores as following: 0, no pain; 1-3, mild pain; 4-6, moderate pain; 7-10, severe pain. After a brief instruction by an investigator, the patients will rate their pain intensity by making a mark on the line.

For randomization procedure, the sealed envelope principle will be used. Three groups of 50 patients each will be formed depending on the recommended VAD usage: group 1 (n=50) with MPFF1000; group 2 (n=50) with Diosmin 600; and group 3 (n=50) with Hesperidin + Diosmin 1000. After the start of VAD intake, the patients will be self-rating the pain intensity on VAS on the weekly basis. After 60 days from the VAD treatment start, the patients will undergo repeated clinical examination and provide an investigator with 8 completed VAS forms. Based on the repeated examination data and the VAS results, a comparative analysis of the clinical efficacy of VADs will be carried out. In a case of side effect or adverse event occurrence during a 2-month treatment course, patients inform the doctor-investigator about it within one day, and the decision is made either to continue, change the regimen of treatment or to discontinue it. Flow chart of the study is presented in ***Figure 1***.

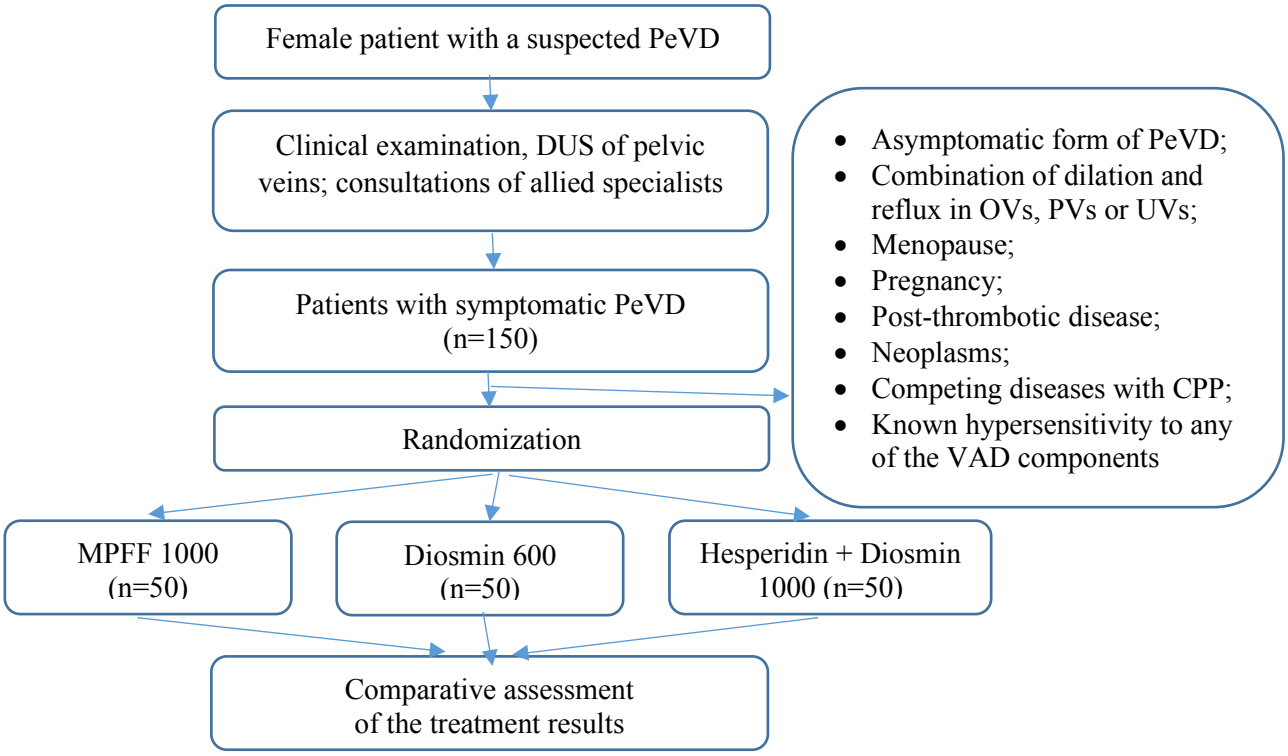

Figure 1. Flow chart of the study. *Abbreviations*: PeVD, pelvic venous disease; DUS, duplex ultrasound scanning; OVs, ovarian veins; PVs, parametrial veins; UVs, uterine veins; CPP, chronic pelvic pain.

1. *Clinical examination* includes obtaining medical history and information about complaints, physical examination, assessment of the local vascular status and measurement of the pain intensity by VAS. The clinical examination is carried out before DUS of the pelvic veins and then is repeated after completion of the VAD treatment course (i.e. after 2 months).
2. *Transabdominal and transvaginal DUS of the pelvic veins* is carried out after clinical examination and includes assessment of the patency and diameters of the pelvic veins, iliac

veins, inferior vena cava and renal veins, as well as identification of the blood reflux through the pelvic veins (gonadal, parametrial, uterine veins). Separately, the status of the left renal vein (LRV) is evaluated based on the measurements of its diameter and blood flow velocities in the area of intersection with the superior mesenteric artery and in the region of the renal hilum, as well as by calculating the diameter ratios and velocity ratios to assess the degree of LRV stenosis.

3. *Venoactive drug treatment.* Diosmin-containing VADs (MPFF 1000, Diosmin 600, Hesperidin + Diosmin 1000) will be used in accordance with the treatment regimens stated above.

The data of clinical examinations and DUS will be recorded in the patient's individual CRF.

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Safety of study and treatment

In a case of the development of VAD-treatment-related side effect or adverse event, the patient informs an investigator about this within 24 hours. The case is registered, and all necessary measures are taken to eliminate this side effect or adverse reaction. Depending on the nature and severity of the side effect or adverse reaction, the principal investigator makes a decision on the necessity to change the VAD treatment regimen or to discontinue it.

Follow-up period

Each patient will be followed-up for 2 months after the end of the study in order to exclude the occurrence of any side effects or adverse events, and to assess changes in the efficacy of performed treatment with time.

Data processing and statistical analysis

Based on the data from individual CRFs, the MS Excel tables will be created, and then the analysis of the data of interest will be performed. Statistical analysis will be carried out using MS Excel,

Statistica 6.0 software and the VassarStats online calculator (open-source project). The arithmetic mean (M) and standard deviation (SD) will be calculated. For comparisons with categorical variables, the Fisher's exact test will be used. For comparisons with continuous variables, the Student's t test or Mann-Whitney U test will be used as appropriate. Differences will be considered statistically significant at P value less than 0.05.

Presentation of the results and publication ethics

In addition to publishing the results of the study in scientific journals, making presentations at scientific forums and conferences, it is planned to use the results of this study when developing guidelines of the Ministry of Health and posting information about the study results on social networks. The leading role in publications belongs to S.G. Gavrilov. The publications will include names of E.P. Moskalenko, A.V. Alenichev and A.S. Grishenkova.

Duration of the study

The duration of the project is determined by achieving the required (150 patients) number of participants. The period of a patient's participation in the study, that includes clinical examinations, DUS, and the VAD treatment course, is 2 months. Investigators will be examining the patients before and 2 months after the VAD treatment course.

Expected issues

The issues with patient recruitment are expected, as the female patients with CPP are most often seen and treated by gynecologists. To solve this problem, information letters will be sent to antenatal clinics and outpatient facilities, and interaction will be established with gynecological hospitals. No financial issues are expected, as the study is carried out as part of the University's research program and does not imply any additional funding.

Responsibilities of investigators

Principal investigator Prof. Sergey Gavrilov:

Recruitment of patients, carrying out DUS, randomization of patients, prescription of treatment to the patients, and control of the patients' eligibility for the study, according to the selection criteria, the completion of documentation, and compliance with ethical standards.

Dr. Ekaterina Moskalenko, investigator:

Carrying out DUS of the pelvic veins, completion of documentation, and statistical analysis of the data.

Dr. Alexander Alenichev, investigator:

Recruitment of patients, prescription of treatment to the patients, completion of documentation, repeated clinical examinations of the patients, and statistical analysis of the data.

Dr. Anastasia Grishenkova, investigator:

Recruitment of patients, prescription of treatment to the patients, completion of documentation, repeated clinical examinations of the patients, and statistical analysis of the data.

Patient information form

Study title: «Comparative assessment of the efficacy and safety of venoactive drug treatment of pelvic venous disorder: results of a single-center prospective randomized trial»

Facility: Pirogov Russian National Research Medical University.

Introduction

Before you agree to participate in this study, it is very important that you read and understand the explanation of all proposed procedures. This document describes the aim, methods, benefits, and inconveniences related to this study. This document also describes other procedures that may be offered to you, and you have a right to withdraw from the study at any time. There can be no guarantees or confidence in the results of the study.

Nature and aim of the study

You are proposed to take part in a single-centre, prospective, randomized trial, the main purpose of which is to evaluate the efficacy of various venoactive drugs in the treatment of pelvic venous disorder. This study includes female patients with symptomatic pelvic varicose veins, accompanied by characteristic symptoms and signs (chronic pelvic pain, pain during and after sexual intercourse, heaviness and discomfort in the lower abdomen, frequent urination, the presence of varicose veins on the external genitalia). All patients who have signed informed consent will undergo a clinical examination by highly professional doctors, ultrasound examinations of the pelvic veins, which are necessary to verify the diagnosis, and study of abnormalities in the pelvic veins.

Study methods

Assessment of the clinical status, obtaining information about medical history and complaints, the assessment of pain using a visual analogue scale, physical examination, assessment of local status, and duplex ultrasound scanning of the pelvic veins.

Treatment methods

Study participants will be advised to take a venoactive drug (MPFF 1000, Diosmin 600 or Hesperidin + Diosmin 1000, by your random choice) for 2 months at the specific recommended dosage. As a study participant, you must fulfill certain requirements, namely: read a product label of the prescribed venoactive drug, take the venoactive drug at the same time every day for 2 months, inform the attending physician (investigator) about any side effect or adverse event that are indicated in the product label, assess every 7 days the intensity of your chronic pelvic pain by self-rating on the visual analogue scale, according to the instructions and explanations of the investigator given to you in advance. You must also report any changes in your physical or mental condition during the study.

Possible risks and inconveniences

While taking a venoactive drug, rare side effects and adverse events indicated in the product label can occur. These include, in particular, pain in the upper abdomen, nausea, diarrhea, skin rash, itching, headaches, dizziness, malaise, isolated swelling of the face, lips, eyelids. If these symptoms and signs occur, you must immediately consult a doctor and inform the investigator.

Findings

Any important information that will be obtained during the study that may affect your health will be available to you.

Voluntary participation/withdrawal

Your participation in this study is voluntary. The refusal to participate in it will not affect your further treatment in this medical institution, and all the medical care that you need will be provided in full. You can withdraw from the study at any time, and if so, you must inform your doctor immediately. Your doctor may exclude you from the study, if you do not follow your doctor's advices, if you are found to be ineligible for the study, if the study is terminated, or for administrative reasons.

Expected benefit

Venoactive drug treatment of pelvic venous disorder is an effective, safe and not burdensome method for patients. Taking a venoactive drug effectively relieves symptoms of pelvic venous disorders such as chronic pelvic pain, pain during sexual intercourse, heaviness and discomfort in the lower abdomen. The treatment duration depends on the severity of the disease and disturbances of the venous blood flow in the pelvic veins identified during clinical examination (ultrasound study), but usually does not exceed 2 months. The study will help determine which venoactive drug is most effective in relieving pelvic pain and other symptoms of pelvic venous disorder. The results of this study have not only scientific, but also significant practical implications.

Confidentiality

All medical records and study materials that identify you will be kept confidential and will not be made public in accordance with applicable laws. If the research results are published in the medical literature, your “incognito” mode will be kept and your identity will not be disclosed.

Monitors, auditors, representatives of the Ethics Committee and official authorities will receive, subject to confidentiality of information, access to original medical documents in order to verify the correctness of the clinical trial procedures and by signing the Informed Consent Form, you consent for this access.

For all questions regarding the examination and treatment offered to you for varicose veins of the pelvis, as well as for additional information, you can contact the investigators:

Prof. Sergei Gavrilov (mobile phone: +7(916)9299947); Ekaterina Moskalenko (mobile phone: +7 (985) 4100545); Alexander Alenichev (mobile phone: +7 (926) 2921111); Anastasia Grishenkova (mobile phone +7 (926) 1131119).

Informed consent form

Informed consent

I (full name), _____

was informed by the doctor-investigator (full name) _____

_____

about all aspects of the planned clinical trial.

I received information about the aim and objectives of this clinical trial, information about examination and treatment methods, the nature of ultrasound studies and venoactive treatment, its positive and negative aspects, the benefits and risks of participating in a clinical trial, and about my rights and responsibilities. I have been warned about possible complications and adverse events during venoactive drug treatment, and about my actions in the event of these complications.

I had an opportunity to discuss with the doctor-investigator all the questions that interested me and was satisfied with the answers I received.

I am informed that I will be included in the study only after I have undergone a complete examination (in accordance with the Protocol) and my medical and physical condition meets the criteria of eligibility for this study.

I voluntarily and consciously agree to participate in a clinical trial on evaluation of the efficacy of diosmin-containing venoactive drugs in the treatment of pelvic venous disorder, and I am informed that I have the right to refuse from or discontinue participation in this study at any time.

I agree to follow instructions, cooperate in good faith with the doctor-investigator, and immediately report to him/her about any problems with my health.

I am informed that if my health is harmed by the use of venoactive drug treatment or a medical procedure included in the plan of clinical and ultrasound examinations, I will be provided with medical care, the costs of which will be reimbursed by the insurance company with which I am insured.

I am informed that information about me and the results of my examination will be confidential and can only be disclosed to official representatives while maintaining anonymity.

By signing this Informed Consent form, I give my permission to access the medical data obtained in the study by those responsible for conducting the clinical trial, representatives of the Ethics Committee, and official representatives of the Ministry of Health of the Russian Federation.

I received a signed and dated copy of the Patient Information Form with a 5-page Informed Consent Form.

Patient's signature:

Patient's full name:

Date

(to be completed by the patient)

Investigator’s signature:

Investigator’s full name:

Date

(to be completed by the investigator)

Funding

The study has no special funding. The study will be carried out as part of the research activity of the Pirogov Russian National Research Medical University.

Other project support

No.

Links to other projects

No.

Participation in other research projects

The principal investigator and other investigator are not involved in other projects.

Funding and insurance

The study has no sponsors or special funding. Insurance of doctors and patients is carried out on the general principles of compulsory medical insurance in Russia.