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**Title:**

Influence of Rivaroxaban for Intermittent Claudication and Exercise Tolerance  
in Patients With Symptomatic PAD

**NCT number:**

NCT04305028

**Document date**

02/13/2020

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## INFORMATION No 1 FOR THE PARTICIPANT

concerning research carried out in the framework of the research project entitled

### ***Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial***

#### **• What are the theoretical basis and objectives of this ~~medical~~ experiment/research?**

The most common cause of peripheral artery disease (PAD) is arteriosclerosis. This disease is chronic and progressive, and its progression is associated with a gradual decrease in blood flow in the arteries of the lower limbs and the occurrence of symptoms of their ischemia. The characteristic signs of the disease include the intermittent claudication (IC), which is characterized by the occurrence of pain, chickens, numbness, and discomfort within the lower limb muscles. These symptoms intensify gradually while walking, forcing the patient to stop. The symptoms are caused by continuous, specific physical effort and quickly disappear when it is stopped. The limitation of the possibility to walk leads to a decrease in quality of life and adds to other consequences of atherosclerosis, i.e., an increased risk of cardiovascular incidents.

Pharmacological treatment of patients with intermittent claudication is aimed at modifying cardiovascular risk factors and improving the quality of life by alleviating pain and prolonging the claudication distance. One of the standard drugs used in this group of patients are anticoagulants, which include acetylsalicylic acid (ASA, other term: aspirin) and recently launched drug rivaroxaban (trade name of the medicinal product Xarelto).

Scientific studies to date indicate that the use of rivaroxaban in peripheral arterial disease together with acetylsalicylic acid can provide more effective cardiovascular protection and reduce the risk of acute/chronic limb ischemia and the risk of large amputations compared to the use of acetylsalicylic acid alone. On the other hand, this drug may increase the risk of bleeding.

Scientific studies indicate that rivaroxaban is also likely to have pleiotropic effects and, in addition to its anticoagulant effect, has the potential to inhibit the development of atherosclerosis. Therefore, it should affect the claudication distance, resulting in a slower reduction in exercise tolerance over time (slowing down or inhibiting further loss of gait). However, so far, no clinical trials have been conducted, which would demonstrate such protective effects of the drug.

**This study aims to evaluate the effect of rivaroxaban administered together with acetylsalicylic acid on the claudication distance in patients with peripheral artery disease in short term observation - 3 months.**

The research is carried out in a single-center, and concerns patients treated and/or diagnosed in the The Lord's Transfiguration Clinical Hospital of Poznan University of medical Sciences. The study is aimed at patients with the II degree of ischemia of the lower extremities caused by PAD, in the four-stage Fontaine classification. By joining this project, you agree to the random

selection of anticoagulant therapy: ASA or ASA + rivaroxaban and apply the chosen treatment regimen for three months. You also agree to perform a double treadmill test at an interval of three months and to appear on the scheduled date for this test. Our studies are carried out, taking into account the risk factors of vascular diseases, including genetic factors, but consent to genetic testing is not obligatory (separate consent of the participant of the study). This project will significantly contribute to the improvement of medical care in the patients covered by this study, deepening the diagnosis and evaluation of disease progression.

- **What are the rules of the ~~medical experiment~~/research, the methods and procedures used?**

If I agree to participate voluntarily in the research, it means that I am aware of the following facts:

1. By joining this project, I agree with the random selection of anticoagulant therapy: ASA or ASA + rivaroxaban and use of the recommended treatment regimen for three months. If Xarelto is included, I will take the first dose of this drug after performing the first treadmill test (a total of three months of therapy - from the moment of performing the first treadmill test).
2. I agree to perform two treadmill tests at an interval of 3 months. Therefore, I will go to the Laboratory of Functional Tests of the Department of Physiology and Biochemistry of the University of Physical Education in Poznan, Królowej Jadwigi Street 27/39; 61-871 Poznan (the test will take 30-60 minutes in total, including repetitions and cardiac qualification).
3. I agree with a double capillary and venous blood collection before and after the treadmill test to assess known and potential biomarkers of fatigue severity (a total of 2 x capillary and 2 x venous blood collection).
4. After the exercise, I will provide information on the subjective evaluation of the degree of fatigue (10 minutes).
5. I will undergo non-invasive tests to assess the condition of arterial vessels: an examination of intima-media complex thickness and stenosis in the carotid arteries (using Doppler ultrasonography), assessment of atherosclerotic lesions in the lower limbs arteries (blood pressure test on the arm and ankle for the calculation the ankle-brachial index, ABI) and percutaneous measurement of tissue blood supply to the lower limb arteries (TcPO<sub>2</sub>, using Precise 8000 device). I am aware that ABI and TcPO<sub>2</sub> measurements will be evaluated twice before and after each treadmill test (a total of 4 x during the study).
6. I am ready to extend the observation period to 6-12 months and therefore I will continue to apply the recommended pharmacotherapy and will attend a third control treadmill test after 6 and/or 12 months (to the Laboratory of Functional Research of the Department of Physiology and Biochemistry of the University of Physical Education in Poznań, 27/39 Królowej Jadwigi Street; 61-871 Poznań).

7. I agree to carry out the recommended laboratory tests, recognizing that in case of abnormal results, the recommended pharmacotherapy may change.

8. I will answer questions about my medical history, pharmacotherapy, cigarette smoking habit and alcohol consumption, and family history of cancer and cardiovascular disease when I qualify for the study. This stage will take no more than 15 minutes.

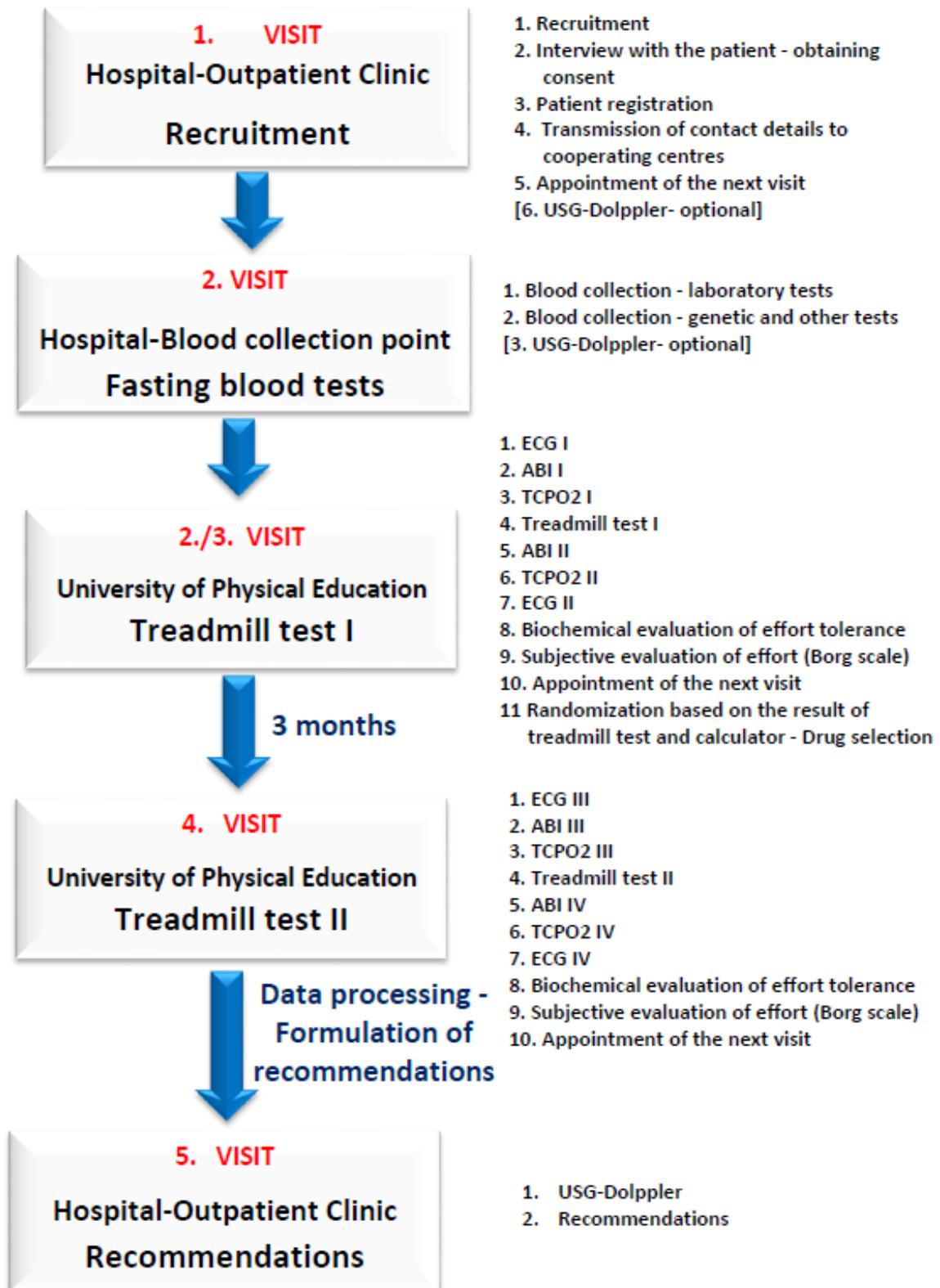
9. At the time of qualifying for the study, I will undergo a routine medical examination, including measurements of blood pressure, weight, height, waist, and hip circumference. This stage will take no more than 15 minutes.

10. At the time of qualifying for the study, I agree to make available the results of cardiovascular tests included in my clinical records, including the results of laboratory, imaging, and other diagnostic tests.

11. I agree with a fasting blood collection for genetic testing and other studies of biomarkers, in volume 9-27 ml. I am aware that blood collection from the ulnar vein is a standard invasive test that causes about 1 minute of discomfort and pain, and the risk of bruising, redness, or skin infection is very low (number of blood withdrawn 1-3x). If it is not possible to perform blood collection from the ulnar vein, I will consent to blood collection from another place (wrist, hand).

The following figure shows a general scheme of the study (Figure 1).

**Figure 1:** Scheme of prospective studies.



- **What are the therapeutic or other benefits to the participant of the study?**

I am aware that participation in the research does not affect the course of my treatment and medical services. The pharmacotherapy protocol, used in this study, does not exceed the standard of treatment in patients with peripheral arteriosclerosis. Therefore, I am aware that I may not benefit directly from participation in the study.

However, I am aware that I can significantly improve my knowledge of my health. The extended diagnostic tests performed will allow for a more precise assessment of my disease and its better control. I will obtain the results of my examination concerning the occurrence and severity of changes in my arteries. In particular, the result of a treadmill test, assessment of carotid artery stenosis (results of Doppler ultrasound examination), ankle-arm index (ABI) value, and lower limb tissue oxygenation (TCPO<sub>2</sub>) degree. I will also be informed about my heart electrocardiography (ECG) result.

In the case of performing above-standard laboratory results (at the expense of the Medical University or the University of Physical Education), I will have access to their results. After the observation period, I will also receive guidelines for further anticoagulant therapy, to find out whether it would be advisable to use additional drugs in addition to acetylsalicylic acid. I will also be informed about the average results for the entire study population.

Besides, I will not pay for outpatient and medical examinations performed on me several times during the project.

### **What are the risks involved in participating in this scientific study?**

This study entails additional but minimal risks for the patient due to the performance of the treadmill test and additional blood sampling.

The treadmill test is a generally safe test, and complications are rare. As with any medical procedure, however, there is a risk of complications, including occurrence:

- (a) Low blood pressure. Blood pressure can drop during or immediately after walking, causing dizziness or fainting. The problem should disappear after the exercise.
- (b) Abnormal heart rate (arrhythmia). The arrhythmias caused by a treadmill test usually disappear shortly after the end of the march.
- (c) Heart attack (myocardial infarction). Although extremely rare, a treadmill test can cause a myocardial infarction.

To reduce the likelihood of these risks, qualification for the test will be based on ECG and blood pressure control tests and will be repeated after the test (ECG test and blood pressure assessment). The treadmill test will be performed by qualified persons under the supervision of a physician.

The tests will require venous and capillary blood collections. The collection of blood from the ulnar vein (9-27 ml in total) is a standard invasive test that causes about 1 minute of discomfort and pain. The risk of bruising, redness, or skin infection is very low. Whenever possible, to reduce the discomfort, additional blood samples will be taken during blood collection for other routine laboratory diagnostic tests. If it is not possible to take blood from the elbow vein, the blood will be taken from a vein in another location (wrist, hand) with the consent of the test person. The capillary blood collection from the fingertip also causes short (30 s) pain and discomfort to the patient, with a very low risk of bruising, redness, or skin infection.

- **Insurance conditions in case of damage suffered by the patient during the examination.**

The subjects and investigators in this project are covered by

- a) the policy of the Karol Marcinkowski University of Medical Sciences in Poznań; 10 Fredry Street, 61-701 Poznań and
- b) the policy of the Academy of Physical Education in Poznań, 27/39 Królowej Jadwigi Street; 61-871 Poznań

### **Is it mandatory to participate in the study, or can I withdraw from it?**

Participation in the study is entirely voluntary, and I have the possibility to withdraw from the study at any stage of the research, with the right to continue treatment in the same Department/Outpatient Clinic.

- **Is my personal data protected?**

All research under this project is conducted in accordance with Article 24(1) of the Act of 29 August 1997 on the protection of personal data (consolidated text: Journal of Laws of 2016, item 922, as amended) and Article 7(2) of the Regulation of the European Parliament and of the Council of the EU 2016/679 of 27 April 2016, the General Data Protection Regulation (the GDPR), by the project administrator, the Karol Marcinkowski Medical University of Poznań, 10 Fredry Street - Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, located at Długa Street 1/2 61-848 Poznań, to the extent necessary to carry out the research project.

Personal data are processed to identify samples, statistical analyses, and conduct prospective observations about the clinical course and to enable possible contact with the patient for health consultations by the project administrator. Providing the data is voluntary, the researched person has the right to access the data and the possibility of supplementing, correcting, and demanding its deletion. None of the data shall be shared with other entities, including third countries. Research results will be published anonymously. Your consent meets all the conditions referred to in Article 7 of the GDPR; you have the right to withdraw your consent at any time, by providing this information by telephone. (61) 854 91 41 or in person at the Department of Vascular and Endovascular Surgery, Angiology, and Phlebology. If the

processing of the patient's data violates the regulations of the GDPR, the person examined has the right to lodge a complaint with the President of the Office for Personal Data Protection. Personal data will be stored for the purpose of achieving a scientific objective.

- **Who finances this research?**

This research is financially supported by the Poznan University of Medical Sciences and the University of Physical Education in Poznan from the funds for scientific research. In the future, we plan to apply for research funding from the Ministry of Science and Higher Education and other institutions financing non-sponsored research.

## **INFORMATION No 2 FOR THE PARTICIPANT**

concerning genetic research carried out in the framework of the research project entitled

### ***Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial***

- **What molecular tests will be performed using the collected biological material - blood samples?**

Blood samples will be used to isolate DNA and other particles of potential importance for the development of cardiovascular diseases (biomarkers). Within the limits of available resources, it is planned to perform genotype analysis for the candidate genes, selected on the basis of literature data, and to study factors influencing gene expression.

Genetic evaluation will include genes affecting the function of blood vessels; e.g. genes associated with the development of blood vessels (*HIF1A*, *VEGFA*) or their enzymatic decomposition (*MMP9*), lipid metabolism (*PONI*, *AopE*), homocysteine metabolism (*MTHFR*, *PONI*) and selenium metabolism (*SEPP1*) in the body, which will allow to select changes potentially associated with the risk of development and progression of atherosclerosis. Among the studied biomarkers, proteins, amino acids, lipids, lipoproteins, circulating cells, molecules of circulating RNA, enzyme activity etc. will be included. On the collected material, as the resources for research are obtained, it is planned to conduct research on the whole genome (a sequence of all genes and non-coding fragments), analysis of its modifications that affect the expression of genes (epigenome), examination of gene expression (transcriptome) and examination of all blood proteins (proteome).

The planned molecular studies are scientific in nature. Results will not be obtained using diagnostic tests, nor will they be subject to clinical interpretation. They will be evaluated collectively, in groups of patients. Therefore, the results obtained will not constitute results of diagnostic value for an individual patient and will not be further disseminated.

### **What will happen to the collected biological material after the study is completed?**

The obtained material for molecular tests: blood and isolated particles (DNA, RNA, proteins, etc.) will be deposited in a bank and used for further scientific research.

Unused material will be destroyed. The participant of the study has the right to withdraw consent to the use of the biological material at any time and to request that DNA samples be destroyed.

## PATIENT INFORMED CONSENT FORM

***Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial***

First and last name .....

The research project concerns the analysis of the effect of rivaroxaban on the intermittent claudication distance and exercises tolerance in patients with symptomatic peripheral artery disease. This is a study that considers patients with ischemia of lower limbs classified as grade II in Fountaine's classification. Recognized and potential risk factors for cardiovascular disease, will be considered in this study.

I declare that:

1. I have been fully informed of the details of the study

I agree to participate in this project as a representative of a study group and to carry out the following activities:

a) Random selection of anticoagulation pharmacotherapy: acetylsalicylic acid (ASA) or ASA + rivaroxaban (medicinal product Xarelto)

b) Apply the recommended treatment regimen for three months.

c) If Xarelto is included, take the first dose on the day following the first treadmill test

d) Perform, after cardiological qualification, two treadmill tests at an interval of 3 months, and for that, I'm going to visit the Laboratory of Functional Research of the Department of Physiology and Biochemistry of the University of Physical Education in Poznań, 27/39 Królowej Jadwigi Street; 61-871 Poznań

e) Donate twice my capillary and venous blood, before and after each treadmill test, in order to evaluate the biomarkers related to the physical effort (a total of 2 x capillary and 2 x venous blood collection).

f) Provide information on the subjective assessment of fatigue after a treadmill test

g) Perform non-invasive tests to assess the occurrence and severity of atherosclerotic lesions in the arteries using the following methods: Doppler ultrasonography, assessment of the ankle-brachial index (ABI, measuring blood pressure on the foot and arm), percutaneous measurement of tissue oxygen supply to the lower limb (oxygen pressure measurement, TcPO<sub>2</sub>). I know that ABI and TcPO<sub>2</sub> assessments will be performed before and after each treadmill test.

h) Perform the recommended laboratory tests.

i) Provide information on my cardiovascular risk factors, including smoking and alcohol consumption, my medical history, pharmacotherapy, cardiovascular diseases, and family history of cardiovascular diseases and cancer.

j) Perform a routine medical examination, including measurements of blood pressure, weight, height, waist, and hip circumference.

k) Donate 9-27 ml of fasting blood to perform additional laboratory tests and analysis of potential biomarkers of vascular diseases including proteins (proteome), circulating cells, circulating RNA molecules, enzyme activity, micro and macroelements, profile: amino acids, metabolites, lipids, and lipoproteins, etc.

l) Share selected information from my medical records for this project, provided that the data protection law is respected.

m) I agree to include my clinical data and laboratory results in a database and their processing for scientific purposes on an anonymous basis.

n) I agree with the use of the results of this study for the development of scientific reports.

3. I consent to the storage of my biological material after the completion of these studies and to their use for other scientific research on diseases of civilisation.

4. I am willing to extend the observation period to 6-12 months and therefore I will continue to use the recommended pharmacotherapy and will attend a control treadmill test after 6 and/or 12 months (to the Laboratory of Functional Research of the Department of Physiology and Biochemistry of the University of Physical Education in Poznan, 27/39 Królowej Jadwigi Street; 61-871 Poznan).

I know I can quit the study at any time. I realize that the information received in the course of the research is strictly confidential and that my identity will not be disclosed.

.....  
date and place of declaration

.....  
signature of the Participant  
or its statutory  
representative

.....  
signature of the Investigator

PATIENT INFORMED CONSENT FORM  
-consent to genetic testing

***Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial***

First and last name .....

The research project concerns the analysis of the effect of rivaroxaban on the distance of intermittent claudication and exercises tolerance in patients with symptomatic peripheral artery disease. It is a study with consideration of patients with ischemia of lower limbs classified as grade II in Fountaine's classification. Recognized risk factors for vascular disease, as well as potential risk factors, will be considered in the study.

I declare that:

1. I have been fully informed of the details of the study

I agree to participate in this project as a participant of the researched group and to carry out the following activities:

- a. Collection and use of my venous blood samples (9 ml) for the isolation of genomic DNA
- b. Performing analysis of variants and mutations in candidate genes, with potential impact on blood vessel function, as well as analyses of the entire human genome and the sequences and modifications responsible for gene expression (epigenome)
- c. Collecting the results obtained in the database and processing them for scientific purposes on an anonymous basis
- d. Using the results obtained to develop scientific reports

3. I consent to the storage of samples of my DNA after this research is completed and to its use for other scientific research on the diseases of civilization.

I know that I may cancel my research at any time. I realize that the information received in the course of the research is strictly confidential and that my identity will not be disclosed.

.....  
date and place of declaration

.....  
signature of the Participant  
or its statutory  
representative

.....  
signature of the Investigator

First and last name of the participant

.....

**STATEMENT BY THE PARTICIPANT IN THE STUDY**  
**- acceptance of insurance conditions**

I hereby declare that I have been informed in detail about the insurance conditions of my participation in the study entitle:

*Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial*

and I accept these terms.

.....  
date and place of declaration

.....  
signature of the Participant  
or its statutory  
representative

.....  
signature of the Investigator



KAROL MARCINKOWSKI UNIVERSITY OF MEDICAL SCIENCES IN POZNAŃ

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[www.ump.edu.pl](http://www.ump.edu.pl)

Ladies and gentlemen,

Karol Marcinkowski Medical University of Poznań, 10 Fredry St., informs that, in accordance with the current Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals concerning the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation), the GDPR:

- 1) The administrator of your personal data is the Karol Marcinkowski University of Medical Sciences in Poznań, ul. Fredry 10 -Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, Długa Street 1/2; 61-848 Poznań.
- 2) Your personal data are processed for the purpose of the research project *Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial*
- 3) Your personal data will be processed by the Karol Marcinkowski University of Medical Sciences in Poznań, 10 Fredry Street - Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, located at Długa Street 1/2 61-848 Poznań for a period depending on the purpose of processing personal data, at least 5 years.
- 4) Your personal data will be transferred by the Karol Marcinkowski Medical University of Poznań, 10 Fredry Street - Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, located at Długa Street 1/2 61-848 Poznań, to processing entities under a contract of entrustment and other entities authorized under the law to carry out the research project.
- 5) You have the right to obtain information concerning the processing of your personal data by the Karol Marcinkowski Medical University of Poznań, 10 Fredry Street - Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, located at Długa Street 1/2 61-848 Poznań, to demand their correction, deletion or restriction of the processing of your data, the right to transfer your data, the right to object to the processing and the right to withdraw your consent to the processing of personal data at any time. Withdrawal of consent does not affect the lawfulness of the processing, which was carried out on the basis of consent before its withdrawal.
- 6) You have the right to complain with the Data Protection Office if you believe that the processing of your personal data violates the law.
- 7) In all matters concerning the processing of personal data and the exercise of rights related to the processing of personal data, you can contact the Inspector of Personal Data Protection by e-mail: [abi.ump@ump.edu.pl](mailto:abi.ump@ump.edu.pl).



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## Consent to the processing of personal data

.....  
First and last name

.....  
Address of residence

.....  
PESEL number

.....  
E-mail

.....  
Phone number

I agree to the processing of my personal data in the scope of identification data (name, surname, PESEL), contact data (address, telephone, e-mail) and medical data obtained from completed questionnaires and results of performed tests, as well as data obtained during observation and supervision by the Karol Marcinkowski Medical University of Poznań, 10 Fredry Street - Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, located at Długa Street ½; 61-848 Poznań, to carry out the research project

*"Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial"*

based on Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals concerning the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation), referred to as the GDPR Article 6(1)(a), Article 9(2)(a).

Signature of the Participant or its statutory representative

.....

Place and date

.....



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First and last name of the Participant

.....

**STATEMENT OF THE PARTICIPANT**  
**(OR ITS STATUTORY REPRESENTATIVE)**  
**- consent to contact**

I, the undersigned, declare that I agree to be contacted by telephone and e-mail regarding the scientific research "*Influence of rivaroxaban 2.5 mg two times a day for intermittent claudication and exercise tolerance in patients with symptomatic peripheral arterial disease (PAD) - a randomised controlled trial*"

**First and last name of the Participant.....**

Date of birth .....

Phone number: .....

E-mail: .....

At the same time I declare that I have the right to withdraw my consent to contact at any time.

.....  
date and place of declaration

.....  
signature of the Participant  
or its statutory  
representative

.....  
signature of the Investigator