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PATIENT INFORMATION AND INFORMED CONSENT FORM

Evaluating the Use of AdvanRx in a Randomized Controlled Trial of Adults Treated for HYPERTENSION (EARLY)

Protocol Number: AD-NA-001

Principal Investigator: *[Enter PI name, address and phone number]*

Study Coordinators: *[Enter Study Coordinator(s) name, address (if different from above)]*

Phone Number: *[Enter phone number, including number for emergencies]*

Study Sponsor: **Advantage Clinical. Toronto Canada**

Protocol Version: **# 1**
Protocol Effective Date: 15 January 2016

INTRODUCTION

Before agreeing to participate in this research study, it is important that you read and understand the following explanation of the proposed procedures. This consent form describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative treatments that are available to you and your right to withdraw from the study at any time. No guarantees or assurances can be made as to the results of the study.

This consent form is intended for the patient who is eligible to participate in this study. However, if the patient is incapable of providing consent, the consent of a relative or other authorized representative will be sought. If at any time during the study, the patient becomes capable of providing consent, informed consent will be sought from them as a condition of their continuing participation.

You have been asked to consider taking part in a research study of an blood pressure medication called AdvanRx that is being tested in patients with high blood pressure.

Before you decide whether or not to take part, it is important for you to know why the research is being done and what it will involve. This form provides all the information we

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think you will need to know in order to decide whether or not you wish to take part in this study. If you wish, please discuss it with family members, friends, the study doctor, the study coordinator, or your family doctor. If you have any questions after you read through this form, or if there is anything that is not clear to you, please ask a study doctor or study coordinator. If all of your questions are answered to your satisfaction, and you decide to take part, you will be asked to sign this consent form. You will be given a signed and dated copy of this consent form to keep for your records.

BACKGROUND AND PURPOSE

You are being asked to take part in this research study because you have a medical condition called hypertension, or high blood pressure. Hypertension is a medical condition resulting from a range of factors, including family history, lifestyle, and genetics.

This is an investigational research study to compare a blood pressure medication called AdvanRx that is used to lower blood pressure, compared to a placebo or inactive medication. "Investigational" means that AdvanRx has not been approved by the Health Canada or the United States Food and Drug Administration (FDA) as a treatment for hypertension, but may be tested in research studies.

AdvanRx has been used in patients in approximately 150 patients in previous clinical studies. This study of AdvanRx will be conducted in multiple hospitals in the United States and Canada.

The study sponsor is Advantage Clinical. Advantage Clinical is a pharmaceutical company located in Toronto, Canada and is providing the funds necessary to conduct this research study. The study doctor is being paid for his/her involvement in the study. Advantage Clinical designed the study and drafted the study plan and manufactures AdvanRx at it's facility in Toronto Canada.

DESCRIPTION OF THE RESEARCH

About 100 patients will participate in this study. You will be expected to participate in the study for up to 90 with four study visits:

- Enrollment Visit
- Day 30
- Day 60
- Day 90- End of Study Visit

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Participation in this study requires informed consent. After you have provided consent for yourself, the first study-related procedure is a set of baseline assessments. The research team will look at your vital signs (heart rate, blood pressure and breathing rate) and obtain blood samples. You will also receive an ECG, which is a test looking at the function of the heart. The ECG will require sensors to be places on your chest to monitor heart activity for 5-10 minutes. You will also receive a physical exam from your study doctor.

You will then be randomly assigned (like flipping a coin) to one of two treatment groups. The probability of receiving any of these treatments is 1 in 2 (50%). You will either receive the AdvanRx 1mg, or you will receive a placebo therapy. The placebo in this study contains no pharmaceutical ingredients.

Depending on which group you are randomly assigned, you will either receive 90 AdvanRx 1mg tablets, or you will 90 placebo (or inactive) tablets. You will not be informed of which treatment you are receiving since this is a double-blind research study (meaning, neither you nor your doctor will know which treatment you will receive). This is done to ensure the results of the research study are not biased and are fair. However, in the case of an emergency, the doctor can quickly find out which treatment you are receiving.

These treatment groups will be used for comparison to find out whether AdvanRx will make a difference in patients receiving the actual treatment compared to those who receive placebo. You will be provided with a bottle of 90 tablets and instructed by your study doctor on taking them.

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STUDY PROCEDURES

Pre-Treatment Procedures

If you sign this consent form, before being given the study treatment, the following study-related procedures will happen (in no particular order):

1. Information will be collected about your general medical history, including your past and current medical conditions and medications you are taking.
2. A physical examination will be performed.
3. Information will be collected to determine how well your organ systems are functioning.
4. Vital signs will be collected, including temperature, heart rate, breathing rate, and blood pressure.
5. An electrocardiogram (ECG) (a painless test that measures the electrical activity of your heart) will be performed.
6. Blood samples (at most about 15 ml, or about 1 tablespoon) will be collected.

Study Treatment and Monitoring

Day 30 and Day 60

At these study visits, the following study-related procedures will be performed:

1. Vital signs, including temperature, heart rate, breathing rate, and blood pressure.
2. Review of medications you are taking.
3. Blood samples will be collected (about 15 ml, or about 1 tablespoon) for laboratory testing.
4. Due to your participation in the study, you will be asked about how you feel and you will be evaluated for any possible side effects you might have during the study.

After Study Treatment

Day 90

After you have been completed the study, or withdrawn, the following study-related procedures will be performed:

1. Vital signs, including temperature, heart rate, breathing rate, and blood pressure, will be collected.

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2. Blood samples will be collected (about 15 ml, or about 1 tablespoon) for laboratory testing.
3. Review of medications you are taking, and to review lab results.
4. You will be asked about how you feel and you will be evaluated for any possible side effects you might have during the study.
5. A physical examination will be performed.
6. An electrocardiogram (ECG) (a painless test that measures the electrical activity of your heart) will be performed.

Overview of Procedures

The blood samples will be used to measure the levels of factors in the blood that will give the study doctors information about your general state of health. The amount of blood that will be drawn over the entire study period for study purposes will add up to about 30 ml (approximately 2 tablespoons).

At each study visit, the study doctor or their staff will ask questions about your health, and if possible, they will ask you how you have been feeling since last being seen by the research team. The research team will also collect data (information) about the medications that you are currently receiving.

ALTERNATIVES TO PARTICIPATION

The alternative is not to take part in the study. If you choose not take part in this study, you will continue to receive the same standard and level of care as any patient with high blood pressure. Standard treatment for high blood pressure includes but is not limited to, the following:

- Blood pressure medication
- Lifestyle Coaching

The study doctor will discuss these treatments and therapies with you.

POTENTIAL HARMS (RISKS, INJURY, DISCOMFORTS OR INCONVENIENCE)

As with any treatment, it is possible that AdvanRx could cause reactions or discomforts and there may be risks to patients participating in this study. As of June 1, 2015, approximately 150 adult patients with high blood pressure have been given AdvanRx in research studies. In general, AdvanRx has been well tolerated in subjects that have completed previous research studies.

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When AdvanRx was administered, some adverse events (bad effects) were observed. In the studies conducted on patients with high blood pressure, there were some adverse events seen that could possibly be considered to be related to the use of AdvanRx. These events may have been related to the PMX cartridge, or they could have been related to the patient's illness.

In human studies of AdvanRx involving patients that had high blood pressure, the most common side effects included:

- Low blood pressure, dizziness, increased urine output

Other risks of taking part in this study may include the following:

- You may experience some temporary discomfort, bruising, or rarely, infection at the site of a needle stick, in the process of drawing blood samples
- You may experience some temporary discomfort by being asked to lie quietly for a short period of time and a slight skin irritation (like removing a band-aid™) in the process of performing the ECG.
- As with any drug, it is possible to experience a drug reaction. A sensitivity reaction may include itching, rash, hives, shortness of breath, or even, in rare circumstances, a severe allergic reaction that may be life threatening.

In addition to the risks named above, AdvanRx treatment and the study procedures might have other risks not known at this time. At any time during this study, you might experience a return or worsening of symptoms related to high blood pressure. Your doctor, nurses and other research staff will be following you closely to look for and treat any possible adverse events (bad effects).

NEW FINDINGS

Any new important information which is discovered during the study and which may influence your willingness to continue participation in the study will be made available to you.

BENEFITS

You may benefit as a result of your participation in this study. There is, however, no guarantee that you will benefit from your participation in this study. Your participation in this research study may help other people with high blood pressure in the future.

PAYMENT FOR TREATMENT OF RESEARCH-RELATED INJURY

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If you are injured as a result of participation in this research study, the study doctor will provide any medical care needed to treat those injuries. To the extent not covered by your medical insurance, all reasonable medical and hospital costs required for the diagnosis and treatment of an injury caused by the study, the study procedures, or laboratory work required by this research study will be provided to you, free of charge. Neither the study doctor nor Advantage Clinical plan to provide any other form of compensation for such things as lost wages, or pain and suffering. However, you do not give up any of your legal rights by signing this informed consent document.

COSTS

There will be no charge to you for participating in this study. The study treatment and study-related procedures will be provided at no charge to you or your insurance company. You will not be given money or otherwise financially compensated to take part in this study. If you have any questions regarding medical and hospital charges, medical insurance coverage, or expenses related to this study, please discuss them with your study doctor.

CONFIDENTIALITY

Although the results of this study may be presented or published for scientific purposes, your identity will be kept confidential. Only your initials and a study number will be recorded. Records of your participation in this study will be held confidential except as disclosure where required by law or as described in this informed consent document (under "Confidentiality" or "Authorization to Use and Disclose Protected Health Information"). The study doctor, the sponsor (or persons working on behalf of the sponsor), and under certain circumstances, the Health Protection Branch of Canada, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify you by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, you will not be identified.

COMPENSATION FOR PARTICIPATION

If you believe you have been injured by the study treatment, or a procedure required to be conducted by the study protocol, you must immediately notify the study doctor. The study doctor will provide you with medical advice. It is in your best interest to follow that advice.

If you suffer a physical injury as a direct result of the study treatment, or the conduct of a procedure required to be conducted by the study protocol, the sponsor (Advantage

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Clinical.) will provide reimbursement for the reasonable and necessary medical costs related to that injury if:

- Your injury was not deliberately caused; and
- You followed the medical advice of the study doctor; and
- The injury was not the result of negligence or misconduct of any agent or employee of the institution or hospital.

The sponsor (Advantage Clinical) will not provide reimbursement if:

- Your injury was deliberately caused
- The injury was the result of negligence or misconduct of any agent or employee of the institution or hospital

There are no plans to reimburse you for things like lost wages, disability or discomfort, loss of consortium (companionship), underlying or unrelated medical conditions, or for medical expenses that have been covered by your medical insurance, or third parties or any government programs providing medical coverage (like Federal, state, or provincial health coverage). Compensation for medical expenses is not an admission of fault or liability by Advantage Clinical, or anyone else.

The cost of any medical treatments or procedures required for any illness, injury or complication related to your high blood pressure, or any other medical problem not related to the study drug, or to a procedure required to be conducted by the study protocol, will remain your responsibility or the responsibility of your health insurance company.

If you suffer a physical injury from (the study drug procedure(s), or participation in this study), medical care will be provided to you in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor release the study doctor(s), sponsors or involved institutions from their legal and professional responsibilities.

EMERGENCY CONTACT / IRB CONTACT

If you have any questions about your rights as a research subject or complaints regarding this research study, you should call or write *[enter IRB name, address and phone number]* during business hours Monday - Friday 8:00 a.m. to 4:30 p.m. EST. *[Enter IRB name]* is an independent committee established to help protect the rights of research subjects.

Study Coordinator and study doctor emergency contact information:

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VOLUNTARY PARTICIPATION / WITHDRAWAL

Your decision to participate in this study is voluntary. You may choose not to participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care.

The study doctor or sponsor can stop your participation at any time without your consent for the following reasons: if it appears to be medically harmful to you, if you fail to follow directions for participating in the study, if it is discovered that you do not meet the study requirements, if the study is canceled, or for administrative reasons.

If you choose to stop taking part or are asked to stop taking part in this research study, you will be asked to complete the procedures described for Day 90.

PRIMARY CARE PHYSICIAN / SPECIALIST NOTIFICATION OPTION

Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.

_____ Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ I do not have a primary care physician/specialist.

_____ The study doctor is my primary care physician/specialist.

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SIGNATURE PAGE

Your signature below, and initials on each page, on behalf of yourself or the person for whom you are designated to provide consent, indicates that you have had an opportunity to ask questions, all information has been explained to your satisfaction and that you have read and voluntarily agree to participate. A copy of the signed consent form has been given to you.

PATIENT:

Signature of Patient (or Legally Authorized Representative*)	Date	Time

Print Name	Phone Number

***By signing this consent form, I verify that I have the authority to give permission for this person (patient) to participate in this study**

STUDY STAFF:

Signature of Person Obtaining Informed Consent	Date	Time

Signature of Principal Investigator	Date	Time