University of Glasgow

College of Medicine, Veterinary & Life Sciences
Institute of Cardiovascular & Medical Sciences

INFORMATION SHEET

(February 2013, version 1)

Study title: A Systems Biology Biomarker Based Approach to the Detection of Microdose Recombinant Human Erythropoietin Doping.

You are being invited to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. This project is being financed and supported by the World Anti-Doping Agency.

Thank you for reading this.

What is the purpose of the study? The project is aimed at validating a number of blood tests that can be used to detect erythropoietin (Epo) abuse. Presently, Epo abuse is detected indirectly in blood or directly in urine samples. The objective of this study is to build on the work already performed in the area of blood testing to detect Epo abuse and potentially provide alternative and robust gene based testing methods in the battle against drugs in sport, and in particular, Epo abuse. This will benefit athletes who believe in drug free sport.

Why have I been chosen? You have been selected as a possible participant in this investigation because of your status as non-smoking healthy male aged 18-35 years who trained at least 3 sessions per week, >1.5 hours per session. 10 volunteers are being sought.

Do I have to take part? It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part? Initially, you will be asked to undergo a medical examination by a qualified medical practitioner to obtain information related to your general health and to establish your suitability as a subject in the study.

If selected, you will be asked to participate in a trial over a 12-week period twice (2 x 12 weeks in total). You will be randomly assigned to group 1 or 2 in a cross-over trial. In a cross-over trial, the groups each have the different treatments in turn. Group 1 will receive subcutaneous injections of recombinant human Epo twice a week for 7 weeks during the first trial, while they will receive a placebo of saline solution during the second trial; In contrast, group 2 will first receive the placebo during the first trial, while they will receive the Epo injection during the second trial. A placebo is a dummy treatment which looks like the real thing but is not. It contains no active ingredient. You will self administer all injections (just under the skin in the abdomen area) using a small needle under the supervision of trained investigators. You will not know in which treatment group you are in until the end of the entire study. The Epo doses will vary during the administration from 20 to 40 units per kilogram body weight.

As the production of red blood cells require iron and because Epo will boost the production of your red blood cells, you will also receive daily iron tablets providing approximately 65 mg of iron during the 7 weeks of Epo administration to make sure that your iron stores are adequate throughout the study. Iron will be substituted by carbonate tablets during the placebo trial.

Overall, you will be asked to come to the lab on 25 occasions in total during each trial.

- On 13 occasions (once a week – time ~25 min), we would like to take a small amount of blood (10 mls equivalent to 2 teaspoons) from your arm with a needle. You will be asked to provide a urine sample. Your resting heart rate and blood pressure as well as your body weight will be measured. You will be asked to fill up a small questionnaire to assess how you are feeling.

- On 7 occasions (once every two week – time ~45min), we would like to take a small amount of blood (15 mls equivalent to 3 teaspoons) from an intravenous line in your arm. In addition to the measurements described above, you will be asked to breath a small non-toxic dose of carbon monoxide through an equipment for measuring breathing in order to determine your total amount of haemoglobin. Haemoglobin is part of your red blood cell which transports oxygen from your lung to your muscles.

- On 6 occasions (once a week during the injections – time 5 min), you will be asked to come to the lab to only receive your injection.

- On 5 occasions (3 times before and twice after the injections – time ~45 min), you will be asked to perform exercise performance tests on a laboratory bicycle, including two maximal oxygen uptake ($\dot{V}O_{2max}$) tests, two repeated sprint ability tests and one familiarisation of the latter test. Prior to each test, you will be asked to fill up a small questionnaire to assess how you are feeling. The $\dot{V}O_{2max}$ test consists of pedalling on the bicycle or running on a treadmill while the load or speed is gradually increased until exhaustion. You will wear a mask during the test which will allow us to measure your gas exchanges. The repeated sprint ability test consists of 10 x 10 s all-out sprints separated by a 50 s rest interval. We would like to take a small amount of blood (15 mls equivalent to 3 teaspoons) from your arm before, during and after the repeated sprint ability test.

We will provide you with a heart rate monitor and ask you to record all training sessions that you do during the 2 x 12 week period for us to be able to monitor your physical activity.

You could be compensated for travel expenses and loss of earnings according to verified documentation but you will receive no other payments.

What do I have to do? You will not be able to consume any alcohol 24 hours prior to each lab visit. You will be excluded from participating in this study if you take drugs (recreational or performance enhancing drugs).

Finally and importantly, you will be ineligible to compete during the 2 x 12 week duration of the study. However, the World Anti-Doping Angency, the sponsor of the study, will not restrict subsequent participation in sporting competitions.

What are the possible side effects, disadvantages and risks of taking part? There are only minimal risks associated with the blood sampling procedure. Slight bruising may occur around the site of collection, but this can be minimised by applying pressure at the site for a minimum of 3 minutes. Blood will be collected by either, a qualified phlebotomist and/or a medically qualified individual.

There have been no reports of significant side effects as a result of Epo injections in normal healthy individuals. However, Epo may increase arterial blood pressure. Other possible but rare side effects of Epo injections are allergies or skin reactions and flu like symptoms (mild and of short duration). In patients, increased risk of blood clot and suppression of natural Epo production are rare side effects of Epo injections. The management of side effects listed above, will include cessation of treatment and withdrawal from further

participation in the study. The effects of Epo in healthy individuals are fully reversible. Doses of Epo have been used up to 1200 units per kilogram body weight per week, far beyond those in the present study.

Mild gastrointestinal discomfort (i.e. loose bowel, constipation) may results from oral iron supplementation, which is relieved upon cessation of the supplementation.

Although high doses of carbon monoxide, not present in this study, can lead to ill health with initial symptoms similar to those associated with viral illness (e.g. headache, dizziness, weakness, nausea), there are minimal risks associated with inhalation of the small non-toxic dose present in this study.

What are the possible benefits of taking part? It is envisaged that this research will result in the formulation of new molecular based method(s) with improved discriminatory power relative to current detection protocols and in doing so significantly reduce (hopefully eliminate) unidentified doping due to inadequate detection as well as unacceptable cases of false positive.

What if something goes wrong? If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. The investigators, although not medically qualified are fully trained in Advanced or Intermediate Life Support. In the event of an untoward incident, the investigators will provide basic life support including chest compressions and ventilation until emergency medical staff is on hand. You may want to consult your GP if you are experiencing any side effects from taking part in the study and should also inform the Principal Investigator.

Will my taking part in this study be kept confidential? All information which is collected about you during the course of the research will be kept strictly confidential. You will be identified by an ID number, and any information about you will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study? Results will be published in a peer-reviewed scientific journal once the study is completed. You will automatically be sent a copy of the full publication. You will not be identified in any publication.

Who is funding the research? This project is being financed and supported by the World Anti-Doping Agency.

Who has reviewed the study? The project has been reviewed by the College Ethics Committee of the University of Glasgow.

If you wish to find out more about this investigation, you can contact:

Thank you.

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