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UNIVERSITÄTSKLINIK FÜR NEUROLOGIE
MEDIZINISCHE UNIVERSITÄT GRAZ

Protocol RIGMUC, Version 1.1 of 28.11.2020

Patient Information Sheet and Informed Consent Form for participation in the clinical study

Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: protocol of a randomised parallel multicentre trial (RIGMUC)

Dear Patient,

We invite you to take part in the above mentioned clinical study. The patient information on the study details will take place as part of a medical consultation.

Your participation in this clinical study is entirely voluntary. You can withdraw from the study at any time without giving a reason. The refusal to participate or a withdrawal from this study will not have any negative consequences for your medical care.

Clinical studies are necessary for obtaining reliable new medical research results. An indispensable prerequisite for the conduct of a clinical study is that you provide written informed consent to participate in this clinical study. Please read the following text carefully - as a supplement to the consultation with your study physician - and do not hesitate to ask questions.

Please only provide written informed consent

- if you fully understand the type and process of the clinical trial,
- if you are ready to agree to participate and
- if you are aware of your rights as a participant in this clinical trial.

The responsible ethics committee issued a favourable opinion to this clinical study as well as on the patient information sheet and the informed consent form.

1. What is the purpose of this clinical study?

Rehabilitation is very important for people with multiple sclerosis (MS) in order to improve their independence in daily life. Physiotherapy serves to improve and maintain the ability to walk. Many novel physiotherapy approaches for people with MS have been developed in recent years. Among other things, the use of music was found to be helpful in training gait rhythm, walking speed and walking distance. The effectiveness of motor imagery on walking and fatigue in people with MS has also been demonstrated. However, some questions remain open: Is pure physical training superior to motor imagery, or is it the other way around? Does a combination of the two have a greater or lesser effect? Are there learning effects in the brain after such a therapy that can be detected with magnetic resonance imaging (MRI)? Which of the three approaches to physical therapy is most popular with people with MS at home? It is our aim to clarify these questions with a multicentre study. The purpose of the study is to examine the effectiveness of three different gait training types with music.

2. How does the clinical study work?

This clinical trial will be conducted at multiple locations and plans to enroll a total of 132 people with MS. Study centres are the Clinical Department of Neurology at the Medical Universities of Innsbruck and Graz and the Rehabilitation Centre in Münster.

The following measures will be carried out exclusively for study reasons:

Your therapy period within this study is expected to be 4 weeks. You can carry out your therapy at home with an electronic study file or CD and will be supported by your study therapist over the phone. A total of 3 examinations with a maximum duration of 90 minutes will take place: The first examination takes place before the 4-week therapy, the second examination takes place immediately after the 4-week therapy, and the third examination takes place 3 months after your last therapy takes place, so your participation in this clinical trial is expected to take 4 months.

You will be informed about the study in a detailed medical discussion and can calmly consider your participation and discuss it with relatives. If you are interested in participating, your suitability for the study will be examined with a questionnaire and a clinical test. In the event of suitability and after you have signed the informed consent form, information on your neurological history will be collected on the basis of existing medical records after your consent.

In the following you will be examined by a physiotherapist and occupational therapist and one of the three therapies will be randomly drawn. The examinations include walking tests, questionnaires and tests for motor imagery. You will then receive information about your therapy at home (4x per week, 30 minutes, for 4 weeks). The therapy groups include the following treatment: motor imagery with music stimulation (30 min, group 1); motor imagery with music stimulation plus gait training with music stimulation (15 & 15 min, group 2); gait training with music stimulation (30 min, group 3). You will also be informed how to use the electronic study files containing music and guidance. The file consists of 4 parts, so you will

receive new training instructions and a new motor imagery and/or gait with music every week. After each week you will receive a call from your therapist for support. If you have any questions or problems, you can also contact your therapist between these phone calls at any time. Four weeks after this therapy period, you will also receive a call from your therapist to ask how you are.

You will be asked to travel to the Clinical Department of Neurology at the Medical Universities of Innsbruck and Graz or the Rehabilitation Centre in Münster for a total of three visits. Adhering to appointments and instructions from the study physician is critical to the success of this clinical trial.

3. What are the benefits of participating in the clinical study?

Based on previous studies, it can be assumed that you will derive direct health benefits from participating in this clinical study. Since these are new therapy interventions, a direct benefit cannot be predicted with certainty. The purpose of this study is to compare three physiotherapy measures to determine whether there is any benefit to a particular therapy.

By participating in this study, you are helping to gain new knowledge about the targeted treatment of patients with MS.

4. Are there any risks, complaints and side effects?

Performing the examinations and home therapy can trigger adverse events and side effects. But this is very unlikely. A short-term increased tiredness can occur or pre-existing balance deficits can be intensified for a short time. It is assumed that falls can occur in rare cases, but that they can also occur outside of the study in daily life in MS patients with a physical impairment. In order to keep the risk of falling as low as possible, you will receive appropriate instructions from the study team.

The travel to the Medical University of Innsbruck or Graz or the Rehabilitation Centre Münster for the study visits, the physical examination and the collection of the assessment scores represent a small additional burden.

5. Additional medication intake?

Please discuss treatments and therapies outside of the study with your study investigator.

6. What should be done if symptoms, side effects and/or injuries occur?

Should any symptoms, side effects or injuries occur in the course of the clinical study, we ask you to inform your study doctor about them, in the case of serious side effects immediately, if necessary by telephone (telephone numbers and other contact details see below).

7. Insurance

As a participant in this clinical study, you have the legally required indemnity insurance coverage that covers all damage to your life or health that may be caused by the clinical

study measures, with the exception of damage due to changes in the genetic material in germline cells.

The insurance has been taken out for you at Zürich Versicherungs-Aktiengesellschaft, Schwarzenbergplatz 15, A-1010 Vienna, phone.: 0800 0808080, policy number 07225462-7. If you wish, you can inspect the insurance documents.

In the event of damage, you can contact the insurer directly and make your own claims. Austrian law applies to the insurance contract. Any insurance claims are enforceable in Austria.

You can also contact the patient representative for support.

In order to not endanger the insurance cover

- You may only undergo other medical treatment during your participation in this clinical study with the consent of your treating study doctor (with the exception of emergencies). This also applies to taking additional medication or participating in another study.

- you need to immediately notify the attending study doctor or the above-mentioned insurance company of any damage to your health occurs that could be a result of this clinical study.

- you need to do everything reasonable to clarify the cause, course and consequences of the insured event and to keep the damage to a minimum. This may also include authorising your treating doctor to provide information requested by the insurer.

Please note that the insurance does not provide cover for an accident that occurs to you on your way to and from the study.

8. When will the clinical trial be prematurely terminated?

You can revoke your willingness to participate and withdraw from the clinical study at any time without giving reasons, without incurring any disadvantages for your further medical care.

Your study doctor will inform you immediately of any new information that becomes known in relation to this clinical study and that could become material to you. On this basis, you can reconsider your decision to continue participating in this clinical study.

However, it is also possible that your study doctor may decide to terminate your participation in the clinical trial prematurely without first obtaining your consent. The reasons for this can be:

a) You cannot meet the requirements of the clinical study.

b) Your study doctor has the impression that your further participation in the clinical study is not in your interest.

9. Data protection

As part of this clinical study, data about you will be collected and processed. There is a fundamental distinction between

1) those personal data by which a person can be directly identified (e.g., name, date of birth, address, social security number, images, ...).

2) Pseudonymised personal data i.e., data in which all information is removed that allows directly draw conclusions about a specific person, or replaced by a code (e.g., a number) or made illegible (e.g., in the case of pictures). Despite compliance with these measures, it cannot be completely ruled out that inadmissible re-identification occurs.

3) Anonymised data that cannot be traced back to the specific person.

The study doctor and other employees of the study centre who are involved in the clinical study or your medical care have access to the data by which you can be directly identified (see point 1). In addition, authorised representatives of the sponsor Medical University of Innsbruck, as well as representatives of national and/or international health authorities and the respective responsible ethics committees can inspect these data insofar as this is necessary or prescribed for the verification of the proper conduct of the clinical study. All persons who have access to this data are subject to the respective applicable national data protection regulations and/or the EU Data Protection Law (DSGVO) when handling the data.

The code that enables the pseudonymised data to be assigned to you will only be stored at your study centre.

Only the pseudonymised or anonymised data will be used for any publications.

In the context of this clinical study, no data will be transferred to countries outside the EU (third countries).

Your consent form is the legal basis for the processing of your personal data. You can revoke your consent to the collection and processing of your data at any time without giving a reason. After your revocation, no further data will be collected about you. The data collected up to the point of revocation can, however, continue to be processed in the context of this clinical study.

According to the DSGVO, you have the right to information, correction, deletion, restriction of processing, data portability and objection, as long as this does not make the aims of the clinical study impossible or seriously impaired and unless other legal regulations contradict this.

The expected overall duration of the clinical study is 26 months. The duration of the storage of your data beyond the end or termination of the clinical study is regulated by legal provisions.

If you have any questions about the handling of your data in this clinical study, please contact your study doctor first. If necessary, they can forward your request to the persons responsible for data protection.

Contact details of the data protection officers of the institutions involved in this clinical study:

- Data protection officer of the Medical University of Innsbruck: datenschutzbeauftragter@i-med.ac.at

- Data protection officer of the Tirol Kliniken: datenschutzbeauftragte@tirol-kliniken.at

- Data protection officer of the Rehabilitation Centre Münster: datenschutz@reha-muenster.at

- Data protection officer of the Medical University of Graz: datenschutz@medunigraz.at, datenschutz@kages.at

- You have the right to lodge a complaint with the Austrian data protection authority about the handling of your data (www.dsb.gv.at; E-mail: dsb@dsb.gv.at

10. Are there any costs for the participants? Is there a reimbursement or compensation?

No additional costs will be incurred for you by participating in this clinical study. Unfortunately, we cannot reimburse you for any travel costs that may arise. You will not receive any financial compensation for your participation in this study.

11. Opportunity to discuss further questions

Your study doctor and his staff will answer any further questions you may have in connection with this clinical study. We will also answer any questions you may have about your rights as a patient and participant in this clinical study.

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Clinical Department of Neurology, Medical University of Innsbruck, [redacted]	
[redacted]	[redacted]
[redacted]	
Rehabilitation Centre Münster, [redacted]	
[redacted]	[redacted]

Department of Neurology, Medical University of Graz, [redacted]	
[redacted]	[redacted]

If you have any questions about the informed consent, you can also contact the Tyrolean patient representative:

[redacted]

Tel.: [redacted]

Fax: [redacted]

Email: [redacted]

WWW: http://www.tirol.gv.at/patientenvertretung

12. Informed Consent Form

Name of the patient: ....

Date of birth: ....

I agree to take part in the clinical study „Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: protocol of a randomised parallel multicentre trial“ (short: RIGMUC). I have been informed that I can refuse participation without any negative consequences, in particular for my medical care.

I have been informed by Ms / Mr (MD) ..... in detail and understandably about the clinical study, possible burdens and risks, as well as about the type, meaning and scope of the clinical study and the requirements resulting for me. I have also read the text of this patient information and informed consent, which comprises a total of 8 [10] pages. Questions that arose were answered comprehensibly and satisfactorily by the study doctor. I had enough time to make up my mind. At the moment, I do not have any further questions.

I will comply with the medical instructions required to carry out the clinical study, but I reserve the right to terminate my voluntary participation at any time without incurring any disadvantages, in particular for my medical care.

I particularly agree that my data collected as part of this clinical study will be processed as described in the "Data Protection" section of this document. Should I withdraw or be excluded from the study, I agree that my data are continued to be stored and analysed as described in this information.

☐ Yes ☐ No

I have received a copy of this patient information and informed consent. The original remains with the study doctor.

....

(Date and signature of the patient)

....

(Date, name and signature of the responsible study doctor)

(The patient receives a signed copy of the patient information and informed consent, the original remains with the study doctor's folder.)

Protocol RIGMUC, Version 1.1 of 14.11.2020

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Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: protocol of a randomised parallel multicentre trial (RIGMUC)

Additional information for Centre 3 only (Department of Neurology, Medical University of Graz)

Magnet Resonance Imaging (MRI)

MRI:

Idiopathic inflammatory, demyelinating diseases of the central nervous system (CNS), such as multiple sclerosis in particular, are caused by inflammation in the area of the nerve sheaths in the brain and spinal cord. Investigations such as magnetic resonance imaging (MRI) are needed to better understand the condition that you are suspected of having or have been diagnosed with. Multiple sclerosis is a disease in which there are foci of the disease at different times, in different places in the brain and spinal cord. MRI has been an examination method that has been used for years, which provides images of these changes in the brain and spinal cord without exposure to radiation. In the planned examinations using a 3-Tesla MRI device, the relatively new examination techniques, including functional MRI (fMRI), are to be used in order to obtain information about the function of the brain that goes beyond the nature and structure.

1. **A) How does the MRI investigation work?**

This clinical study will be carried out at the Department of Neurology, Medical University of Graz, and a total of 36 people with MS and 15 healthy people are expected to take part.

The examinations are carried out at the Department of Neuroradiology at the LKH University Hospital Graz. An MRI machine is an elongated tube that creates a magnetic field. The process uses **neither ionising radiation nor radioactive substances and is therefore not associated with any radiation exposure.** Rather, the images are created by signals from water particles in the body, which are generated with the help of a strong magnet and high-frequency pulses (radio waves).
This technology is used worldwide and, according to the current state of knowledge, is completely harmless to the human organism and free of biological risks.

During the investigation you lie on your back, whereby a special mirror device allows you to look out of the tube (e.g., at an image projection). We also have "eye contact" with you via a camera. Verbal communication can take place via an intercom. In addition, you will be given an alarm button ("signal ball") with which you can indicate that the examination should be stopped immediately if you feel uncomfortable for any reason. The examination itself is relatively loud, which is why we will protect your hearing with headphones. During the exam, you should keep your head as still as possible.

However, if you are known to suffer from claustrophobia, you should not participate in this study.

As part of the MRI examination, the structure and function (using functional magnetic resonance tomography (fMRI for short) of your brain are precisely recorded. With this study, we want to investigate the way in which the brain reacts to changes in tissue function, such as those in the context of your disease can occur, reacts or tries to limit their consequences.
During the fMRI examination you will be asked to perform certain movements, look at pictures or solve tasks. We will rehearse the processes that you are supposed to carry out during the fMRI examination together with you before the actual examination outside of the MRT machine.

With the help of this technology, we receive images on which parts of the brain “light up” that are activated during such tasks. However, do not expect to receive conventional radiological findings from this examination. **No contrast agent** is required for the fMRI examination. The total duration of the MRI examination is approx. 30 minutes.

3. Are there any risks, burdens and side effects?

If the following safety measures are observed, no harmful effects are to be expected:

Since a strong magnetic field is generated by the MRI machine, interference from pacemakers or heat build-up or relocation of metal parts in the body can occur. If one of these circumstances could apply (for example the presence of a pacemaker or metal parts in the body, such as metal clips after operations on the brain or after old injuries, especially in the eye area, etc.), you cannot participate in this study. This also applies to pregnancy. If you have any questions, we will of course be happy to answer any further questions you may have.

If you change your mind, you can of course revoke your consent at any time without giving reasons, without incurring any disadvantages.