Patient information and informed consent form for participation in the study

"NATURE-MET-S"

Nature-based therapy for Metabolic Syndrome – Salzburg

(German title: Naturbasierte Therapie bei metabolischem Syndrom – Salzburg)

Dear Participant,

We invite you to participate in the "NATURE-MET-S" research study to test a novel nature-based therapy to improve the health and well-being of people with metabolic syndrome. You will receive detailed information about the study during a discussion with the study lead or the study physician on duty.

Participation in this study is voluntary, and you may withdraw at any time without providing a reason. Refusing to participate or withdrawing early will not have any negative consequences for your medical care.

Trials are necessary to obtain reliable, new medical research results. However, it is essential that you give your written consent to participate in this study. Please read the following information carefully and do not hesitate to ask any questions.

Please only sign the informed consent form

- If you fully understand the nature and procedure of the study,

- if you are willing to participate, and

- that you understand your rights as a participant in this study.

This study and the patient information and consent form have been approved by the local ethics committee.

_____

Principal investigator / Study leader
a.o. Univ.-Prof. Dr. Arnulf Hartl

1 What is the purpose of the study?

The purpose of this study is to examine how nature-based therapy impacts the health and well-being of individuals with metabolic syndrome in comparison to a control group. The goal is to assess the impact of a five-week program consisting of simple hikes and mindfulness training in the Salzburg mountains on the following medical and psychological factors:

- Does the health-related quality of life change?
- Does the allostatic load change?

  Allostatic Load describes the state of various organ systems and is determined from saliva, blood and vital parameters such as resting heart rate (see also point 2.3 Planned examinations, page 6)
- Do general health parameters such as complete blood count or pulmonary function parameters change?
- Does exercise behavior change?
- Do psychological parameters like mindfulness, resilience, well-being, and closeness to nature change?
- How sustainable are any changes?

The research project is embedded in the RESONATE project. One of the aims of this project is to increase the integration of nature-based therapies in health care. Therefore, this study collects not only medical data but also information crucial for the future development of nature-based therapies:

- How cost-effective is nature-based therapy compared to other interventions?
- What environmental issues should be considered?
- How do participants evaluate the therapy program?

The study will include a study group and a control group. The study group will receive a 5-week structured nature-based therapy program, while the control group will initially receive no therapy. The aim is to investigate the difference between a nature-based intervention and maintaining the current lifestyle. Once all studies are completed, all people in the control group will be able to participate in the nature-based therapy.

There will be four medical exams before and after the therapy program. The medical examinations will measure various aspects of your health. Details about what will be measured can be found under the item 2.3 Planned examinations.

2 How is the study conducted?

This study is being conducted by the Institute of Ecomedicine at the Paracelsus Medical University of Salzburg and the University Clinic for Internal Medicine I at Salzburg University Hospital. A total of 140 people will participate. The participants will be **randomly divided into two groups:**

1) **Intervention group** with guided nature-based lifestyle intervention, 70 participants
2) **Wait-list control group** with no intervention during the observation period of the intervention group, 70 participants

The study will be conducted in two rounds:

1) September 2024 to February 2025
2) March 2025 to August 2025

During each of the two rounds, 35 participants in the intervention group will receive guided nature-based therapy, which includes easy hikes in the Salzburg mountains and mindfulness training. Meanwhile, 35 people will participate in the control group without nature-based therapy.

However, the nature-based therapy is also offered to the control group after each study round.

2.1 Trial schedule if you are assigned to the intervention group for September 2024 or March 2025

Your participation in this study will last approximately six months. This will include follow-up visits, guided nature therapy, and three check-ups at the Paracelsus Medical University of Salzburg. The last, fourth examination after six months consists of questionnaires that you can complete online from home (see Figure 1).

In addition to the examinations, we will conduct qualitative interviews with randomly selected participants to learn about their perceptions of the intervention. This information will be used to develop nature-based therapies in the future.

Detailed schedule:

- The study will begin with an initial examination (t1) at the Paracelsus Medical University (Strubergasse 22, 5020 Salzburg).
- The nature-based therapy will then begin for you:
    - During the first week, you will participate in **three guided nature-based therapy sessions**.
    - These sessions consist of easy hikes in the Salzburg mountains and integrated nature-based mindfulness training. Each session lasts approximately 1.5 - 2 hours and is led and accompanied by a certified hiking guide and a mindfulness trainer who is psychologist and psychotherapist. The sessions take place in a group setting. Hikes are tailored to your fitness level. Hikes are offered for different fitness levels. You will wear a heart rate monitor during the study. The study team will explain to you in advance what heart rate range is ideal for you to maintain during the therapy sessions.
    - Guided hikes are also offered daily for the next 4 weeks. You can choose to participate in these sessions in a group setting, or you can do the walks and mindfulness training on your own. In either case, **we ask that you complete 3 walks and mindfulness training sessions per week** during these 4 weeks.
    - At the end of these 5 weeks (t2), we will ask you to come back to Paracelsus Medical University for a check-up.

- During weeks 6-10, you will conduct nature-based therapy sessions independently. There will be no guided walks offered during this time.
- At timepoint 3, which is 10 weeks after the start of the study, you will be required to return to Paracelsus Medical University for a check-up.
- After six months (t4), we will ask you to complete some questionnaires again. You will be able to do this online from home.
- Throughout the 6-months study period, you will be asked to use a smartphone application to document your therapy sessions. Section **Error! Reference source not found.**. provides a more detailed description.

	Dates to choose from (location: PMU)			Period for completing the questionnaires online
Study round	**Check-up t1**	**Check-up t2**	**Check-up t3**	**Check-up t4**
September 2024	30.08.2024 31.08.2024 01.09.2024 02.09.2024	05.10.2024 06.10.2024 07.10.2024	07.11.2024 10.11.2024 11.11.2024	24.02. to 02.03.2025
March 2025	27.02.2025 28.02.2025 01.03.2025 02.03.2025	04.04.2025 05.04.2025 06.04.2025	09.05.2025 10.05.2025 11.05.2025	25.08. to 31.08. 2025

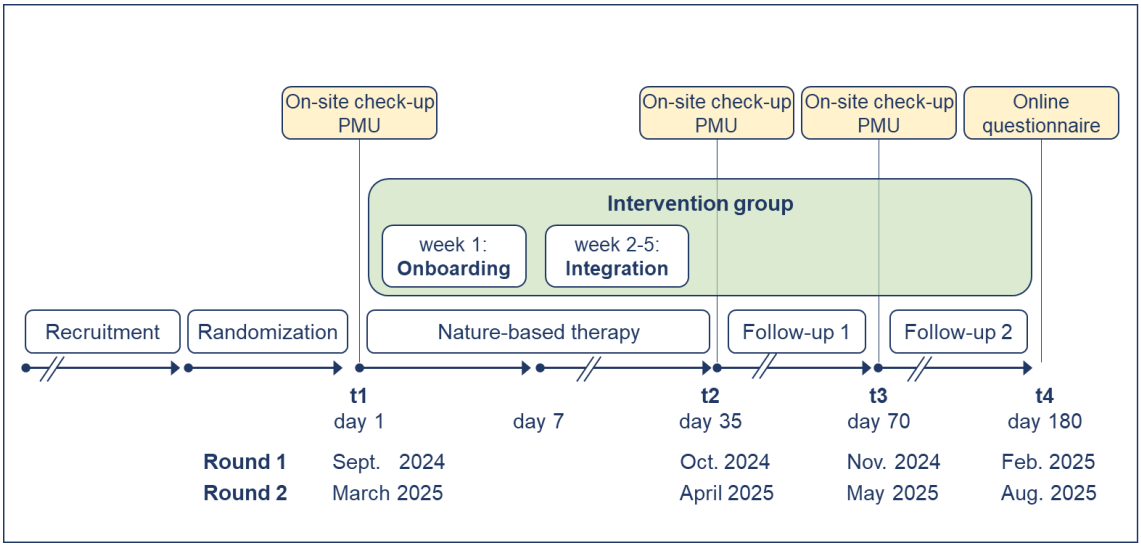

Figure 1: Study schedule for the intervention group

It is crucial to the success of the study that you attend all appointments, including follow-up visits.

During the entire study period (6 months from start), please refrain from participating in any other interventional clinical trial or therapeutic weight loss program.

2.2 Trial schedule if you are assigned to the waiting list control group for September 2024 or March 2025

As a participant in the control group, your involvement in this study, including follow-up visits, will last approximately six months. You will not receive any intervention during this time. We will ask you to come to the Paracelsus Medical University of Salzburg three times for examinations. You can complete the final examination by filling out online questionnaires from home. Our staff will examine you four times throughout the study to collect data (see Figure 2). Additionally, you will receive nature-based therapy for five weeks.

- The study will begin with an initial examination (t1) at the Paracelsus Medical University (Strubergasse 22, 5020 Salzburg).
- You will be asked to return to Paracelsus Medical University for a second check-up after 5 weeks (t2) and a third check-up after 10 weeks (t3). During this time, you should continue to live your life as usual, and we will not provide any therapy.
- After 6 months (t4), we will ask you to complete an online questionnaire from home.
- After the final examination (T4), you will have the opportunity to participate in nature-based therapy. This therapy includes easy hikes in the Salzburg mountains and integrated mindfulness training in nature. Each session lasts approximately 1.5-2 hours, and the guided hikes will be offered three times a week for five weeks. During this time, there will be no exams, but you will be asked to document your nature-based therapy sessions using a mobile phone app.

	Dates to choose from (location: PMU)			Period for completing the questionnaires online
Study round	**Check-up t1**	**Check-up t2**	**Check-up t3**	**Check-up t4**
September 2024	30.08.2024 31.08.2024 01.09.2024 02.09.2024	05.10.2024 06.10.2024 07.10.2024	07.11.2024 10.11.2024 11.11.2024	24.02. to 02.03.2025
March 2025	27.02.2025 28.02.2025 01.03.2025 02.03.2025	04.04.2025 05.04.2025 06.04.2025	09.05.2025 10.05.2025 11.05.2025	25.08. to 31.08. 2025

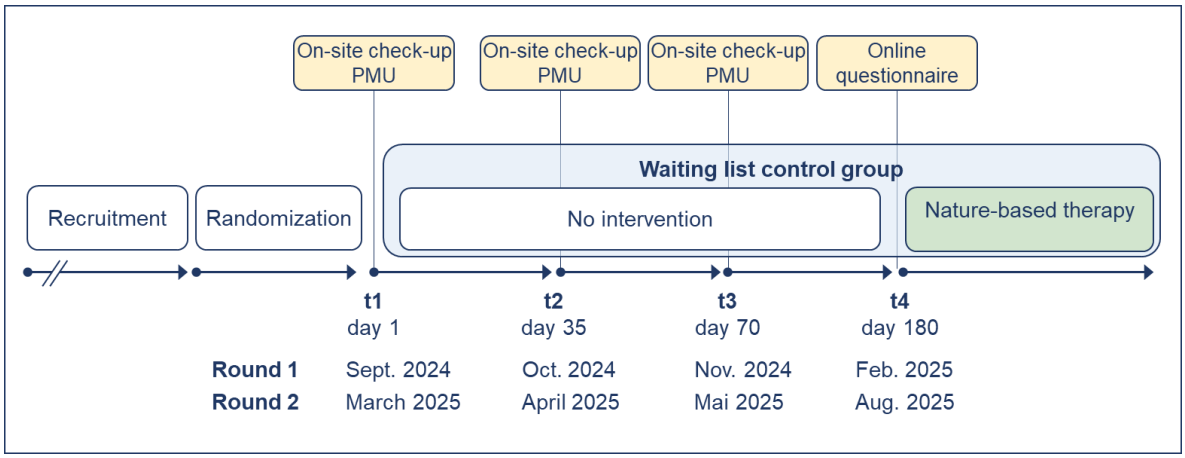

Figure 2: Study schedule for the waiting list control group

It is crucial to the success of the study that you attend all appointments, including follow-up visits.

During the entire study period (6 months from start), please refrain from participating in any other interventional clinical trial or therapeutic weight loss program.

2.3 Planned examinations

2.3.1 At the on-site medical check-ups (PMU, 3x)

During this study, the following measures will be taken for study purposes only:

- **Vital signs:** Your vital signs, such as blood pressure, pulse, and oxygen saturation, will be measured. Your height, weight, and waist circumference will also be measured.
- **Saliva samples:** You will be asked to collect saliva in a small tube. The saliva sample will be used in the laboratory to measure parameters that give us information about inflammation levels and the strength of your immune system.
- **Blood sample:** Blood samples will be taken by venipuncture. Your inflammation levels and blood lipid levels will be determined from the blood samples. It is not necessary to fast for the blood test.
- **Lung function:** You will be asked to breathe in and out of a test machine. This measures how much air you can breathe in and out, how strong your breathing muscles are and how well your lungs exchange gases.
- **Questionnaires**: Questionnaires will be used to record health and psychological parameters. You will be asked to complete questionnaires on various topics including quality of life, mindfulness, physical activity, nature experience, social aspects, motivation, environmental aspects and well-being.
- **Interviews**: In order to better tailor nature-based therapies to users' needs in the future, we will ask individual participants to complete an interview on topics such as satisfaction, user-friendliness, etc. These interviews will take place after the completion of the nature-based therapy program. The interviews are voluntary. You will receive separate information and consent for the collection and processing of your interview data.

2.3.2 During the individual nature-based therapy sessions

During individual therapy sessions, you will be asked to complete a short questionnaire via the MyCap smartphone app ((https://projectredcap.org/). This will provide us with information on the following questions

- Where are you having the session?
- How did you get here?
- Are you doing the intervention alone or in a group?
- How strong are your positive and negative feelings?
- How strenuous did you find the physical activity?
- How connected do you feel to nature?
- How do you perceive the nature that surrounds you?
- How satisfied are you with the therapy session?

The study team will take some photographs during the guided hikes. These will be used for project documentation and scientific presentations. You will receive a separate explanation and consent for photography from the study team. Your consent is voluntary. If you do not agree to have your photograph taken and used, you will not suffer any disadvantages.

2.4 Future research and analyses

Blood and saliva samples that are not analyzed immediately will be frozen at the Institute of Ecomedicine at the Paracelsus Medical University of Salzburg. This will allow for the analysis of biomarkers at a later date.

3 What are potential benefits of participating in the study?

Many scientific studies have shown that exercising in nature can improve quality of life, well-being, and reduce certain disease risks, such as cardiovascular disease.. However, it is possible that you may not experience any noticeable health benefits from participating in this study.

Participation in the study will provide you with the following benefits:

- Free participation in a structured nature-based program of guided hikes and mindfulness training in the Salzburg City Mountains
- Possible improvement of your health and well-being
- An expense allowance in the form of a drugstore voucher (DM) in the amount of € 100.

By participating in this study, you will help develop a better understanding of the health effects of nature-based therapies in people with metabolic syndrome. This study will also enable nature-based therapies to be better tailored to the needs of users in the future.

During the entire study period, you will have free accident insurance for all activities. Please note that this insurance does not cover leisure accidents.

4 Are there any risks, discomforts, or side effects?

The study procedures may cause discomfort, such as pain during blood sample collection. Measuring lung function may be strenuous.

Additionally, during the study, you will participate in outdoor hikes, which may cause shortness of breath or muscle aches. There is also a risk of falling during these hikes. Our hiking guides will inform you of any potential risks and show you how to minimize them. For instance, they will advise you to wear appropriate footwear.

5 Taking additional medication?

NO drugs or medications will be administered in this study. No other interventions will be performed in the study.

6 Will participating in the study affect your lifestyle in any other way, and what commitments will you need to make?

6.1 If you are assigned to the intervention group for September 2024 or March 2025:

Participation in the study involves easy walks over a period of at least 10 weeks. In week 1, you will participate in 3 guided walks with mindfulness training. In weeks 2-5, you can choose to do the walks (3 per week) in a group setting (guided) or alone. In weeks 6 to 10, you will be asked to do the therapy sessions 3 times a week on your own.

In addition, participation in the study includes 3 examination appointments at Paracelsus Medical University Salzburg and the completion of an online questionnaire. The intervention program is free, but you will need to cover your own travel expenses to and from the intervention and examination locations.

6.2 If you are assigned to the waiting list control group for September 2024 or March 2025:

To participate in the study, you will need to attend three examination appointments at the Paracelsus Medical University Salzburg and complete an online questionnaire six months after the study begins. Additionally, after the six months, you will have the opportunity to take part in the nature-based therapy program free of charge. Please note that you will be responsible for your own travel to and from the intervention and study sites.

7 What should I do if symptoms, side effects and/or injuries occur?

If you experience any symptoms of illness, side effects, or injury during the study, you must notify the study investigator and your treating physician immediately. It is important to do so by telephone if necessary, especially in the case of serious side effects.

8 Insurance

As a participant in this clinical trial, you are covered by statutory no-fault insurance. This insurance, in accordance with Section 40 of the Medicines Act, covers all damage that may be caused to your life or health by the measures carried out on you in the clinical trial. The only exception is damage due to changes in the genetic material in germline cells.

The insurance has been taken out for you with Zürich Versicherungs-Aktiengesellschaft (Schwarzenbergplatz 15, 1010 Vienna, Tel.: +43 1 50125-1654) under policy number SF-95106769-5. You may inspect the insurance documents upon request. The entire insurance period is from 25.08.2024 to 01.03.2026, and your individual insurance cover refers to your respective participation period of 180 days (intervention group) or 250 days (control group).

In the event of a claim, you can contact the insurer directly and pursue your claims independently. Austrian law applies to the insurance contract and insurance claims are enforceable in Austria. You may also contact a patient advocate, patient representative or patient ombudsman for assistance.

To avoid jeopardizing your coverage:

- You may not receive any other medical treatment (except in emergencies) for the duration of the clinical trial without the consent of your investigator. This includes taking additional medications or participating in another trial.
- You must immediately notify your investigator or the insurance company mentioned above of any adverse health event that may have occurred as a result of the clinical trial.
- You must do everything reasonable to determine the cause, course and consequences of the covered event and to minimize any damages. This may include authorizing your treating physicians to provide information requested by the insurer.

9 When will there be an early study termination?

You can withdraw from the study at any time without giving any reasons or incurring any disadvantages. The study management will promptly inform you of any new findings related to the study that may be significant for you. Based on this information, you can reconsider your decision to continue participating in the study. The study management may terminate your participation in the study without your consent for the following reasons:

- You do not meet the study requirements.
- The study leader believes that it is not in your best interest to continue participating in the study.

10 Data protection

As part of this clinical study, we will collect and process personal data. It is important to distinguish between:

1) Personal information that can be used to **directly identify an individual** (e.g., name, date of birth, address, social security number, photographs, etc.),
2) **pseudonymized personal information**, i.e., information from which all information that could be used to directly identify an individual has been removed, replaced with a code (e.g., a number), or made unrecognizable (e.g., in the case of images). However, despite these measures, it is not possible to completely rule out the possibility of unlawful re-identification.
3) **Anonymous data** where it is not possible to trace the data back to a specific individual.

The investigator and other staff members of the study center who are involved in the clinical trial or your medical care have access to your directly identifiable data (see point 1). In addition, authorized representatives of the sponsor, Paracelsus Medical University Salzburg, Institute of Ecomedicine, who are bound to secrecy, as well as representatives of domestic and/or foreign health authorities and the relevant ethics committees may have access to this data, insofar as this is necessary or prescribed for the verification of the proper conduct of the clinical trial. All persons who have access to this data are subject to the applicable national data protection regulations and/or the EU General Data Protection Regulation (GDPR) when handling the data.

After you have given your consent to participate, your sensitive personal data will be converted into pseudonymized research data, stored and processed in a manner that is effectively anonymous, i.e., it will not be possible to trace you back to your person using the study ID.

The code that allows the pseudonymized data to be associated with you will be stored only at your study site (Paracelsus Medical University Salzburg).

The data will only be passed on in pseudonymized or anonymized form.

Your data will be transferred via the scientific database system REDCap to a secure server at the University of Vienna (RESONATE Lead Partner). From there, the data will also be transferred via the secure REDCap database system to the respective partner organizations of the RESONATE project (see also point 1).

All project partner organizations are listed below, including contact information for their data protection officers (p. 12f).

As part of the study, you will also be asked to use the MyCap mobile application (https://projectmycap.org/) to evaluate individual naturopathic sessions. This is a free mobile application designed for study participants that you can install on your smartphone. All data collected on your smartphone will be automatically and instantly synchronized with the REDCap[1] scientific database system. If data is collected while you are offline, i.e. without an active internet connection, the data will be synchronized as soon as the internet connection is restored and the app is opened.

[1] https://projectredcap.org/

This app is designed specifically for clinical trials and therefore offers the following additional security features that affect your data:

1) Your data is stored locally on the device in an encrypted database. The data remains on the device when there is no Internet connection.

2. When an Internet connection is available, the data is transferred directly to REDCap.

3) The data you enter (i.e. the answers to the questionnaires) is not stored or sent to other locations. The data resides on the participant's device or on the server.

4. The data is deleted from the device after the Mycap application has verified that the data has been successfully transferred. Note that there is an optional MyCap feature that allows you to view some of the data you entered for a single survey. By default this data will be deleted.

5) You will receive a 6-digit PIN code that is used to open the application. You can disable this PIN feature.

The study team will provide you with the Terms of Use and Privacy Policy for the application, along with detailed installation instructions, before you install the application on your device.

Only pseudonymized or anonymized data will be used for any publications.

As part of this clinical study, pseudonymized data will also be transferred to countries outside the EU (third countries). These third countries are not subject to the GDPR. Not all third countries have an adequacy decision that guarantees an equivalent level of data protection to that provided in EU countries under the GDPR. As a result, there is a risk that you may not be able to enforce the rights to which you are entitled under the GDPR. However, the recipient of the data will be required to protect your data appropriately. By participating in this clinical trial, you consent to the transfer of your data to a third country.

Your consent is the legal basis for the processing of your personal data. You may revoke your consent to the collection and processing of your data at any time without giving reasons. After your revocation, no further data will be collected about you. However, the data collected up to the time of withdrawal may still be processed in the context of this clinical study.

Under the GDPR, you generally have the right of access, rectification, erasure, restriction of processing, data portability, and objection, provided that this does not make the objectives of the clinical trial impossible or seriously impaired, and provided that this does not conflict with other legal provisions.

The expected duration of the clinical trial is 6 or 9 months. The length of time your data will be kept after the clinical trial ends or is discontinued is governed by applicable law.

If you have any questions about the handling of your data in this clinical trial, you should first contact your investigator. They may be able to forward your request to the Data Protection Officers.

Contact information for the data protection officers at the sites involved in this clinical trial:

Contact information for the Data Protection Officers of the institutions involved in this study:

Data Protection Officer of Paracelsus Medical University
Salzburg (study center 1):
E-Mail: datenschutz@pmu.ac.at,
Tel.: 0043662 2420-8000

Data Protection Officer of the Salzburg University Hospital (study center 2):
datenschutzbeauftragter@salk.at

You have the right to lodge a complaint with the Austrian data protection authority about the handling of your data.

Contact:

www.dsb.gv.at
E-Mail: dsb@dsb.gv.at

Contact to RESONATE project partners:

Lead Partner:

Universität Wien
Universitätsring 1 | 1010 Wien
Data protection officer: dsba@univie.ac.at
Requests for information in accordance with Article 15 of the EU General Data Protection Regulation (GDPR): beauskunftung.dsba@univie.ac.at
Data protection hotline: +43 1 4277 110 00

Project partner 1:
ISGlobal
Barcelona Biomedical Research Park (PRBB). Doctor Aiguader, 88
08003 Barcelona
Data protection officer: lopd@isglobal.org

Project partner 2:
University of Exeter
Compliance, Governance and Risk
Lafrowda House
St. German's Road
Exeter
EX4 6TL
Data protection officer: informationgovernance@exeter.ac.uk

Project partner 3:
Fundacion Azti – Azti Fundazioa (AZTI)
Txatxarramendi ugartea z/g
48395 Sukarrieta - Bizkaia
Data protection officer: canal@azti.es

Project partner 4:
Etifor Srl Società Benefit
Piazza Alcide De Gasperi 41, 35131 Padua

Data protection officer: privacy@etifor.com

Project partner 5:
EuroHealthNet – The European Partnership for Health, Equity and Wellbeing
Rue Royale 146, 1000 Brussels
Data protection officer: info@eurohealthnet.eu

Project partner 6:
Università degli Studi di Padova (UNIPD)
Via 8 Febbraio, 2 - 35122 Padova
Data protection officer: privacy@unipd.it

Project partner 7:
NBSI – The Nature Based Solutions Institute
Algatan 26. Malmö
Data protection officer: dan.seddon@franklynjones.com

Project partner 8:
Meditcinsky Universitet-Plovdiv (MUP)
Vassil Aprilov Blvd. 15A, 4002 Plovdiv Bulgaria
Data protection officer: admin_en@meduniversity_plovdiv.bg

Project partner 9:
Uppsala Universitet (UU)
P.O. Box 256, SE-751 05 Uppsala
Data protection officer: dataskyddsombud@uu.se

Project partner 10:
Københavns Universitet (UCPH)
Nørregade 10, 1165 København K
Data protection officer: dpo@adm.ku.dk

Project partner 11:
Natuurvoormensen Omgevingspsychologisch Onderzoek (NVM)
https://www.agnesvandenberg.nl/
Data protection officer: info@agnesvandenberg.nl

Project partner 12:
University of Twente (UNTWE)
PO Box 217, 7500 Ae Enschede
Data protection officer: dpo@utwente.nl

11 Are there any costs for participants? Is there any reimbursement or compensation?

If you participate in the research project, you will receive a drugstore voucher (DM) worth € 100.

There are no costs for you or your health insurance to participate in the nature-based therapy program.

Travel expenses to and from the study site (Paracelsus Medical University Salzburg) and the intervention sites (Salzburg City Mountains) will not be reimbursed.

12 Opportunity to discuss further questions

The study team is available to you for further information, concerns and complaints. They will also answer any questions you may have about your rights as a participant in this study.

Name of contact person	**Always available at:**
a.o. Univ.-Prof. Dr. Arnulf Hartl	+43 662 2420-80530 arnulf.hartl@pmu.ac.at
Christina Pichler, BA MSc.	+43 662 2420-80531 christina.pichler@pmu.ac.at

If you have any questions regarding the declaration of consent, you can also contact the Salzburg Patient Representative Office..

Salzburg Patient Representative Office:
Sebastian-Stief-Gasse 2
5020 Salzburg
Tel.: 0662 8042-2030
Fax.: 0662 8042-3204
E-Mail: patientenvertretung@salzburg.gv.at

13 Should other treating physicians be informed of participation in the study?

Please inform your primary care physician or other treating physician of your participation in this study.

14 Informed consent

I agree to participate in the study "Nature-Based Therapy for Metabolic Syndrome - Salzburg" (NATURE-MET-S).

I have been fully informed in an understandable manner of the possible risks, as well as the nature, significance, and scope of this study and the resulting requirements for me. I have read the 15-page text of this patient information and consent form. Any questions that arose were answered clearly and sufficiently by the investigators. I have had sufficient time to make a decision. I have no further questions at this time.

I will follow the medical instructions necessary for the conduct of the study, but I reserve the right to terminate my voluntary participation at any time without prejudice to my continued medical care.

I expressly consent to my data collected as part of this study being processed as described in the "Data protection" section of this document.

Name: ……

Date of birth: …… SS.Nr.[2]: ……..

In the event that I withdraw from the study, I agree that my samples will continue to be stored and analyzed as described in this information and, if applicable, in the substudy information: ☐ yes ☐ no

I have received a copy of this patient information and consent form. The original will remain with the investigator.

.....

Place, Date and Signature

.....

(Place, Date and Signature of study leader)[3]

[2] Your social security number is only required to purchase student insurance. There is no additional cost to you.

[3] The participant receives a signed copy of the patient information and informed consent form, the original remains in the investigator's study folder.