The effect of soft sounds on the sleeping brain
Investigating the effects of closed-loop auditory stimulation on sleep and behavior in patients with epilepsy and healthy controls: a developmental study

Dear participant,

We invite you to participate in our clinical sleep study on the effect of soft sounds on the sleeping brain. In the following document, we will first provide you general information about our project in a summary and in the second part of the document you can learn more details from full description.

Summary

1	**The aim of the study** We would like to ask you if you would be interested to participate in a clinical sleep study. The study investigates the effect of soft sounds on the sleeping brain of healthy volunteers and patients with epilepsy. We conduct this study to better understand how soft sounds influence sleeping brain activity and the role of sleep in learning and memory. Also, this study will help us to enrich our knowledge about brain activity in deep sleep that can be found only in epilepsy patients.
2	**Recruitment** You are either healthy or diagnosed with epilepsy (EEG[1] shows typical epileptic discharges). That's why we provide you this study information.
3	**General information about the study** In this study, brain activity is recorded during sleep using EEG. An EEG measures the electrical activity of the sleeping brain via electrodes attached to the head before going to bed. During the night, soft sounds are played at specific moments. These are so short and soft that they do not disturb sleep. You can also participate in various cognitive and motor tests and fill the questionnaires during the study. The full duration of the study is 20 days with only 2-3 nights (2 study nights, opt. adaptation night) spent in the sleep laboratory.
4	**Procedure** The study website provides detailed information about this study. If you are interested in participating in the study, you can use an online entry questionnaire to find out if you meet the study participation criteria. If you are reading this information, you probably meet the requirements for study participation. After the entrance questionnaire, you can clarify any open questions by phone, e-mail or on-site. On the next step, we will ask for your written consent to participate in the study, and you will be officially enrolled.

[1] Please refer glossary for the definition of this and other terms

	You will initially have the opportunity to visit the laboratory so that you can familiarize yourself with the environment in advance, if necessary. After that, you will sleep as usual at home for one week. You will wear a bracelet that measures the everyday activity by collecting information about arm movements (actimeter) and you will be asked to fill out a sleep diary (time needed: 5-10 minutes/day). The first test night will take place at the end of this week. In the evening, you will come to the sleep laboratory, where we will meet you. You may already be familiar with the environment from the first lab visit. This time, you will fill out a few questionnaires and complete cognitive and motor tests prior to bedtime. The electrodes will be placed on your head and filled with electrode gel. Then you will go to bed according to your usual schedule. During the night we might play soft non-disturbing sounds to you. The next morning cognitive and motor tests take place again, then you can take a shower if necessary, have breakfast and go home. After it, you will sleep as usual at home for another week. The second test night will take place at the end of the week. All the procedures and tests will be exactly the same as on the first test night. After the second test night, the debriefing will take place. Afterward, you can shower, have breakfast and go home. 5 days after each test night, you will complete the cognitive tests one last time at the Children's Hospital or, if not otherwise possible, at your home computer. After a total of approximately 20 days, depending on your availability, you will successfully complete the study. During the 20 days, two test nights and an optional MRI measurement will be performed. The remaining 18 days you can spend at home, not changing your lifestyle.
5	**Benefits** You will not have any health benefits. However, participation in the study will give you and you an exciting insight into science and sleep research. In addition, the knowledge gained could be the starting point for the development of a new therapeutic approach for epilepsy patients.
6	**Rights** You can decide voluntarily whether you want to participate in the study or not. You may ask any questions about the study at any time.
7	**Obligations** The interpretability of the collected data depends on your activities before and during the study. If you participate, we, therefore, ask you to comply with certain requirements: As a general rule • Please answer the questions as honestly as possible. • Inform the investigators of any adverse events that may affect your sleep or well-being during the experiment. From 7 days before the test nights • You maintain her/his normal sleep-wake rhythm. • You wear the actimeter and you fill out the sleep diary.

	From 3 days before the test nights • You do not consume any caffeinated substances, such as cola, iced tea, guarana, energy drinks, mate, coffee, black or green tea and lots of chocolate. • You abstain from alcohol, nicotine, marijuana (cannabis) and any other drugs. • You may take prescribed medication. You mention any medication you are taking in the sleep diary. On the day of the test nights • All the above mentioned • You do not do excessive exercise and does not visit a sauna.
8	**Risks** The study does not entail any significant risk. However, we would like to inform you about theoretically conceivable risks. Sleeping in unfamiliar surroundings can lead to insomnia.
9	**Results** You will be notified in the case of incidental findings that are relevant for your health. If you do not want to be informed, please let us know.
10	**Confidentiality of data and samples** All parties are subject to confidentiality. The data obtained from the study is protected and immediately encrypted such that it can no longer be associated with your identity. The data will be used for other scientific research projects in the anonymous form if you provide your separate consent. We comply with all legal provisions of the Data Protection Act.
11	**Withdrawal** You can leave the study at any time without justification, and without any consequences. The data collected will be used for analysis.
12	**Compensation** You will receive 100 CHF for every night you spend in the sleep laboratory. All travel costs will be covered.
13	**Liability** The University Children's Hospital of Zurich will be responsible in case you were to suffer health damage as a consequence of the study. However, this liability only applies if you can prove that the damage is caused by a procedures of the study. If you experience any health or other harm during or after the study, please contact the study leader or one of the study coordinators.

14	**Financing** The funding (salary and trial costs) is provided by the HMZ flagship project "SleepLoop", the grants of the Swiss National Science Foundation and operating funds of Prof. Huber.
15	**Contacts** Do you have any further questions? If so please feel free to contact us.

Study leader
Prof. Dr. Reto Huber
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 8160
reto.huber@kispi.uzh.ch

Principal investigator/ Neuropediatrician
PD Dr. Dr. Georgia Ramantani
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 7852
georgia.ramantani@kispi.uzh.ch

Principal investigator/ Neuropediatrician
Dr. Bigna Bölsterli
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 7701
bigna.boelsterli@kispi.uzh.ch

Study coordinator
Sven Leach
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 3217
Mob: +41 78 633 391
sven.leach@kispi.uzh.ch

Study coordinator
Sara Fattinger
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 8186
Mob: +41 79 545 32 20
sara.fattinger@kispi.uzh.ch

Study coordinator
Elena Schmidt
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 3217
Mob: +49 176 477 90 396
elena.schmidt@kispi.uzh.ch

Detailed information

1. Aim of the study

This study aims to investigate the effect of soft non-disturbing sounds during sleep on the brain activity of healthy participants and patients with epilepsy. In addition, we will test the association between sleep and memory functions. This study will also contribute to our understanding of brain activity during deep sleep and especially some features typical for patients with epilepsy. Our long-term goal is to develop a new therapeutic approach to normalize brain activity and daytime performance in patients with epilepsy.

2. Participant selection

You are above 18 years old and right-handed. You attended a regular school and can follow the instructions of the experimenter. You did not travel across 2 time zones in the last few months. You, if childbearing, are not pregnant. You **do not** suffer from any of the following symptoms:

- Psychiatric, neurological, physical, sleep-related or nervous system related disorders
- Irregular sleep-wake rhythm
- Skin allergy or very sensitive skin
- Drug and medication use or abuse
- Obesity
- Excessive sweating

You do **not consume**:

- A lot of caffeine (>3 serving per day), including coffee, black and green tea, mate, guarana, cola, energy drinks, ice tea and a lot of chocolate
- A lot of alcohol (>8 servings per week) like beer, wine, champagne or schnapps.
- A lot of nicotine (daily consumption), including cigarettes, waping, snus or nicotine patches.
- Regular consumption of cannabis (>1 time per week).
- Occasional use of other drugs (> 6 consumption days per year), such as MDMA, ecstasy, amphetamines, LSD, psilocybin mushrooms, steroids, speed, cocaine, methamphetamine (Crystal), heroin, methadone, bath salts (Meph), G , Ketamine, liquid ecstasy (GHB, GBL, G), benzodiazepines, opium, etc. This list is not exhaustive. Therefore, please decide carefully if any other substance you use falls into this category.
- The last consumption of any other drugs must be more than 6 weeks before the start of study.
- Regular medication (>1 intake per week)

3. General information

Patients with certain forms of epilepsy show so-called epileptiform activity (discharges) in the EEG. Number of the epileptiform discharges often increase in deep sleep. So far, little is known about why epileptiform discharges increase in deep sleep and how they can affect sleep quality.

The EEG in deep sleep is characterized by very slow, big waves. They are involved in the recovery processes and stabilizing of memories acquired during the day. Scientific evidence suggests that these very slow, large waves also favor the occurrence of epileptiform discharges, which might be associated with cognitive impairment.

More specifically, the amplitude (size) and slope (steepness) of the waves play an important role. Theoretical considerations suggest that the bigger the wave, the higher the probability that it will provoke epileptiform discharge. Several studies have already shown that the amplitude of the waves can be influenced by intentionally played sounds during sleep. Therefore, presentation of these sounds will be able to influence the frequency of epileptiform discharge in sleep. We believe that by reducing

the amount of epileptiform discharge during sleep we can improve the restorative function of sleep and maybe improve their cognitive functioning.

The study is conducted at the Interdisciplinary Center for Sleep Medicine at the Children's Hospital Zurich. A total of 160 subjects will be included in the study. The total duration of the study will be 6 years. To complete the study, you will spend two nights in our sleep lab. We will attach EEG electrodes to you before going to sleep and the data will be recorded throughout the night. As soon as the special program will recognize that you are in a deep sleep, the soft non-disturbing sounds will be played. The volume chosen such that you do not wake up. A detailed description of the procedure can be found in section 4.

This national study is conducted in accordance with the law of Switzerland. In addition, we follow all internationally recognized guidelines for good clinical practice. The Cantonal Ethics Commission of the Canton of Zurich (CEC) has examined and approved the study.

A description of this study can also be found on our website https://epi.schlaflab.com and the Federal Office of Public Health's (FOPH) portal for human research in Switzerland: www.kofam.ch.

4. Procedures

You can find all the relevant information about this study on the study website. If you are interested to participate in the study, you can fill an online entrance questionnaire to find out if you meet the study participation criteria.

If you are reading this information, you probably meet the requirements for study participation. After the entrance questionnaire, you can clarify any open questions by phone, e-mail or on-site. On the next step, we will ask for your written consent to participate in the study, and you will be officially enrolled.

You will initially have the opportunity to visit the laboratory so that you can familiarize yourself with the environment in advance, if necessary. After that, you will sleep as usual at home for one week. You will wear a bracelet that measures the everyday activity by collecting information about arm movements (actimeter) and you will be asked to fill out a sleep diary. The first test night will take place at the end of this week. In the evening, you will come to the sleep laboratory, where we will meet you. You may already be familiar with the environment from the first lab visit. This time, you will fill out a few questionnaires and complete cognitive and motor tests prior to bedtime. The electrodes will be placed on your head and filled with electrode gel. Then you will go to bed according to your usual schedule. During the night we might play soft non-disturbing sounds to you. The next morning cognitive and motor tests take place again, then you can take a shower if necessary, have breakfast and go home.

After it, you will sleep as usual at home for another week. The second test night will take place at the end of the week. All the procedures and tests will be exactly the same as on the first test night. After the second test night, the debriefing will take place. Afterward, you and you can shower, have breakfast and go home.

After three weeks, you will be invited to do the cognitive tests one last time at your home using a computer. If necessary, you can also carry out the tests at the Children's Hospital.

5 days after each test night, your child will complete the cognitive tests one last time at the Children's Hospital or, if not otherwise possible, at your home computer. After a total of approximately 20 days, depending on your availability, you will successfully complete the study. During the 20 days, two test nights and an optional MRI measurement will be performed. The remaining 18 days you can spend at home, not changing your lifestyle.

Start of the study
Several questionnaires (online + paper)
Day 1 – 7
Control week 1
(Home)
Sleep diary & document medication intake
Wear activity tracker
Day 1-4: max. 1, Day 5-7: no standard portion of caffeine / Tag
Go to bed / wake up at the same time every day
Day 8
Study night 1
(Lab visit)
Sleep with EEG, quiet tones during sleep
Memory tasks
Attention tests
EpiTrack Junior
Questionnaires about well-being + EpiTrack® Junior
Day 9 – 14
Control week 2
(Home)
As control week 1
Tag 13
Follow-up 1
(Home)
Memory tasks
zoom
Day 15
Study night 2
(Lab visit)
As study night 1
Day 16 – 20
Control week 3
(Home)
Only regular sleep rhythm
Day 20
Follow-up 2
(Home)
As follow-up 1
End of study
Day xx
MRI assessment
(lab visit)
Optional. Only conducted when explicitly discussed with you.
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Control week
Study night
Follow-up

On behalf of your health the principal investigator can exclude you from the study at any time. For the sake of your safety, we would examine you in this case one more time. Your family doctor may be notified if necessary.

5. Benefits

You will not have any health benefits. However, participation in the study will give you an exciting insight into science and sleep research. In addition, the knowledge gained could be the starting point for the development of a new therapeutic approach for epilepsy patients.

6. Rights

You can decide voluntarily whether you want to participate in the study or not. You may choose not to participate. If you decide to participate in this research survey, you may withdraw at any time. You can ask any questions about the study at any time. For this purpose, please contact the person indicated at the end of this information document.

7. Obligations

The interpretability of the collected data depends on your activities before and during the study. If you participate, we, therefore, ask you to comply with certain requirements:

As a general rule

- Please answer the questions as honestly as possible.
- Inform the investigators of any adverse events that may affect your sleep or well-being during the experiment.
- Tell the investigator if you are experiencing new symptoms or complaints in respect to your epilepsy.
- Inform the investigator if you receive concomitant treatment or therapy from another doctor for your epilepsy.

From 7 days before the test nights

- You maintains normal sleep-wake rhythm. Changes in the sleep schedule, like shifting your normal bedtime and wake-up time for more than one hour should be avoided. This also means that your child must avoid night-time activities (for example, parties, watching Netflix or TV at the expense of sleep, etc.) and no activities that affect your sleep (e.g., travel through time zones). Please decide yourself which other activities might disturb a normal sleep-wake rhythm.
- You wear the actimeter and you fill out the sleep diary together.

From 3 days before the test nights

- You do not consume any caffeinated substances, such as cola, iced tea, guarana, energy drinks, mate, coffee, black or green tea and lots of chocolate.
- You abstain from alcohol, marijuana (cannabis) and any other drugs.
- You may take prescribed medication. You mention any medication you are taking in the sleep diary (prescribed by the doctor or purchased independently without a prescription, also herbal remedies and herbal teas or alternative medicine, such as homeopathy).

On the day of the test nights

- All the above mentioned
- You do not do excessive exercise and does not visit a sauna.

If you get ill the days before the planned study, please contact us to discuss the next steps.

8. Risks and burdens for the participant

The study does not entail any significant risk. Some of the mild possible risks are outlined below:

EEG measurement

EEG recording of brain activity is non-invasive and does not involve any X-rays, radiation, or injections. EEG has been used for many years and is considered very safe. Slight redness may occur in the locations where the electrodes were placed, but this will wear off after a few hours. In rare cases, electrode gel may cause mild irritation to the skin, but these are individuals who tend to have multiple skin allergies, eczemas, etc.

Overnight in the sleep laboratory

Overnight stays in an unfamiliar environment, especially in a sleep laboratory while wearing an EEG cap, can make sleeping difficult. Nevertheless, we strive to create the best conditions for a good night's sleep for you.

Auditory stimulation

In closed-loop auditory stimulation, non-disturbing soft sounds are played in deep sleep via headphones. In a pilot study carried out by us, all participants tolerated the sounds well and we did not reveal any significant risks.

Costs

Participation in the study is free of charge. Neither you, nor the health insurance or the disability insurance will not have any additional costs related to your participation in the study. All travel costs will be covered at the end of the study (we will ask you to provide a proof of payment, e.g. official receipt).

9. Results from the study

We will inform you about any new findings during the study that could affect your safety, your willingness to participate and your consent. Also, you will be notified in the case of incidental findings (like pathological patterns of EEG) that are relevant for your health and can help to prevent, diagnose or treat existing illness. If you do not want to be informed, please let us know.

10. Confidentiality of personal data and biological material

As part of this study, personal data (e.g. name, address, date of birth) will be collected and coded. "Coding" means that all data that could identify you are replaced by a randomly generated code. The decoding code will always remain within the institution. Only a few people within the Children's Hospital will have access to your non-coded data and only to perform tasks necessary for the project. All persons who are in possession of the data in the study are bound by confidentiality. People who do not know the code will not be able to draw any conclusions about your identity. For publication, we will render publicly available your individual coded EEG data, actigraphy data, and non-sensitive questionnaire data (e.g. handedness, gender). Therefore, the data cannot be traced back to you. Your name will never appear on the Internet or in a publication. Data protection regulations are respected and you as a participant have access to your data at any time.

It is possible that the study could be subject to inspection. This verification could be done by the ethics committee or the institution that organizes the study. The project management will eventually have to make your personal and medical data available for these checks. Your name will not be published in any report or publication, nor printed form, nor on the Internet.

It may also be that in the event of unlikely damage, a representative of the insurance company has to look at your non-coded data.

It is possible that your data could be used later for other studies. For this "re-use" and online publication, we invite you to sign a separate consent, which you will find at the end of this document. We believe it is important for research publications to be fully transparent, and therefore we would like to make the data collected in this study data freely available for other research groups to analyze. In addition, since the collection of clinical data is associated with great effort, this practice is essential for scientific and clinical progress.

All persons involved with the study in any way must maintain absolute confidentiality. We will not publish your name anywhere, in any report, in any publication, not printed and not on the Internet. Sometimes there is a requirement for a magazine to publish the individual data (so-called raw data). If individual data needs to be published, then the data is always encrypted and thus also not traceable to you as a person.

Responsible for compliance with national and international data protection guidelines is the sponsor Prof. Dr. Reto Huber. As a participant, you have the right to access your data at any time.

11. Withdrawal

You can leave the study at any time without justification, and without any consequences. The data collected will be used for analysis. Your data will continue to be encrypted so that people who do not know the code will not be able to identify your. Please check if you agree before joining the study.

12. Payments for study participants

You will receive 100 CHF for every night you spend in the sleep laboratory. All travel costs will be covered. There are no costs for you or your health insurance due to participation. The results of this study may help to develop commercial products. By participating in the study, you are not entitled to any commercial development claims (e.g., patents).

13. Liability

The University Children's Hospital of Zurich will be responsible in case you were to suffer health damage as a consequence of the study. However, this liability only applies if you can prove that the damage is caused by a procedures of the study. If you experience any health or other harm during or after the study, please contact the study leader or one of the study coordinators.

14. Study funding

The funding (salary and trial costs) is provided by the HMZ flagship project "SleepLoop", the grants of the Swiss National Science Foundation and operating funds of Prof. Huber.

15. Contacts

In case of doubts, fears or emergencies that may arise during or after the study, you can contact study leader or coordinators at any time.

Study leader
Prof. Dr. Reto Huber
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 8160
reto.huber@kispi.uzh.ch

Principal investigator/ Neuropediatrician
PD Dr. Dr. Georgia Ramantani
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 7852
georgia.ramantani@kispi.uzh.ch

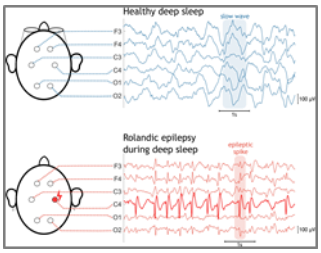
Principal investigator/ Neuropediatrician
Dr. Bigna Bölsterli
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 7701
bigna.boelsterli@kispi.uzh.ch

Study coordinator
Sven Leach
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 3217
Mob: +41 78 633 391
sven.leach@kispi.uzh.ch

Study coordinator
Elena Krugliakova
Kinderspital Zürich
Steinwiesstrasse 75
CH-8032 Zürich
Tel: 044 266 3217
Mob: +41 76 725 479
elena.krugliakova@kispi.uzh.ch

16. Glossary

EEG
Electroencephalography is a passive recording technique for measuring electrical signals produced by your brain. Your brain cells communicate via electrical impulses and are active all the time, even when you're asleep. Small flat metal discs with wires (called electrodes) are embedded in the textile cap, which is attached to the scalp. A special gel should be added between electrodes and skin. It is necessary for better EEG signal quality. The electrodes analyze the electrical impulses in the brain and send signals to a computer that records the results. This activity shows up as wavy lines on an EEG recording.



Epileptiform discharges
The EEG of a sleeping person is characterized by very slow large waves. Patients with certain forms of epilepsy may show a special EEG pattern, called epileptiform discharges. These are fast sharp waves in the EEG. Properties of these sharp waves can help to diagnose the type of epilepsy. They are also thought to be involved in poor sleeping and memory problems associated with epilepsy.

Closed-loop auditory stimulation
During closed-loop auditory stimulation, non-disturbing soft sounds are played in deep sleep via headphones. With the sounds played in sleep, it is possible to deepen sleep. Previous studies have also shown that deep sleep is associated with better learning.

Actimeter
The actimeter can be worn like a watch and measures your activity during the day and at night. An integrated accelerometer registers the movements of your wrist.

UNIVERSITY CHILDREN'S HOSPITAL ZURICH
Children's Research Center CRC

Declaration of written consent for participation in a study

Carefully read this form. Do not hesitate to ask questions if something is not clear to you or if you want an explanation. If you decide to participate in our study, you must sign this form.

BASEC study number: (after the approval of the ethics committee)	2019-02134
Study title:	Investigating the effects of closed-loop auditory stimulation on sleep and behavior in patients with epilepsy and healthy controls: a developmental study (unofficial name: Effect of soft sounds on the sleeping brain)
Responsible institution **(Study principal investigator):**	University Children's Hospital of Zurich Prof. Reto Huber Kinderspital Zürich Steinwiesstrasse 75 CH-8032 Zürich Tel: 044 266 8160 reto.huber@kispi.uzh.ch
Study location:	
Study coordinator at the study location: (last name and name in block letters)	
Participant: (last name and name in block letters) Date of birth: Sex assigned at birth:	_____ _____ ☐ female ☐ male ☐ _____

- I have been informed orally and in writing by the investigator about the purpose, the conduct of the study, the disadvantages and the advantages as well as any risks.
- I participate voluntarily in the study and accept the contents of the written information document provided in relation to the above-mentioned study. I had enough time to make my decision.
- I received full answers to my questions regarding participation in this study. I can keep the written information document about the study and receive a copy of my written consent statement.
- I agree that my family doctor will be informed about my participation in the study.
- I agree that the project management and the ethics committee responsible for this project may inspect my unencrypted data for audit and control purposes, but in strict compliance with confidentiality.
- I will be personally informed in case of new developments or incidental findings, which could have direct repercussions on the state of my health or willingness to participate.
- I know that my health-related and personal data can be transmitted in encrypted form for the research purposes (also abroad).

- In the case of further treatment outside the trial center, I authorize my physicians to submit my post-treatment data relevant to the study to the investigator.
- I can withdraw my consent at any time and without giving any reasons. My further medical treatment is always guaranteed regardless of study participation. I agree that my data and the biological material detected up to that point will still be evaluated.
- The civil liability of the hospital will respond to any damages. I am aware that insurance covers any damage caused by the study.
- I am aware of the need to respect the obligations mentioned in the information document during the study.

☐ Ich bestätige, dass ich Englisch ausreichend verstehe, um dieses Dokument zu verstehen. / I understand English sufficiently to comprehend this document.

Place and date	Signature of the study participant (Note: adolescents > 14 years old can sign the form themselves)

Investigator statement: I declare that I have explained to the participant in question the nature, importance and scope of the study. I guarantee to fulfil the obligations inherent to this study according to the current law. If at any time during the study I become aware of aspects that could influence the patient's willingness to participate in the study, I will inform him / her immediately.

Place and date	Last name and first name of the study coordinator / responsible physician in block letters Signature

Declaration of consent for the re-use of data in coded form

Participant: (last name and first name in block letters)	
Date of birth:	
Sex assigned at birth:	☐ female ☐ male ☐ _____

I authorize my data from this project to be reused for research. This means that the anonymized material is kept in an online, publicly and freely available database for an indefinite period for further research projects that are not yet defined. This consent has indefinite validity.

I understand I can decide to discontinue from participation at any time. When I discontinue my participation, my data will be anonymized. When I make this decision I inform the study coordinator and do not have to justify this decision.

I understand that the data and the material are coded and that the decoding code is kept in a safe place. The data can be sent to other databases in Switzerland and abroad for analysis if they comply with the same standards as in Switzerland. All data protection guidelines are followed.

Usually, the data is analyzed once data collection is completed in all participants and the results are published as an average. If an important result concerning my heath will be found, it is possible that I will be contacted by the study coordinator. If I do not want to be notified, I should communicate this to the study coordinator.

If the results deriving from data and biological materials are marketed, I have no claim to participate in commercial use.

Place and date	Participant's signature

Declaration of the informing investigator: I declare that I have explained to the participant in question the nature, meaning and scope of the reuse of their data.

Place and date	Last name and first name of the informing study coordinator/informing physician in block letters Signature