STUDY PROTOCOL

Project title
Keeping It Simple Study (KISS) – Pain science education for patients with chronic musculoskeletal pain undergoing community-based rehabilitation: A multicenter Randomized Controlled Trial.

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Project Group

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Clinical Trials NCT06297447

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Experimental Protocol

Background

Problem: The number of patients living with chronic musculoskeletal (MSK) pain has steadily increased over the past decade with costs rising equally. Long-standing pain is associated with significant maladaptive beliefs about pain, psychological characteristics and associated behaviors which involve structural and functional neurobiological characteristics which share common pathophysiological mechanisms as chronic pain. Our recent priority setting partnership investigated the research priorities from 1000 patients with chronic MSK pain, relatives, and clinicians (1). Better pain education was rated as one of the three most important research areas (1).

Solution: Pain science education has the potential to target maladaptive psychological and behavioral components that may contribute to the maintenance of chronic pain. The KISS project will evaluate the effect of a pain neuroscience education program (PNE4Adults) on rehabilitation outcomes in patients with chronic MSK pain. This intervention has the potential to change beliefs and behaviors surrounding pain in patients with chronic MSK pain. If this is successful in disrupting maladaptive cycles contributing to chronicity, this may improve outcomes for many thousand citizens.

Introduction: Between 20% and 33% of people across the globe live with a painful musculoskeletal (MSK) condition (2). Costs correspond to almost 2% of the gross domestic products of European countries (3), posing a challenge for health care systems across the world (4,5). Patients with chronic musculoskeletal pain have a high use of healthcare, reduced work ability, loss of productivity, and loss of quality of life (6–8). Current care guidelines underline that pain science education (PSE) is a vital part of the care delivered to people suffering from chronic pain (9–13). PSE is thought in part to attenuate central sensitization and improve self-efficacy potentially mediated through decreased pain catastrophizing (14) and modulating nocebo-related effects (15). On a patient level, PSE has been shown to reduce pain catastrophizing, pain intensity, and fear-avoidance in addition to improved physical functioning, self-efficacy, and pain knowledge (16–18). Combining exercise and PSE shows greater short-term improvements in pain, disability, kinesiophobia, and pain catastrophizing compared to exercise alone (10,19–21) and the RESTORE-trial showed the benefit of adding cognitive components (22). On a societal level, PSE has further shown to minimize health expenses (16,23). However, some of the proposed barriers include training of the therapist delivering the education (24), access to training material, time during consultation, and patients' health literacy levels (25). Even in Denmark, a country with a highly educated population, the prevalence of people with inadequate health literacy is high, with nearly 4 out of 10 people facing difficulties accessing, understanding, appraising, and applying health information (25). This underlines the need to consider novel ways of delivering PSE across all levels of health literacy.

Due to the lack of tools to facilitate PSE programs, the investigators adapted an existing pain science education program that was developed by Pas et al. (2018) (26) (PNE4Kids) to teach children with chronic pain about the underlying biopsychosocial mechanisms contributing to pain. The adapted version, named PNE4Adults, consists of a manual for the therapist and a board game to enhance engagement and participant involvement. It provides

the therapist with a clear "how-to" manual and an accessible way for patients to understand the complex concept of pain (27). This new PSE program may also hold promise for adult patients with low levels of health literacy and enhance learning due to its practical tools and build-in teach-back. The focus on integrating PSE into rehabilitation may enhance the therapeutic alliance needed to facilitate the patients' ability to manage their own symptoms (28–31). Our feasibility study in adult patients with chronic MSK pain in community-based rehabilitation (*Eiger, Rathleff et al. 2024 – under review*) showed that PNE4Adults was well accepted (100%) and understandable by all (100%) patients, including those with low levels of health literacy. Qualitive interviews revealed that patients (irrespective of their health literacy) acquired a deeper understanding of their own situation and their pain. This novel approach may reduce the inequality in delivering of pain education.

Strategy for Literature Search

The basis of the study has been found among peer-reviewed articles, publicly available material, and Aalborg University's own research. Ninety-eight unique articles were found, and 52 references used (please see the section List of References) for this study which form the basis for the research within pain science education in a municipality setting rehabilitation.

The literature has been found by reviewing of the search databases: Embase, Cochrane, CINAHL, Scopus, Web of Science and Pubmed. The following search words were used in combinations for review of the literature: ((('musculoskeletal pain' OR 'msk pain' OR 'chronic pain' OR 'locomotor pain' OR 'chronic intractable pain' OR 'chronic persistent pain' OR 'persistent pain') AND (('pain science education' OR 'pain neuroscience education' OR 'explain* pain' OR 'therapeutic neuroscience education' OR 'pain education' OR 'neurological education' OR 'neurophysiological education' OR 'neurophysiology education') OR therapeutic* NEAR/3 educat* OR neurophysiolog* NEAR/3 educat*) AND (municipality OR city OR cities OR town OR 'community-based' OR outpatient OR outpatients OR 'out patients' OR 'out patient')) AND (2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py)) AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND ([danish]/lim OR [english]/lim OR [german]/lim OR [norwegian]/lim OR [swedish]/lim).

No Cochrane reviews were available.

Only studies with interest within human research have been used and the studies have been produced within the last 10 years.

Purpose

Purpose of Sub-project 1

The primary aim of the KISS-project is to evaluate the added effect of PSE ('PNE4Adults') to "usual care" compared to "usual care" alone in community-based rehabilitation.

Our hypothesis is PSE plus "usual care" will result in a larger improvement of musculoskeletal health (MSK-HQ) after 3 months (primary endpoint) compared to patients undergoing "usual care" in the municipality.

Purpose of Sub-project 2

The secondary aim is to use a process evaluation to understand how it works, and for whom the program works.

The purpose of our process evaluation is to understand how it worked and for whom, and not *if* it worked (32). The investigators will combine in-house registrations from the municipality, clinician observations, individual interviews, and focus-group interviews to answer what works for whom and under which circumstances. This will give additional insights into the novel PSE intervention, shedding light on how it induces change and uncovering any potential unintended consequences. This will support future implementation pending results.

Subjects

This randomised controlled parallel group superiority trial will include patients referred to rehabilitation at a community-based rehabilitation center with chronic MSK pain. Patients are recruited from community-based rehabilitation in Køge, Solrød, and Holbæk Municipalities (letters of collaboration has been obtained).

The following selection criteria will be used:

Inclusion

- Patients referred for rehabilitation in the municipalities Køge, Holbæk, and Solrød
- With chronic (>3 months) musculoskeletal pain.
- Adult patients (≥18 years) – no upper limit (33)
- Able to understand, speak, and write Danish.

Exclusion

- Known cognitive deficits (e.g., dementia).
- Diagnosed with cancer or other serious pathologies, e.g., cauda equina.
- Pregnancy
- Drug addiction defined as the use of cannabis, opioids, or other drugs.
- Neurologic or psychiatric diagnoses that hinder participation, e.g., stroke and borderline.
- Lack of ability to cooperate.

Design and Methods

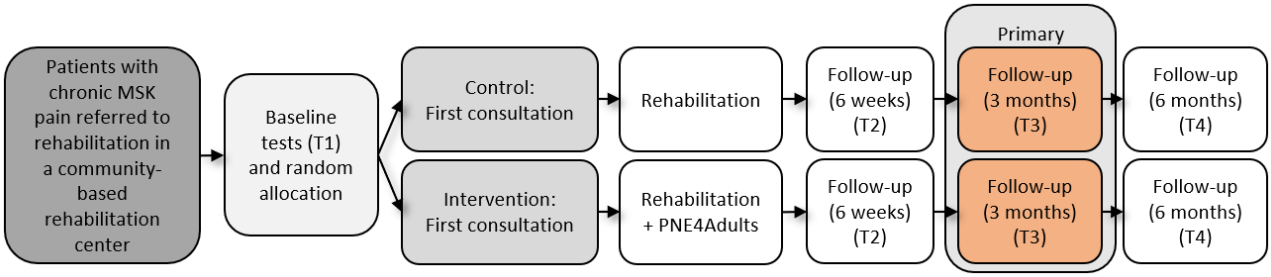
Design:

This study will be a multicentre randomised controlled, superiority trial with a 2-group parallel design. Reporting of the protocol follows the SPIRIT statement (34) and the TIDieR (35). The preparation of the trial, including publishing this trial protocol, is done in accordance with the PREPARE Trail guide (36). Before inclusion of the first participant, the trial will be registered on ClinicalTrials.gov.

Study setting:
The study will be coordinated from Department of Health Science and Technology at Aalborg University. Participants will be recruited from the municipality rehabilitation centres in Køge, Solrød, and Holbæk, and the interventions will be implemented in all three locations.

Project team:
The principal investigator (BE) is responsible for planning the trial. BE has more than 27 years of clinical experience as a physiotherapist, has a Master of Pain Science and Multidisciplinary Pain Management and is now in the process of conducting a PhD study. BE will train the physiotherapists delivering the intervention and will supervise them during the project. Prof. Michael Skovdal Rathleff and David Høyrup Christiansen have extensive research experience and Assoc. Prof. Kelly Ickmans is the original co-developer of PNE4Kids. Prof. Charlotte Overgaard has extensive experience in evaluating complex interventions in health care.

Measurement methods:
Data collection will be performed via online questionnaires at baseline, 6 weeks, 3 months, and 6 months sent to the participants' digital mailbox, e-Boks, which is accessed with MitID to ensure identity. Alternatively, if they don't have online access, the patients can arrange to come to the rehabilitation centre and receive help filling out the questionnaires online. Primary outcome is musculoskeletal Health (MSK-HQ) at primary endpoint at 3 months. All survey data will be collected through Research Electronic Data CAPture (REDCap) tools hosted at Aalborg University and stored on a secure server.
At baseline (T1), socio-demographic data will be collected: age, sex, marital status, work status, education level. Additionally, diagnoses and co-morbidities, pain duration, self-report pain medication usage, and sick-leave, Central Sensitization Inventory (CSI) (37) and Brief Health Literacy scale for Adults (B-HLA)(38) to characterize their clinical condition will be collected. Any adverse events will be noted by the physiotherapist. The recommendations from the IMMPACT initiate on outcomes for trials on chronic pain will be used (39).



Primary outcome will be Musculoskeletal Health measured with the Musculoskeletal Health Questionnaire (MSK-HQ) (40) at 3 months (T3). Secondary endpoints will be at 6 weeks (T2) and 6 months (T4).

Secondary outcomes include mean pain intensity (average of two numeric rating scales – most severe during past 24 hours, and average during past 14 days, on a 0-10 numeric rating scale) (41), pain interference (Interference part of the Brief Pain Inventory (BPI)) (42,43), concept of pain (Concept of Pain Inventory – adult (COPI-adult(DK))) (44), pain catastrophizing (Pain Catastrophizing Scale (PCS)) (45), pain self-efficacy (Pain Self-Efficacy Questionnaire (PSEQ)) (46), fear of movement (Tampa Scale of Kinesiophobia (TSK-11)) (47), patient specific functional limitations (Patient-Specific Functional Scale, 0-10 scale) (48,49)), patients impression of change (Global Impression of Change scale (GICS) (39) as a single-item rating by participants using a 7-point rating scale with the options *"very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse,"* and *"very much worse"*), patient satisfaction with current symptom state (Patient Acceptable Symptom State (PASS)) with the wording: *"Taking into account your level of pain and also your functional impairment, if you were to remain for the next few months as you are today, would you consider that your current state is satisfactory?"* (50), any adverse events and the time spent on consultations. As recommended for complex interventions (51), a qualitative, process evaluation in addition to the main quantitative analysis will be performed and a subsection of the included patients will be invited to participate in an interview. The investigators expect that this will include 12-14 patients. In addition, at each site the leaders and 1-2 of the physiotherapists delivering the intervention will be interviewed.

Randomization and blinding:
After filling out informed consent and baseline questionnaires, participants will be automatically randomized using REDCap. Randomization will be stratified by cite. Block randomization in random concealed block sizes of 4 to 12 (1:1) into two parallel groups is used to avoid imbalance in the randomization between intervention groups. A researcher, not otherwise affiliated with the study will generate the allocation sequence using sealedenvelope.com and upload it to REDCap and is the only person who will know the block sizes.

The randomization will be coded (Group 1 or 2), thus the primary investigator (BE) will not know the code to the groups.

As patients are engaging in a behavioural intervention, they are not blind to allocation, and neither are the physiotherapists delivering the intervention/ usual care. Treatment expectation is measured after randomization by a single tailored question: *"How confident are you that this treatment option will be successful in improving your MSK pain"?* The person conducting the analysis and primary investigator (BE) will remain blinded. The intervention is an add-on to "usual care". Pragmatically, there are no restrictions to "usual care" in either group. It is determined by patient preferences, physiotherapists' clinical reasoning, and available resources.

Control group:
The control group receives unrestricted "usual care". It could include a patient interview with individual goal setting and subsequent rehabilitation using cardio and strengthening exercises towards achieving the determined goals. It will be delivered by an authorized physiotherapist, and the intervention is determined by patient preferences, physiotherapist's clinical reasoning, and available resources.

Intervention:
In the intervention group, the participants will receive an add-on individualized PSE in addition to the usual care with the PNE4Adults resource. The PNE4Adults session will follow the developed manual (http://www.paininmotion.be/pne4kids) and will be delivered by a physiotherapist in two sessions of each 30-45 minutes, shortly following the first meeting. Firstly, the function of a normal pain system is introduced, with examples of the pain being overly or under protective. Then, the patient teaches back giving the therapist the opportunity to evaluate the understanding and, if necessary, repeat essential key messages. Secondly, the sensitized pain system is explained. Thirdly, the subject is asked to reflect on this new information in relation to his/her own situation. Subsequently, the new knowledge is integrated in "usual care" with any additional measures that need to be included, e.g., graded exposure, stress relief, graded activity, and cognitive therapies.

Physiotherapists delivering the intervention:
The physiotherapist delivering the intervention will be five physiotherapists from Køge, four from Holbæk, and two from Solrød. The physiotherapists have been selected by the leaders at each site. Pragmatically, no prior knowledge of pain science or level of experience was asked beforehand, but all are licensed physiotherapists. The "usual care" delivered to the control group, will be delivered by other physiotherapist in the municipalities, and not by any of the above-mentioned physiotherapists trained in delivering the intervention. As far as possible, the patients in the intervention group will be separated from the control group.

Description of the competency building for the physiotherapists intended to deliver the PNE4Adults intervention:
Five full days of teaching is planned, with 7.5 hours of teaching in person per day. In addition, follow-up sessions are planned throughout the course of the RCT to ensure fidelity to treatment and to support the physiotherapist in delivering the novel intervention.

The subjects being covered are:

- Pain as a truly bio-psycho-social experience.
- The definition of pain from IASP 2020 including footnotes.
- Classification of pain as per ICD-11.
- Neurophysiology of nociceptive pain, the sensitized pain system and descending modulation.
- Facilitatory and inhibitory contextual factors (internal, external, and relational factors).
- Therapeutic alliance, theory and how to enhance this.

- Motivational interviewing and cognitive behavioural approaches to facilitate behavioural change.
- Planning exercise therapies to chronic pain patients with different pain profiles (localized or generalized pain, pronociceptive), including introduction to pacing, graded activity and *in vivo* exposure.
- A special focus on “Plain talking” to include those with low levels of health literacy.
- The education will include lectures with power points (that are handed out), videos, but also a strong focus on practical learning and a reflection on one’s own practise.

The physiotherapists will practice using the PNE4Adults as the tool to educate patients on pain science and will also address ways to support learning during rehabilitation. Motivational interviewing and shared decision making will be practiced with a reflective team to give constructive feedback. Cases will be presented to encourage clinical reasoning in introducing physical activity to different types of patients and will be discussed to enhance reflective learning. The full days of teaching are planned with intervals of 2-3 weeks to ensure practical learning and practice in clinical situations following the more theoretical learning situations. Supervision groups are encouraged at each site.

Risks, Side Effects and Disadvantages

Safety and adverse events:
Adverse events are not expected, as the intervention is educational (52). However, information will be gathered on any adverse events in agreement with the IMMPACT recommendations (39,53). Muscle soreness or mild increase in pain in considered normal when initiating physical rehabilitation and is not considered an adverse event. There will be a Safety Monitoring Committee (SMC).

Safety Monitoring Committee:
Ensuring the safety of all participants in this study is important. With the single purpose of handling any adverse events a Safety Monitoring Committee (SMC) will be set up. The SMC will consist of the principal investigator (BE), main supervisor (MSR) and a medical doctor, Jens Lykkegaard Olesen, who is not otherwise involved in the study. In case of an adverse event, there will be an online meeting at which the event will be assessed and possibly graded (according to the Common Terminology Criteria for Adverse Events v4.03 (54)), the relation to the study determined, assisting the clinician in determining course of action, and deciding whether the participant can continue or should be withdrawn from the study. Action and treatment of adverse events will start immediately following the usual treatment protocols. Muscle soreness and slight increase in existing pain is considered a normal reaction to initiating physical rehabilitation and is not considered an adverse event. Once annually a list of any adverse events will be reported to the Ethical Committee.

Statistics

Sample size and statistical plan*:* The sample size calculation was performed using Stata vers 16.0 and is based on our feasibility study and done in collaboration with a statistician. Our estimate of a sample size is based on the ability to detect a clinically relevant difference

in MSK-HQ of 8.6 points between the two groups (40). To estimate a difference of 8.6 points (40) , with a common standard deviation of 15 points, a two-sides type I error rate of 0.05, and a power of 95%, the sample size was estimated as 49 participants per group. Considering an attrition rate of 15% and a potentially larger variation than previous studies due to heterogeneity of participants, this requires 70 participants per group. The investigators anticipate that a sample-size of 70 participants per group will be sufficient to test for clinically meaningful differences between groups and ensure statistical power even if the variance in the outcome is larger than anticipated. To allow for explorative subgroup analyses on the interaction effect of health literacy the investigators will increase this sample-size to 100 patients per arm. Statistical analyses will be performed blinded according to a pre-established analysis plan. The primary intention-to-treat analysis will investigate the between-group difference in our primary outcome. The investigators plan to use a linear mixed effects model with participant as random effect and time (6 weeks post randomization and follow-up at 3 and 6 months), group allocation (novel PNE4Adults + usual care vs usual care), study site, and baseline value of the outcome as fixed effects.

Ethical Considerations

Before initiating this study, the protocol has been evaluated by The North Denmark Region Committee on Health Research Ethics, and The Scientific Ethics Committee for Region North Jutland has at its meeting on 23 January 2024, concluded that the project is not covered by the Committees Act (Act no. 1338 of 01/09/2020) definition of a health science research project and must therefore not be notified to and approved by the committee, cf. section 14, subsection of the Committees Act. 1, cf. section 2, nos. 1-3. The Aalborg University Research Ethics Committee has approved this study, Case No: 2024-505-00157.

As this is an add-on to usual care, all participants will receive an intervention at least as good as standard care today.

The investigators wish to implement the PNE4Adults pain science education tool into clinical practice to optimize rehabilitation outcomes in adult patients with chronic pain including those with low degrees of health literacy. The intervention is educational and there is no risk of adverse events. However, according to IMMPACT recommendations (39), information on any adverse events will be gathered in this study and any that may occur will be handled. It is an add-on to “usual care” with the hope it will improve rehabilitation outcomes. The investigators follow the Helsinki Declaration in the planning and conducting of this study.

All survey data will be collected through Research Electronic Data CAPture (REDCap) tools hosted at Aalborg University and stored on a secure server. The study will be reported on ClinicalTrails.gov and has been registered internally at Aalborg University, and the protocol has been approved by the Ethical Committee at Aalborg University prior to inclusion of the first patient.

Insurance

The subjects are covered by the Danish Patient Compensation Association (Patient erstatningen).

Personal Data

Data will be stored after termination of the project. These data can only be used for the interpretation of this project and will therefore not be of interest to third party.

Data are stored in accordance with the stipulations in the General Data Protection Regulation and the Danish Data Protection Act. Data will be stored in REDCap hosted at Aalborg University.

The project is registered through internal registration in the Article 30 Register of AAU.

Information from Medical Charts

Before informed consent, the administrative personnel at each rehabilitation centre will extract information from the referrals from the hospital and/or medical charts to identify eligible participants for the study. The following information will be retrieved: Age, reason for referral, indications of MSK chronic pain, information on cancer, serious pathologies, neurological disorders, pregnancy, drug addiction and cognitive deficits. The investigators expect to screen a total of 300 referrals to include 200 participants. In the municipality only see the referral can be seen, not the medical charts.

After enrolment in the study, the following information will be retrieved from the referral of the participants: Diagnose, comorbidities and time and type of contact during rehabilitation in the municipality and dose of the intervention. Everything else is self-report.

The information from the medical charts is used to characterize their clinical condition.

The consent from the participant gives the principal investigator (*Bettina Eiger, Musculoskeletal Health and Implementation, Department of Health Science and Technology, Aalborg University)*, sponsor *(Michael Skovdal Rathleff, Head of Musculoskeletal Health and Implementation, Department of Health Science and Technology, Aalborg University)* and sponsor's representatives, and any control authority direct access to obtain information in the subject's medical chart, etc. (including electronic medical chart) to see information about the health conditions of the subject, which is necessary to conduct the research project and to conduct the mandatory control schemes, including self-regulation, quality control and monitoring.

Project Economy

The experiment has been initiated by Bettina Eiger, PhD Student, and Michael Skovdal Rathleff, Professor, both Department of Health Science and Technology, Aalborg University.

The experiment is financed with DKK 100,000 from *Danske Fysioterapeuter,* DKK 400,000 from *Helsefonden*, DKK 2,150,965 from *Karen Elise Jensens Fond* and DKK 400,000 from *Køge Kommune*. The amounts are administered by Træningsenheden, Køge Kommune.

None of the researchers have financial interest in the experiment. Bettina Eiger is employed at Køge Kommune, but Køge Kommune will have no influence in analysing the results.

Compensation to Subjects

The subjects will not receive compensation for the participation in the experiment.

Publishing of Results

All results of the project will be published regardless of the outcome of the project.

Time Schedule

Recruitment is set to commence earliest on March 7th, 2024, and terminate when 200 patients have completed the follow-up. The investigators expect to have included 200 patients per March 1st, 2025, and have completed follow-up by December 1st, 2025.

Guidelines for Oral Information and Informed Consent

Summoning Potential Subjects

When potential subjects are addressed by the staff at the rehabilitation centres, the following should be stated:

- That it is a request for participation in a scientific research project.
- The purpose of the project.
- That participation is voluntary and that the subject can withdraw from the project at any time without consequences.
- That the potential subject has time to consider his/her participation before giving consent to participation in the project and that the potential subject is welcome to ask a family member or a friend to join the information meeting. The potential volunteer will receive the leaflet “The Rights of a Trial Subject in a Health Scientific Research Project”/ "Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt" which includes information on confidentiality, right of access to documents and right to complain.
- That the material “Information for Participants”/ ”Deltagerinformation” will be forwarded in e-Boks (or per mail, if they are exempt from e-Boks) to the potential subject for him/her to know more about the project before the information meeting.
- Finally, time for the information meeting is arranged.

The Information Meeting

The information meeting is held in a quiet room where it is possible to have an uninterrupted conversation. The information meeting is held by the person responsible for the project or a project physiotherapist, who has been authorized to give the information.

The meeting is to include the following information/questions:

- Participation is voluntary and the subject can withdraw from the project at any time without consequences.
- The subject has time to consider his/her participation before giving ethical consent to participation in the project, and the subject is welcome to ask a family member or a friend to come to the information meeting.
- The subject is asked whether he/she wants a family member/friend to be present at the meeting.
- The purpose of the experiment is presented, and it is explained how the experiment is conducted. The “Information for Participants”/”Deltagerinformation”, which has been sent to the potential subject in advance, is the starting point for the information meeting.
- The leaflet “The Rights of a Trial Subject in a Health Scientific Research Project”/ "Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt" is handed over. It is explained that it includes information on confidentiality, right of access to documents and right to complain.
- The subject is asked whether he/she has read “Information for Participants”/ ”Deltagerinformation”. If this is not the case, we will ask the subject to read it.
- When it has been ensured that the subject has read the “Information for Participants”/”Deltagerinformation”, he/she is asked whether he/she has questions about the experiment.
- It is underlined that participation is voluntary, and that the subject has time to consider his/her participation (please note that The National Committee on Health Research Ethics recommends 24 hours of deliberation time)
- Again, it is underlined that participation is voluntary and that the subject can withdraw his/her consent at any time without consequences.
- The subject is informed that if he/she does not need time to consider the participation, the ethical consent can be given at the information meeting.
- In case the potential subject needs time to consider the participation, he/she is again informed about the right to consider the participation and the information meeting is terminated. Then, a new information meeting will be scheduled when the potential subject indicates by phone or email that he/she has had adequate time to consider the potential participation.
- When the subject has given consent to participate, time/place for the experiment is agreed.
- Finally, information about the contact person of the experiment is given (it is shown to the subject that the name and contact details appear from the “Information for Participants”/”Deltagerinformation”) and it is informed that this person can be contacted at any time if further questions should arise.

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