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Work Package 5:	Protocol for the SELFBACK Randomised controlled trial
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Protocol for the SELFBACK trial:

Effectiveness of a tailored app-delivered self-management program for reducing pain-related disability in people with low back pain - a protocol for the SELFBACK randomised controlled trial.

This protocol follows the recommendation for items from the Standard Protocol items: Recommendation for Intervention Trials (SPIRIT, 2013) [1] and Consolidated Standards Of Reporting Trials (CONSORT, 2010) guidelines [2]. Additionally the E-health extension to the CONSORT checklist has been used as a guideline for describing the digital intervention [3].

Protocol version:
1.2 (date of last update 2019.02.20).

Trial registration:
Trial registry will be completed at www.clinicaltrials.gov. The randomised controlled trial (RCT) is registered under id no: NCT03798288. Registration was completed before recruitment of participants to the RCT was initiated.

Roles and responsibilities:
The partners involved in the SELFBACK project include:

1. The Norwegian University of Science and Technology (NTNU), Trondheim, Norway
2. The University of Glasgow (GLA), Glasgow, Scotland
3. The Robert Gordon University (RGU), Aberdeen, Scotland
4. Trade eXpansion (TRX), Tommerup, Denmark
5. National Research Centre for the Working Environment (NFA), Copenhagen, Denmark
6. Health Leads BV (HLE), Amsterdam, Netherlands
7. University of Southern Denmark (UoSD), Odense, Denmark

NTNU is leading the development of the underlying structure for the database and decision support system (DSS), RGU has been leading the physical activity monitoring and TRX has been leading the mobile app development. The medical partners (NTNU, GLA, RGU, NFA and UoSD) have developed content for the app. The RCT is a multi-centre trial, patients are recruited at NTNU and UoSD; UoSD is lead in the planning and conducting of the RCT; UoSD is lead in the process evaluation. NTNU is leading the overall project.

Funding
The SELFBACK project has received funding from the European Union Horizon 2020 research and innovation programme under grant agreement no 689043. The funding body supervises the conduct of the overall project, but is not involved in the planning, implementation and interpretation of data from the RCT.

1. Introduction

Low back pain (LBP) is worldwide a major contributor to years lived with pain and disability. In the Global Burden of Disease studies of 2010 and 2015, it was estimated that LBP is the leading cause of years lived with disability in most countries [4, 5]. In the vast majority of people experiencing LBP specific pathoanatomical causes cannot be identified and more than 85% of people seen in primary care are categorised as having "non-specific" LBP [6]. The economic costs of health-care, sickness absence, lost ability to work, social benefits and treatment costs of non-specific LBP are high and can be considered a societal burden [7-9].

Clinical guidelines recommend patient education, exercise therapy, multidisciplinary treatments and combined physical and psychological interventions to manage LBP [10-14]. Although national clinical guidelines may differ in scope and context, the recommendations are rather consistent across countries [10-12, 15-17]. Self-management programmes that include elements of such recommended treatment components have been suggested as a promising option for chronic conditions including non-specific LBP [18]. Self-management may be defined as the individual's ability to care for own health by managing symptoms, physical and psychological consequences and impact on life [18]. In LBP, the effectiveness of self-management has been reported to be moderate for pain and small to moderate for disability [19, 20]. The lack of effect is likely to be explained by lack of tailoring of the programme to the individual and support to persist with self-management [21], and such factors may also have a negative effect on adherence to self-management programmes. Lastly, as self-management is broadly defined, the content of self-management programmes varies between the reported trials [19].

Digital solutions, such as mobile applications (apps), have been suggested as platforms for supporting self-management of chronic conditions [22, 23]. Within recent years, a vast number of apps has been introduced to the commercial market for self-management of LBP. A 2016 systematic review identified 61 apps and concluded that available apps have poor quality, included poor quality information from questionable sources and that none of the apps had been tested for effectiveness [24]. While a recent systematic review by the SELFBACK team highlighted that the literature is heterogeneous, and the evidence base remains weak [25], the SELFBACK project aims to fill this knowledge gap by developing an evidence-based and data-driven decision support system (DSS) delivered via a smartphone app to facilitate, improve and reinforce self-management of non-specific LBP [26]. The DSS suggests self-management plans consisting of physical activity advice, patient education and recommendations for physical exercise tailored to the individual's specific health information. The effectiveness of the DSS will be evaluated in a RCT. Additionally, a process evaluation will be carried out in parallel to the RCT (section 8) [27], as this will be important to aid understanding of uptake and utilisation as well as future implementability.

1.1. Objectives

The objective is to evaluate the effectiveness of the SELFBACK DSS in addition to usual care versus usual care only in a RCT. Primary outcome is pain-related disability at three months (primary endpoint). We hypothesise that participants randomised to using the SELFBACK app in addition to usual care will have at least two points difference in pain-related disability at three months, measured by the Roland-Morris Disability Questionnaire (RMDQ), compared to participants receiving usual care only.

The effectiveness of the intervention on secondary outcomes, including quality of life, use of non-prescriptive medication, sleep problems, depressive symptoms, stress, functional ability and pain

intensity, will be assessed at three months. We will also evaluate the effect on these outcomes at six and nine months.

2. Methods

2.1. Trial design

The SELFBACK study is designed as an international multi-centre superiority RCT with two parallel groups, testing the relative effectiveness of the SELFBACK DSS in addition to usual care (intervention group) versus usual care only (control group) for participants with non-specific LBP.

2.2. Study setting

The recruitment of participants will be conducted in two countries: Trondheim, Norway (NO) and Odense, Denmark (DK). In both NO and DK, participants will be recruited from general practice, physiotherapy and chiropractic clinics. Additionally, in DK recruitment will also be from the Spine Centre in the Region of Southern Denmark. The Spine Centre is an outpatient hospital that reviews patients with back pain referred from primary care. The Spine Centre provides diagnostic assessment of patients and prescribes treatment plans according to national treatment guidelines. Patients seen at the Spine Centre without serious pathologies will be referred to the SELFBACK study.

2.3. Selection criteria

Participants must meet all the following eligibility criteria:

- Seeking care from primary health-care practice or a specialised outpatient hospital facility (DK) for non-specific LBP within the past 8 weeks
- LBP of any duration
- Mild-to severe pain-related disability rated as 6 or above on the Roland Morris Disability Questionnaire (RMDQ)
- Age ≥18 years
- Own and regularly use a smart phone (with at least Android 6.0+ or iOS11.0+) with internet access (Wi-Fi and/or mobile data)
- Have a working email address and have access to a computer with internet access to complete questionnaires in a web browser.

Presence of any of the following criteria will exclude participants from enrolling in the RCT:

- Not interested
- Unable to speak, read or write in the national language (Danish/ Norwegian)
- Cognitive impairment or learning disabilities
- Mental or physical disease or health problem limiting participation in the study (Examples are fractures or pathologies, such as cancer, inflammatory diseases, and signs of radiculopathy (severe leg pain, loss of leg strength, or loss of or altered sensation in a myotomal or dermatomal distribution))
- Unable to take part in exercise/physical activity (such as non-ambulatory patients, use of walking aids/assistance, unable to get down and up from the floor independently)
- Fibromyalgia (diagnosed by a health care professional (HCP))

- Pregnancy
- Previous back surgery
- Ongoing participation in other research trials for LBP management.

The assessment of whether the criteria are considered to limit participation is performed either by the referring HCP during the recruitment phase (see green box in **Figure 1**) or by participant self-report during the screening call (see blue box in **Figure 1**).

2.4. *Identification and recruitment of participants by health care professionals (HCP)*

The recruitment period is planned to start in March 2019. A total of 350 participants are to be recruited to the RCT. Of these, 75% (n=262) will be recruited in DK and 25% in NO (n=88). In each country, collaborations with local clinics and HCPs will be established to facilitate recruitment. The number of clinics and HCPs needed to ensure sufficient recruitment rate has been informed by the pilot study (August 2018–January 2019).

The recruitment process is outlined in the green box in **Figure 1**. Patients seeking care due to non-specific LBP will be invited to participate in the trial. The HCP will refer potentially eligible participants based on a short description of eligibility. Final eligibility will be assessed by the research team during a screening phone call (blue box in **Figure 1**). The referral to the SELFBACK trial will take place after the HCP has performed routine diagnostic assessment or treatment (usual care). Participants are recruited through two pathways, *registry data* or *live recruitment*.

Recruitment from registries will be conducted at the Spine Centre in DK. Participants are sent an invitation letter including written information about the project. The written information describes three ways to contact the research team, if the participant is interested in the project: 1) by email, 2) telephone (call or text message), or 3) a link where contact information can be entered. For the registry recruitment in DK, a list of patients will be extracted every week from the Spine Centre's registry, who consulted in the past week with LBP according to the inclusion criteria.

For the live recruitment of participants, the HCP identifies patients seen in their clinical practice who are eligible for self-management of LBP. The HCP briefly informs the patient about the project and provides the patient with written information. This information is the same as given in the registry recruitment. If interested, patients can contact the research team by 1) email, 2) telephone (call or text message), or 3) add their contact information to a sign-up sheet at the clinic.

2.5. *Screening for eligibility and enrolment by researchers*

The screening process is outlined in the blue box in **Figure 1**. Participants who have indicated that they are interested in the project are contacted via telephone by a researcher in the SELFBACK team. During this call, oral information about the trial is given to the participant and questions about the project and project participation can be answered. A detailed eligibility screening is performed via a pre-defined screening form including the inclusion and exclusion criteria described above.

The enrolment process is outlined in the grey box in **Figure 1**. If eligible and willing to participate, the participants give their verbal consent to participate and are sent an email with a link to the web-based baseline questionnaire. After a participant has completed the baseline questionnaire the informed consent will be signed, and the randomisation performed via a web-based randomisation system (see section 2.6). A small difference in this procedure is evident between countries due to

difference in requirements from the local Ethics Committees. In NO, the written consent form is included in the written information provided by the HCP. The participant can return the signed informed consent in a pre-stamped envelope as provided by the HCP or alternatively, the participant can take a picture of the signed consent form and send it via a text message to the researchers. Hereafter, the researcher will call the participant and inform about the result of the randomisation and give instructions according to group allocation. If randomised to the control group, all instructions are completed on the phone. If randomised to the intervention group, the participant is required to attend a face-to-face meeting to have the app installed on their phone and be given the wristband to wear. In DK, all participants are invited to a face-to-face meeting, where the consent form is signed and hereafter the randomisation is performed. All instructions are given verbally at this meeting.

If randomised to a) the selfBACK DSS in addition to usual care, participants are given wearable device along with instructions and assistance on how to download, install and pair the wearable device with the app and how to connect the apps on the smartphone (see section 3.2.1). Moreover, the participant is given information about their follow-up assessments and information on how to contact the researcher if needed. If a participant declines participation at the face-to-face meeting, the researcher will ensure that the information from the baseline questionnaire is deleted.

If randomised to b) usual care, participants are instructed on the principles of usual care, and are given the same information as the SELFBACK intervention group about the follow-up assessments and how to get in touch with the researcher if needed.

The flow of participants through the trial is described in **Figure 1**.

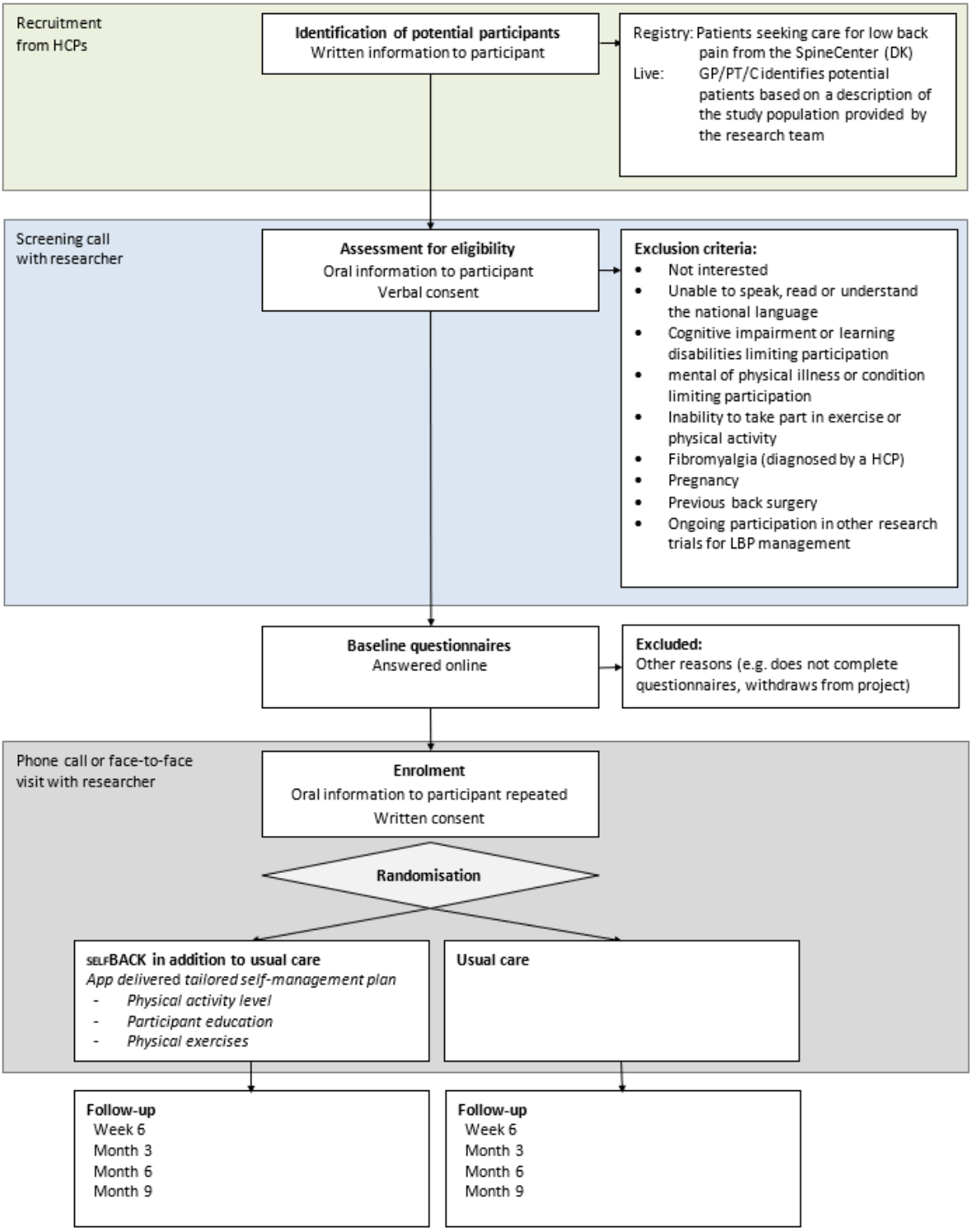

Figure 1: Participant flow through SELFBACK trial. Abbreviations: GP: general practitioner, PT: physiotherapist, C: chiropractor, HCP: Health care provider, LBP: Low Back Pain

2.6. Randomisation

Participants are randomised to either a) SELFBACK DSS in addition to usual care or b) usual care only. The randomisation is performed as a block randomisation with permuted blocks of random size unknown to the research team and stratified by country and care provider (i.e. general practitioner, physiotherapist,

chiropractor, or Spine Centre). The allocation ratio between the SELFBACK DSS in addition to usual care and the usual care groups is 1:1. Randomisation will be performed by a web-based randomisation system (Web Case Report Form; WebCRF) developed and administered by Unit of Applied Clinical Research, Faculty of Medicine and Health Sciences, NTNU, Trondheim, Norway. This unit is not otherwise involved in the trial management or trial conduct. A contractual agreement has been signed with the Unit of Applied Clinical Research concerning their role and responsibilities in the project. The WebCRF system will hold a minimal data set on all screened participants (variables include: a trial id number, country, care provider, recruitment site, age, gender).

2.7. *Blinding*

The study is a single-blinded study. Participants are not blinded to group allocation. The analysis and interpretation of the study results will be performed by researchers blinded to group allocation. Once the study is completed, a copy of the data will be extracted in pseudonymised form for statistical analyses. All personal information that may lead back to specific participants (i.e. e-mail address, username etc.) will be removed from the data. The information concerning group allocation will be added to the dataset with the intervention and control group randomly labelled as A and B. The randomisation key (i.e. document entailing information on which group is which) is kept at the Unit of Applied Clinical Research at NTNU. They will provide the randomisation key to the research team once a blinded interpretation of the results is finalized (see section 5.2).

3. Interventions

3.1. *Usual care*

Participants randomised to usual care will follow any diagnostic or treatment-related pathway (e.g. receive information, advice or treatment) as instructed by their HCP. They are also allowed to seek care, treatment or help elsewhere as normal. After the completion of the trial at 9 months, participants who have completed all follow-up assessments are contacted and offered a wearable device similar to the SELFBACK intervention group.

3.2. *SELFBACK in addition to usual care*

The SELFBACK intervention is a digital DSS for self-management of LBP provided to the participant via a smartphone app (SELFBACK app) [26]. In addition, the participant is provided with a wearable device (i.e., a step-detecting wristband) that interacts with the SELFBACK app. Based on the step count and participant's self-reported data, the SELFBACK app provides individually tailored self-management plans including educational messages, physical activity advice and exercise recommendations matched to the participant's health status, as generated by the DSS. Importantly, the intervention is not intended to replace follow-up by HCPs, but to supplement the ordinary care by the HCP, and the participant is informed accordingly. Thus, participants randomised to the SELFBACK intervention may continue to seek care, treatment or help as normal.

Stakeholder and user involvement are increasingly seen as essential especially in the context of complex interventions. It is seen as important to enhance engagement, empowerment and to maximize long-term sustainability. User involvement has been a key feature during the development of the selfBACK system and the design of trial procedures. We have had direct input from patients through a range of mechanisms that are described elsewhere [26]. The content of the intervention was developed using

Intervention Mapping (IM). IM is a six-step process with each step consisting of several tasks, which, once completed, inform the next step, as detailed by Bartholomew et al. [28]. The IM process aims to facilitate participation and consultation from all relevant stakeholders. It provides a structure for the integration of theory, empirical findings from the literature, and information collected from the target population. In short, the first step of the IM process of this project consisted of a review of international clinical practice guidelines for management of LBP. The guidelines consistently endorse important elements such as education about LBP, and uptake of evidence-based self-management behaviours by participants; including physical activity and specific exercises as well as cognitive behavioural therapy (CBT) to promote self-management for people with LBP [10, 12, 15-17]. Additionally, literature on self-management of LBP and studies on physical activity, exercise or education (including CBT) was reviewed for inspiration for specific content for each component. Finally, patient leaflets and other patient information delivered through websites or apps were reviewed for content of self-management for LBP. The intervention mapping process for the SELFBACK intervention will be described in detail in a separate publication.

3.2.1. The digital DSS

The SELFBACK system constitutes a data-driven predictive DSS that uses the Case-Based Reasoning (CBR) methodology [29] to capture and reuse participant cases in order to suggest the most suitable self-management plan for participants. The data sources for the CBR system comprise 1) the initial participant data collected by the baseline web-based questionnaire, 2) a weekly report by the participant in the SELFBACK app (including pain, function, fear-avoidance, workability, sleep, self-efficacy, stress, health belief and barriers), and 3) the step-detecting wearable. On a weekly basis, this information is used to revise the self-management plan by matching the characteristics of the current participant case with existing successful participant cases in the SELFBACK case-base. The weekly tailoring questions will only be given if relevant for the participant. As an example, if a participant has indicated sleep problems at baseline, then a tailoring question will be asked in appropriate time-intervals, and, based on the answer, a set of educational messages on e.g. sleep hygiene will be offered to the participant. Consequently, the DSS will deliver an individualised self-management plan for the coming week via the SELFBACK app. All interaction between the participant and the SELFBACK DSS happens via the SELFBACK app. There is no interaction between the DSS and HCPs. The architecture of the DSS and the interaction between the participant, the wearable device, the SELFBACK app and the database is outlined in Figure 2. A full description of the DSS is published elsewhere [30].

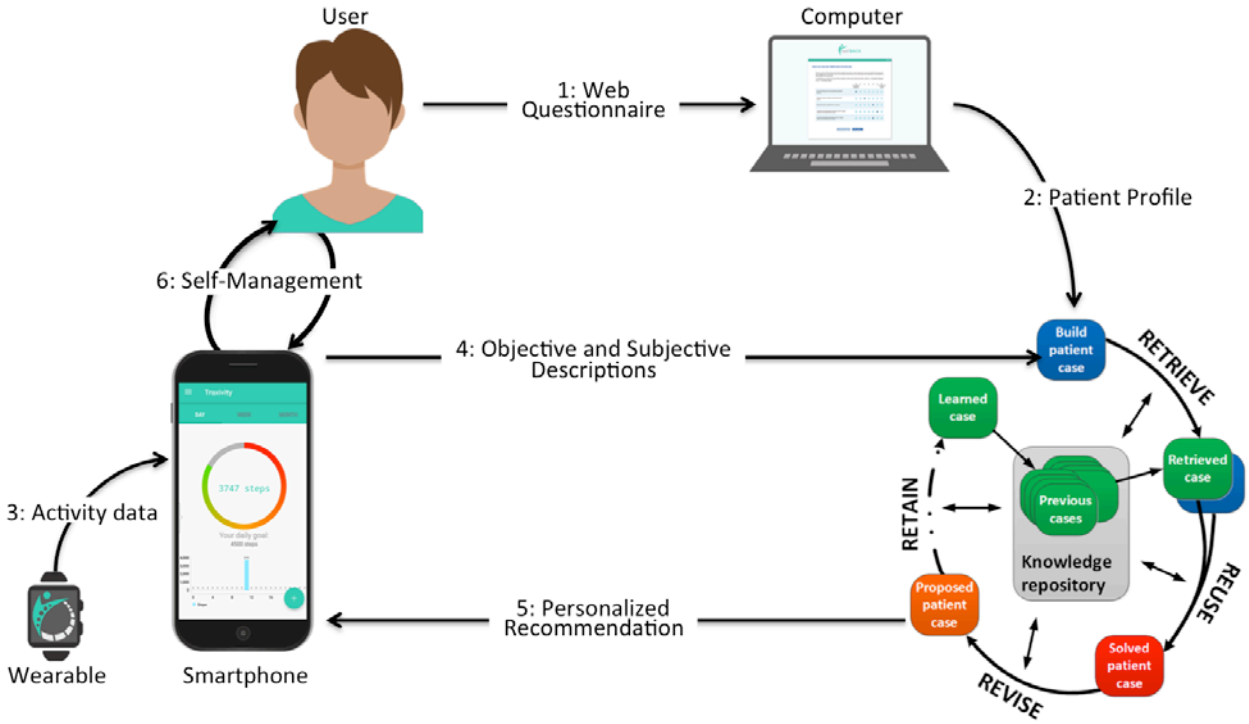

Figure 2: Overview of the SELFBACK decision support system.

3.2.1. Wearable device and supporting apps

The Xiaomi Mi Band 3 wristband is used to track number of steps. The step count is synchronized with the GoogleFit app on Android devices and Apple HealthKit app on iOS devices throughout the day. The wristband registers movement in all three planes (frontal, horizontal and sagittal) via an ADI (Analog Devices, Inc.) ultra-low power acceleration sensor and computes step-count from this information. It connects to the phone via Bluetooth (V4.2 BLE) and requires Android 4.4+ / iOS 9.0+.[1] The wearable device is to be worn on the participant's wrist continuously while participating in the intervention but could be taken of during sleep and water-based activities. To connect the wristband and step count function to the SELFBACK app, the MiFit app is required to be installed on the participant's smartphone. Additionally, Apple HealthKit needs to be activated on iOS devices, and GoogleFit needs to be activated or downloaded if not preinstalled on Android devices. The three apps (i.e., MiFit, Apple HealthKit and GoogleFit) are freely available, and can be downloaded without cost for the participant. An account needs to be created for the apps for every participant. An installation guide has been developed to help participants install and connect apps, and a researcher will be present at the time of installation to ensure the correct setup.

3.2.2. The SELFBACK self-management plans

The DSS builds the self-management plan from three types of content: 1) physical activity level (i.e., step count) and goals, 2) a bank of physical exercises, and 3) a bank of educational material. An overview of the available content is presented in Figure 3.

[1]More details:
https://www.mi.com/in/mi-band-3/specs/

Physical activity

Physical activity is tracked as described for the wearable device (see section 3.2.1). The SELFBACK app prompts the participant to set a goal for physical activity by suggesting a gradual increase in daily steps if the past week's goal was achieved. A 10% increase is suggested, until a goal of 10.000 steps per day is reached. The participant can adjust the suggested goal, before accepting it. During the week, the participant can see the achieved step-count per day and track his/her progress. The lowest step count goal that is possible to set is 3000 steps per day. This limit is based on average step count numbers from previous studies in workplace pedometer intervention (average ~6000 steps) [31] and home-based pedometer intervention in older adults with knee problems (average ~3500 steps) [32]. The minimum step count goal of 3000 per day was chosen to reflect that participants in the trial have functional disability that may also affect their physical activity level. Based on the achieved daily step count from the previous week, the step count goal for the coming week is adjusted, and educational messages and notifications aimed to motivate more physical activity is pushed through the SELFBACK app.

Exercise programme

The physical exercise material is compiled of 70 exercises organised in 6 targets (back-, abdominal-, gluteal-, and core muscle strength, pain relief and flexibility). Each participant is given an individualised exercise programme, the default recommendation is to perform exercises in 3-5 sessions per week of 20 minutes (e.g. four exercises with an estimated duration of five min per exercise). The number of exercises is adjusted according to the participant's indication of time available for doing exercise and to the anticipated level of difficulty defined by baseline questionnaire. An exercise programme will always include either 1) a strength exercise for abdominal and back extensor muscles, or 2) one strength exercise for the core muscles. Additionally, exercises targeting strength in hip and gluteal muscles, flexibility of the spine, or pain-relieving exercises may be included in the programme. If a participant presents with an acute pain flare-up or high pain ratings, the app will offer pain-relieving exercises only until an acceptable pain level is achieved.

An exercise is presented to the participant in the app with a short video accompanied by a written instruction that includes recommendations on number of sets and repetitions. The participant will be prompted in the app to report completed number of sets and repetitions per exercise. The DSS will offer a new exercise at a more difficult or easier level in the coming week, based on the level of completion registered. In addition, participants can request new exercises (at the same level of difficulty and within the same group of exercises) if they experience problems completing the suggested exercise. The included exercises were extracted from studies identified in international guidelines for treatment of LBP [10, 33], and systematic reviews on effect of exercises in LBP treatment [34-39]. The organisation, targets and progression of exercises were guided by consensus discussions among experienced clinicians and researchers within the SELFBACK project team.

Education

The educational material is structured under 14 main categories ("information about LBP", "understanding mind-body", "self-management for LBP", "thoughts, behaviour, attitude and feeling", "fitting in self-management in a busy life", "first aid when your back hurts", "LBP and comorbidities", "goal-setting and action planning", "pacing and graded activity", "problem solving", "relaxation", "sleep and LBP", "social support" and "overcoming barriers for self-management of LBP"). For each

main category, a tree-structure of educational messages has been created. Every short message is about 140 characters long. Some messages may include links to longer, more explanatory text (max 500 characters) or tools that can be used to help with self-managing LBP, e.g. goal setting tool, sleep advice, etc. Some short messages are also rewritten into "quizzes", where the educational content is rephrased into a yes or no type question. When answering a quiz, a response is displayed to the participant stating the correct answer with additional explanation. A total of 230 short messages or quizzes are available in the educational material.

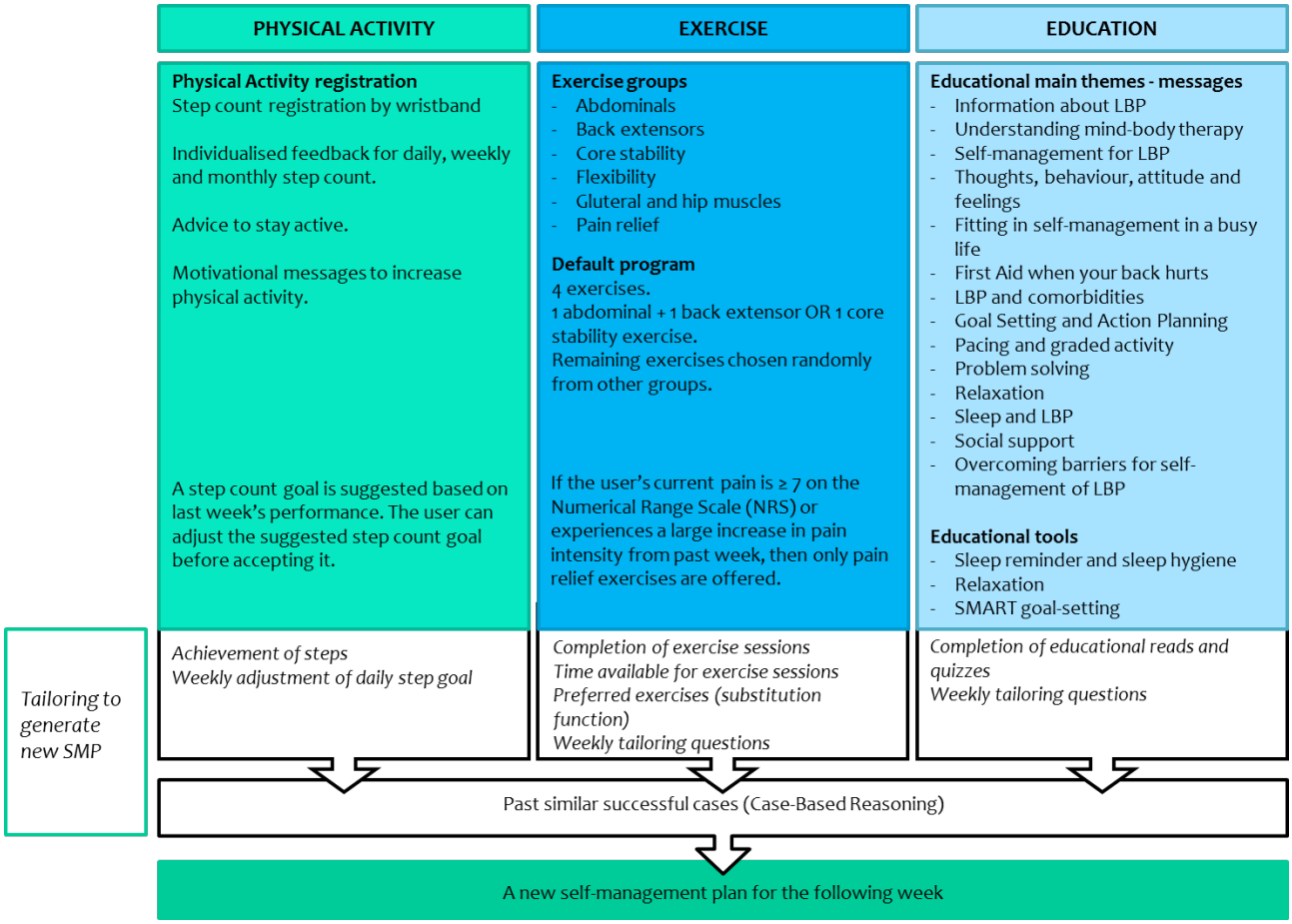

Figure 3: Overview of available content within the SELFBACK app

3.2.3. SELFBACK mobile app

The individually tailored self-management plan is delivered via the SELFBACK app. The SELFBACK app is developed by TRX in close collaboration with the other SELFBACK partners. The development of the first version of the app has been completed (by December 2017). The SELFBACK app was tested in a pilot study starting August 2018 (section 7). Feedback from the pilot participants was implemented into the app; however, the core content and features did not change. The app and DSS will be frozen and tested in the RCT. To increase transparency and facilitate replicability of the intervention, the version of the app and DSS used in the RCT will be preserved. A short video representation of the app will be made publicly available after the RCT has been completed.

3.2.4. Access, frequency and mode of delivery

The participants access their self-management plan via the SELFBACK app and enter data into the DSS by answering tailoring questions in the app and by wearing the connected wearable device. These data are combined with the participant self-reported outcome as outlined in Figure 2. The participant is encouraged to use the SELFBACK app daily or at least once a week, in order to be offered a new self-management plan. The app will send push-notifications reminding the participant to open the app and view the new self-management plan. The participant can disable or adjust the frequency of notifications in the app settings. The goal of the intervention is that participants learn to self-manage their LBP, which may potentially result in participants discontinuing their use of the app. Consequently, discontinuation is not necessarily a sign of low compliance but may indicate a high self-management level.

3.3. Ancillary and post-trial management

All participants randomised to the SELFBACK intervention can continue their use of the wearable device after the trial. However, their access to the SELFBACK app will cease after the 9 months follow-up, by disabling the participants username, thereby restricting login to the app. All participants randomised to the usual care group are offered a wearable device after completing all follow-up assessments. No further post-trial management is planned.

4. Outcomes

All outcomes are collected at baseline, six weeks, three, six and nine months. Additionally, participant characteristics and demographic variables are collected at baseline. Participant characteristics include age, gender, height, weight, and relevant comorbidities. The demographic variables include family relations, ethnicity, educational status, employment, and work characteristics if employed. The outcomes included in the trial were based on recommendations for LBP trials [40-42].

4.1. Primary outcome

The RMDQ assesses pain-related disability [43]. The questionnaire includes 24 items asking participants to indicate if they experience functional impairments by answering "yes" or "no" to a series of descriptions of functional abilities [44]. The RMDQ score ranges from 0 to 24, where a higher score indicates higher levels of disability due to LBP [44, 45]. The RMDQ is a validated and recommended tool for measuring pain-related disability in LBP populations [41, 45, 46]. The minimal clinically important difference for the RMDQ has been reported to be five points in LBP populations with baseline scores ranging between 14-16 points [47]. The SELFBACK trial aims to detect a two-point difference after three months. This is less than the suggested five-point reduction stated as minimally clinically important. Also, if the two-point difference does not exceed the measurement error of the RMDQ, the results will then be difficult to apply on an individual level in clinical practice. The measurement error of the RMDQ has been reported to range between 1.4-3.7 in studies comparing the RMDQ to the Oswestry Disability Index, with three studies reporting measurement error to range between 1.4 to 1.8 and one study reporting 3.7 [48]. Given that the SELFBACK intervention is an add-on to usual care and supposed to be a supplement to existing treatment rather than a substitution, a smaller difference can be justified.

4.2. Secondary outcomes

The *average* and *worst LBP intensity* within the past week will be assessed by asking "Please indicate your average/worst low back pain level during the last week", using an 11-point numerical rating scale (NRS) ranging from zero to 10. The NRS is a valid and commonly used outcome for measuring pain in adults [40, 49, 50]. *Pain duration* measures length of participants' current back pain episode and total duration of time with LBP by asking "What is the length of time you have had low back pain during this episode?" with scoring ranging from less than 1 week to more than 12 weeks and "What is the total length of time that you have had low back trouble during the last 12 months?" with scoring ranging from 0 days to everyday. Measures of pain intensity and duration are recommended as a core set of outcomes for LBP trials [40]. *Pain medication* evaluates the frequency of non-prescription pain medication use for LBP by asking "How many days during the last week have you taken non-prescription pain medication for low back pain?"

The *Fear-Avoidance Belief Questionnaire (FABQ)* assesses participant's beliefs about how physical activity and work affect their LBP [51]. The FABQ is a 5-item questionnaire, where the participants score their beliefs about their LBP on an ordinal scale ranging from zero [completely disagree] to six [completely agree]. The *Pain Self-Efficacy Questionnaire* (PSEQ) assesses the participant's level of confidence in carrying out specific activities despite their pain [52, 53]. The PSEQ is a 10-item questionnaire scored on an ordinal scale ranging from zero [completely disagree] to six [completely agree].

Activity Limitation evaluates if LBP has limited work and leisure time activities. The questionnaire consists of two single items with response options "yes" and "no." *Work Ability* is measured by a single-item and rated on an 11-point NRS scale ranging from zero [completely unable to work] to 10 [work ability at its best] [54].

Self-reported physical activity is evaluated by a revised version of the *Saltin-Grimby Physical Activity Level Scale*, where participants indicate their amount of time per week performing leisure activities with four levels of intensity ranging from sedentary to vigorous physically active [55]. Function is evaluated by the *Patient Specific Functional Scale* (PSFS) where the participants, on up to two self-selected activities, are asked to rate if they are unable to do or are having difficulty with their ability to perform self-selected activities regarded as important by the participants themselves [56, 57]. The ability to carry out the activity/activities is rated from zero [unable to perform] to 10 [able to perform].

Sleep is assessed by self-report using four items concerning problems with falling asleep, waking up repeatedly, waking up too early, and feeling sleepy during the day [58]. Items are scored in three categories; [seldom or never], [sometimes] or [several times a week]. The information retrieved from these four items approximates the information necessary to diagnose insomnia according to the DSM-V criteria [59]. Stress is evaluated with the *Perceived Stress Scale* (PSS), a 10-item questionnaire asking about frequency of thoughts and feelings related to perceived stress [60]. Participants indicate their frequency of experiencing stress-related issues on a 5-point Likert scale, ranging from [never] to [very often].

Three outcome measures are included to assess general health and perception of illness. Health-related quality of life is evaluated with the *EuroQoL 5-dimension* (EQ-5D) questionnaire [61]. A 5-point Likert scale ranging from [no problems] to [complete inability] is used to assess the health-related quality of life within each of the five dimensions (i.e., mobility, self-care, activities, pain/discomfort and anxiety/depression). The *Brief Illness Perception Questionnaire* (BIPQ) [62] evaluates the participants' illness perception in an 8-item questionnaire. Items are scored on an ordinal scale ranging from zero [no

problems] to 10 [worst severity] [62]. The *Patient Health Questionnaire-8* (PHQ-8) is an 8-item questionnaire used to evaluate the participants' depressive symptoms [63]. Items are scored on a 4-point Likert scale scoring frequency of experiencing symptoms of depression [63]. Also, a single item question for *Patient's Global Perceived Effect* will be asked at all follow-ups, where participants are asked to rate improvement or deterioration of their LBP compared to before the intervention.

Participants randomised to the SELFBACK DSS in addition to usual care are also asked a set of weekly tailoring questions used to individualise their self-management plan. The tailoring questions include items on pain (NRS for pain intensity [41]), function (item 5 from the Chronic Pain Grade Questionnaire [64]), kinesiophobia (1-item Tampa [65]), work ability (1-item WAI [54]), sleep (single item, modified from s-HUNT-Q [58]), pain self-efficacy (item 5 and 9 from PSEQ [66]), stress (4 items from PSS [60]), symptoms of depression (2 items from PHQ-8 [63]), and barriers for self-management (single item, customised to SELFBACK). In total, this comprises 17 tailoring questions; however, participants will only be asked a maximum of 7 questions per week (most commonly 4 questions). The selection of the relevant questions is based on a set of rules implemented in the backend of the DSS, taking into account the progression of the self-management process and the individual participant characteristics.

5. Statistics

5.1. Sample size estimations

The study is designed as a superiority trial with two parallel groups, SELFBACK in addition to usual care versus usual care only. We hypothesis that the intervention group (SELFBACK in addition to usual care) will have a two-point difference in pain related disability (RMDQ) compared to the control group (usual care) at three months follow-up. The sample size calculations have been performed in two ways. First, we conducted a simple calculation assuming only one follow-up measure and a standard deviation (SD) of the RMDQ score of six points. The expected SD was informed by previous high-quality studies in DK and UK investigating similar LBP populations [67-70]. Based on these calculations we estimated that a sample size of 382 (191 in each group) was necessary to detect a two-point difference with 90% power and a two-sided alpha level of 0.05.

We then performed a simulation using 1000 repetitions of a mixed model regression for repeated measures, assuming 1) three data points per participant (i.e. baseline, six weeks and, three months), 2) an effect of treatment of two points, 3) a SD of six points, and 4) a correlation between repeated measures of 0.4. The latter was based on information from previous trials with repeated measures for the RMDQ in similar LBP populations [71, 72]. As in the simple calculations reported above, we used an alpha level of 0.05. Based on these assumptions, sample size calculations showed that 250 participants (i.e. 125 participants in each group) give a power of 92% (95% confidence interval [CI 90-93]) to detect a two-point difference in RMDQ between study groups at three months. Furthermore, simulations assuming a two-point difference between groups at both six weeks and three months indicated that a sample size of 180 (90 in each group) give a power of 94% (95% CI, 92-95). Taken together, these sample size calculations indicate that a sample size of ~250 persons (125 in each group) will be sufficient under the given assumptions if the statistical analyses utilise the repeated measure design. A recent systematic review showed that attrition rates ranged between 4-94% for digital self-management interventions lasting between two weeks and 12 months in LBP populations [25]. To allow for a 30%

drop out rate at three months follow-up we aim at including a total of 350 participants in the trial; 175 participants in each arm.

5.2. *Statistical analysis*

The primary analysis will estimate the mean difference with a 95% confidence interval (CI) in RMDQ score at three months follow-up between groups (SELFBACK in addition to usual care versus usual care only). The analyses will be conducted according to the intention-to-treat principle using a linear mixed model for repeated measures. This model includes all available data for all participants at each time point (i.e. baseline, six weeks, and three months). In the regression model, individual participants will be specified as a random effect, accounting for the within subject covariance structure. The effect of group and time will be specified as fixed effects using a joint variable of intervention and time. Here, baseline levels are pooled over the two study groups assuming that any baseline differences are due to chance [73]; this also controls for any baseline differences in the outcome variable. The analysis will investigate the effect of the intervention as constant over time, as well as an interaction between time and group allocation. The between group difference will be estimated both in a crude model, and adjusted for the two variables used for stratification in the randomisation i.e. country and care provider [74]. Further adjustment for baseline levels of other prognostic factors will be considered.

Any missing values are inherently accounted for in the mixed model approach [75], but multiple imputation methods and complete case analysis will be applied in sensitivity analyses. Possible modifiers of the effect of intervention on the primary outcome will be assessed in supplementary analyses stratified by gender, age groups, socioeconomic status and different levels of LBP severity etc., and accompanied by tests of statistical interaction.

Secondary outcomes will be analysed using a similar approach as described above for the primary outcome, with linear mixed models for repeated measures. Analyses of data from six- and nine-months follow-up will also be analysed according to the above description for the primary outcome. The precision of the estimates from the statistical analyses will be assessed by 95% CI.

To increase the transparency, a statistical analysis plan will be agreed upon and made publicly available before the inclusion of participants is completed. Also, to reduce the risk of biased interpretation of results the following procedure will be undertaken: Two interpretations will be drafted based on a review of the primary outcome data with groups arbitrarily labelled as A and B [76]. One interpretation assumes that A is the selfBACK DSS in addition to usual care and B is usual care, the other interpretation assumes that A is the usual care and B is the selfBACK DSS in addition to usual care. After agreeing on both interpretations, the randomisation code is then broken and the correct interpretation will be chosen.

6. Data collection

The outlined data collection and data management is valid for the RCT and process evaluation (see section 8).

6.1. *Data collection*

Outcome measures are collected at baseline, six weeks, three, six and nine months. Data collection is performed online, and consequently all data are entered directly into the SELFBACK database by the participants. The website created for data collection has been extensively tested before the start of the

trial to ensure that all items of the outcome questionnaires are included, that the structure from the original questionnaires are kept in the online version, and that the scoring for each included questionnaire is consistent with the original scoring instructions. Time to complete the baseline questionnaire is approximately 20-25 minutes, the follow-up questionnaires are shorter and time to complete is approximately 20 min.

For baseline, six weeks, three, six- and nine-month follow-up, participants will be sent an email with a link that directs them to logon to the SELFBACK questionnaire website using their username and password provided at the start of the trial. To ensure as high a response rate as possible in the follow-up questionnaires, two reminder e-mails will be sent, the first after three days and the second after six days. If still no answer, a researcher will contact the participant via text-message or by phone call and ask if he/she is willing to answer the RMDQ on the phone.

In addition to the outcomes obtained at baseline and follow-ups answered via the website, participants in the intervention group will answer a set of tailoring questions on a weekly basis in the app (described in section 3.2.1). These answers will be tracked over time as a separate dataset and used in secondary analysis of the trial data.

6.2. Access to data

Ownership of the data collected in the SELFBACK trial is shared between the participating partners (NTNU, GLA, RGU, TRX, NFA, HLE, UoSD). A data steering committee will be established, who will be competent to decide over the use of the data. The steering committee will comprise one member from each participating partner. The SELFBACK consortium supports the concept of data sharing and enquires from outside research partners to use the data are welcomed and will be discussed and decided upon by the steering committee. All personal identifiable data collected in the trial will be kept for five years. These data are kept to be able to track any adverse events reported post completion of the trial, and to enable the project to contact enrolled participants should any plan of additional long-term follow-up be funded. After this five-year period the data set will be fully anonymised. The anonymised full data set will be kept for up to 30 years for research purposes and will be used to create a data model that can inform the further development of a potential commercial version of the SELFBACK app. Data will be stored at NTNU, NO.

7. Pilot testing

A pilot study was conducted, starting August 2018 and ending January 2019. The primary reason for conducting the pilot study was to test a fully operative version of the SELFBACK app as well as to gain information about practical procedures regarding recruitment and screening as described in this protocol. Consequently, the pilot study provided information on the number of recruitment sites needed in each country and also identified challenges to the recruitment process that could be adjusted before the RCT.

The pilot was conducted with the methods described for the RCT in this protocol. Recruitment ran until recruitment had been tested from all described channels. All participants in the pilot study were given the SELFBACK app in addition to usual care (intervention). Outcomes were collected at baseline and after 6 weeks. The outcome data collected will not be included in the RCT analyses. The pilot study also informed which variable was to be selected as a measure of adherence for the RCT. The

process evaluation (see section 8) was included in the pilot. Data on app usage and participants' experiences with the app from interviews informed any adjustments needed in the app prior to the RCT.

8. Process evaluation

As an integrated part of the RCT, a process evaluation will be conducted, which explores how the digital self-management intervention will be implemented and received and used by participants. We intend to follow the RE-AIM framework [77]. The process evaluation will be informed by quantitative and qualitative data. The Virtual Climate Care Questionnaire (VCCQ) [78] (in a 15-item version) concerns perceived support for autonomy in a virtual care setting and three rating questions (on overall rating, ease of use and recommendation to others) using a 5-point system, will be collected. In addition to the questionnaires, data on physical activity (step count) and data analytics on app usage will be collected. Semi-structured interviews with a purposive sample of participants from both intervention and control groups from across DK and NO will be undertaken. These interviews will collect information from the participants about their experiences of self-management and, for the intervention group users, of using the SELFBACK app to promote self-management of LBP. The interviews will also explore barriers and facilitators to engagement with the SELFBACK app and embedding its use within daily routines. The qualitative components will be theoretically underpinned by the Normalization Process Theory [79, 80]. Furthermore, adoption of the intervention by clinicians and their appraisal of the self-management plans generated by the DSS will be investigated through an electronic survey to all participating clinicians and semi-structured interviews with a purposive sample of participating clinicians.

9. Trial management

9.1. Research ethics approval

Approvals for the pilot study, RCT and process evaluation have been obtained from the relevant ethical committees in DK and NO separately. In DK the approval was sought for from the Regional Scientific Ethical Committee for Southern Denmark and in NO from the Regional Committee for Medical and Health Research Ethics. Correspondingly, approval from institutional review boards and/or data protection agencies have been obtained in both DK and NO. In DK, approval was obtained from the Danish Data Protection Agency through application to the University of Southern Denmark's legal office and in NO from the National Data Protection Authority.

9.2. Protocol amendments

Any amendments to the protocol will be registered with a detailed description of the change marked with date of implementation. Any amendments to the protocol will be filed with the relevant ethical committees or data protection agencies and registered at (www.clinicaltrials.gov) for transparency.

9.3. Trial monitoring

9.3.1. Harms

No serious adverse events are expected for this trial. As the suggested self-management plans may include advice to increase physical activity and exercise volume, increased muscle soreness and transient increase in joint pain are expected. Such events are known in exercise interventions and as they are transient, they pose no harm to the participants. Additionally, participants are informed that

such events may occur and that they are normal. Furthermore, any detection of unusual pain increase is automatically noted and reacted to by the DSS, and a suggestion to adjust volume of physical activity or exercise and advice on handling muscle pain is given to the participant. In addition, within the app a "caution" checklist can be consulted if participants are experiencing worsening of symptoms or pain flare-ups. In the checklist, participants are advised to seek care with their primary HCP or emergency clinics as they normally would. Consequently, as serious adverse events are unexpected, no interim analysis or a priori defined stopping rules are defined or implemented for this trial.

For each country, all enquiries from participants reporting technical or medical problems are registered. The app contains a link to a webpage with Frequently Asked Questions (FAQ) that can guide participants with technical issues. Should a participant report any worsening of symptoms, the participant will be advised to seek care from their HCP as they normally would. All enquiries will be recorded and discussed in an internal audit and reported with the study results.

9.3.2. Auditing

On a regular basis, a researcher from each recruiting country (DK, NO), a representative from the app development company (TRX), a technical partner connected to the DSS system and primary investigator of the trial will review the recruitment, enrolment, data collection, conduct of the intervention, completion of the trial, reported adverse events and discuss appropriate actions to address any inconsistencies or unexpected events. The purpose of this internal audit is to detect any inconsistency between the planned trial conduct and the performed trial conduct as well as suggesting measures to address such inconsistencies.

9.4. Declaration of interests

The overall aim of the SELFBACK project is to develop a digital DSS and mobile app to support participants to self-manage their LBP. The results and experiences from the pilot and RCT will inform the further development of the app, which may be introduced into a commercial market. In order to secure an unbiased interpretation and dissemination of the RCT, the interpretation of the results will be performed blind to group allocation. Upon publication of study results, this commercial potential in the app development will be clearly stated and the publication will undergo peer-review to ensure methodological and scientific rigor. Additionally, the overall conduct of the trial is overseen by half-yearly review from the European Union, who is funding the project.

9.5. Dissemination policy

The results of this RCT will be reported in accordance with the CONSORT 2010 reporting guideline and the 2013 amendment CONSORT-EHEALTH checklist for reporting web-based and mobile-based RCTs [2, 81]. Data collection is expected to be complete by July 2020 and dissemination of trial results is planned from then.

REFERENCES

1. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
2. Schulz, K.F., et al., *CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.* Trials, 2010. **11**: p. 32.
3. Eysenbach, G. and C.-E. Group, *CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions.* J Med Internet Res, 2011. **13**(4): p. e126.
4. Disease, G.B.D., I. Injury, and C. Prevalence, *Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015.* Lancet, 2016. **388**(10053): p. 1545-1602.
5. Buchbinder, R., et al., *Placing the global burden of low back pain in context.* Best Pract Res Clin Rheumatol, 2013. **27**(5): p. 575-89.
6. Deyo, R.A. and J.N. Weinstein, *Low back pain.* N Engl J Med, 2001. **344**(5): p. 363-70.
7. Walker, B.F., R. Muller, and W.D. Grant, *Low back pain in Australian adults: the economic burden.* Asia Pac J Public Health, 2003. **15**(2): p. 79-87.
8. Dagenais, S., J. Caro, and S. Haldeman, *A systematic review of low back pain cost of illness studies in the United States and internationally.* Spine J, 2008. **8**(1): p. 8-20.
9. Maniadakis, N. and A. Gray, *The economic burden of back pain in the UK.* Pain, 2000. **84**(1): p. 95-103.
10. Pillastrini, P., et al., *An updated overview of clinical guidelines for chronic low back pain management in primary care.* Joint Bone Spine, 2012. **79**(2): p. 176-85.
11. Savigny, P., et al., *Early management of persistent non-specific low back pain: summary of NICE guidance.* BMJ, 2009. **338**: p. b1805.
12. Koes, B.W., et al., *An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.* Eur Spine J, 2010. **19**(12): p. 2075-94.
13. Almeida, M., et al., *Primary care management of non-specific low back pain: key messages from recent clinical guidelines.* Med J Aust, 2018. **208**(6): p. 272-275.
14. Oliveira, C.B., et al., *Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview.* Eur Spine J, 2018. **27**(11): p. 2791-2803.
15. Chou, R., et al., *Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society.* Ann Intern Med, 2007. **147**(7): p. 478-91.
16. Stochkendahl, M.J., et al., *National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy.* Eur Spine J, 2018. **27**(1): p. 60-75.
17. NICE, t.N.I.f.H.a.C.E., *Low back pain and sciatica in over 16s: assessment and management. Assessment and non-invasive treatments.* 2016.
18. Barlow, J., et al., *Self-management approaches for people with chronic conditions: a review.* Patient Educ Couns, 2002. **48**(2): p. 177-87.
19. Oliveira, V.C., et al., *Effectiveness of self-management of low back pain: systematic review with meta-analysis.* Arthritis Care Res (Hoboken), 2012. **64**(11): p. 1739-48.
20. Du, S., et al., *Self-management program for chronic low back pain: A systematic review and meta-analysis.* Patient Educ Couns, 2017. **100**(1): p. 37-49.
21. Liddle, S.D., G.D. Baxter, and J.H. Gracey, *Chronic low back pain: patients' experiences, opinions and expectations for clinical management.* Disabil Rehabil, 2007. **29**(24): p. 1899-909.
22. Zhao, J., B. Freeman, and M. Li, *Can Mobile Phone Apps Influence People's Health Behavior Change? An Evidence Review.* J Med Internet Res, 2016. **18**(11): p. e287.

23. Beatty, L. and S. Lambert, *A systematic review of internet-based self-help therapeutic interventions to improve distress and disease-control among adults with chronic health conditions.* Clin Psychol Rev, 2013. **33**(4): p. 609-22.
24. Machado, G.C., et al., *Smartphone apps for the self-management of low back pain: A systematic review.* Best Pract Res Clin Rheumatol, 2016. **30**(6): p. 1098-1109.
25. Nicholl, B.I., et al., *Digital Support Interventions for the Self-Management of Low Back Pain: A Systematic Review.* J Med Internet Res, 2017. **19**(5): p. e179.
26. Mork, P.J., K. Bach, and B.C. self, *A Decision Support System to Enhance Self-Management of Low Back Pain: Protocol for the selfBACK Project.* JMIR Res Protoc, 2018. **7**(7): p. e167.
27. selfBACK-consortium, *Grant Agreement No 689043 selfBACK*. 2015.
28. Bartholomew, L.K., G.S. Parcel, and G. Kok, *Intervention mapping: a process for developing theory- and evidence-based health education programs.* Health Educ Behav, 1998. **25**(5): p. 545-63.
29. Aamodt, A. and E. Plaza, *Case-Based Reasoning - Foundational Issues, Methodological Variations, and System Approaches.* Ai Communications, 1994. **7**(1): p. 39-59.
30. Bach, K., et al., *Case Representation and Similarity Assessment in the SELFBACK Decision Support System.* Case-Based Reasoning Research and Development, Iccbr 2016, 2016. **9969**: p. 32-46.
31. Mansi, S., et al., *Investigating the effect of a 3-month workplace-based pedometer-driven walking programme on health-related quality of life in meat processing workers: a feasibility study within a randomized controlled trial.* BMC Public Health, 2015. **15**: p. 410.
32. Talbot, L.A., et al., *A home-based pedometer-driven walking program to increase physical activity in older adults with osteoarthritis of the knee: a preliminary study.* J Am Geriatr Soc, 2003. **51**(3): p. 387-92.
33. Bernstein, I.A., et al., *Low back pain and sciatica: summary of NICE guidance.* BMJ, 2017. **356**: p. i6748.
34. Steffens, D., et al., *Prevention of Low Back Pain: A Systematic Review and Meta-analysis.* JAMA Intern Med, 2016: p. 1-10.
35. Saragiotto, B.T., et al., *Motor control exercise for chronic non-specific low-back pain.* Cochrane Database Syst Rev, 2016. **1**(1): p. CD012004.
36. Macedo, L.G., et al., *Motor control exercise for acute non-specific low back pain.* Cochrane Database Syst Rev, 2016. **2**: p. CD012085.
37. Gordon, R. and S. Bloxham, *A Systematic Review of the Effects of Exercise and Physical Activity on Non-Specific Chronic Low Back Pain.* Healthcare (Basel), 2016. **4**(2).
38. Searle, A., et al., *Exercise interventions for the treatment of chronic low back pain: a systematic review and meta-analysis of randomised controlled trials.* Clin Rehabil, 2015. **29**(12): p. 1155-67.
39. van Middelkoop, M., et al., *Exercise therapy for chronic nonspecific low-back pain.* Best Pract Res Clin Rheumatol, 2010. **24**(2): p. 193-204.
40. Chiarotto, A., et al., *Core outcome measurement instruments for clinical trials in nonspecific low back pain.* Pain, 2018. **159**(3): p. 481-495.
41. Chiarotto, A., et al., *Core outcome domains for clinical trials in non-specific low back pain.* Eur Spine J, 2015. **24**(6): p. 1127-42.
42. Deyo, R.A., et al., *Report of the NIH Task Force on research standards for chronic low back pain.* J Pain, 2014. **15**(6): p. 569-85.
43. Roland, M. and R. Morris, *A study of the natural history of low-back pain. Part II: development of guidelines for trials of treatment in primary care.* Spine (Phila Pa 1976), 1983. **8**(2): p. 145-50.
44. Roland, M. and R. Morris, *A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain.* Spine (Phila Pa 1976), 1983. **8**(2): p. 141-4.
45. Smeets, R., et al., *Measures of function in low back pain/disorders: Low Back Pain Rating Scale (LBPRS), Oswestry Disability Index (ODI), Progressive Isoinertial Lifting Evaluation (PILE), Quebec*

Back Pain Disability Scale (QBPDS), and Roland-Morris Disability Questionnaire (RDQ). Arthritis Care Res (Hoboken), 2011. **63 Suppl 11**: p. S158-73.
46. Deyo, R.A., et al., *Outcome measures for low back pain research. A proposal for standardized use.* Spine (Phila Pa 1976), 1998. **23**(18): p. 2003-13.
47. Jordan, K., et al., *A minimal clinically important difference was derived for the Roland-Morris Disability Questionnaire for low back pain.* J Clin Epidemiol, 2006. **59**(1): p. 45-52.
48. Chiarotto, A., et al., *Roland-Morris Disability Questionnaire and Oswestry Disability Index: Which Has Better Measurement Properties for Measuring Physical Functioning in Nonspecific Low Back Pain? Systematic Review and Meta-Analysis.* Phys Ther, 2016. **96**(10): p. 1620-1637.
49. Hawker, G.A., et al., *Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP).* Arthritis Care Res (Hoboken), 2011. **63 Suppl 11**: p. S240-52.
50. Jensen, M.P., P. Karoly, and S. Braver, *The measurement of clinical pain intensity: a comparison of six methods.* Pain, 1986. **27**(1): p. 117-26.
51. Waddell, G., et al., *A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability.* Pain, 1993. **52**(2): p. 157-68.
52. Nicholas, M.K., *Pain self efficacy questionnaire (PSEQ).* 1989.
53. Nicholas, M.K., *The pain self-efficacy questionnaire: Taking pain into account.* Eur J Pain, 2007. **11**(2): p. 153-63.
54. Ahlstrom, L., et al., *The work ability index and single-item question: associations with sick leave, symptoms, and health--a prospective study of women on long-term sick leave.* Scand J Work Environ Health, 2010. **36**(5): p. 404-12.
55. Grimby, G., et al., *The "Saltin-Grimby Physical Activity Level Scale" and its application to health research.* Scand J Med Sci Sports, 2015. **25 Suppl 4**: p. 119-25.
56. Stratford, P., M.D. Westaway, and J. Binkley, *Assessing disability and change on individual patients: a report of a patient specific measure.* Physiotherapy Canada, 1995. **47**: p. 258-263.
57. Hefford, C., et al., *The patient-specific functional scale: validity, reliability, and responsiveness in patients with upper extremity musculoskeletal problems.* J Orthop Sports Phys Ther, 2012. **42**(2): p. 56-65.
58. Engstrøm, M., *The Reliability of a New Sleep Screening Questionnaire for Large Population-Based Studies: The Third Nord-Trøndelag Health Study.* The Open Sleep Journal, 2011. **4**(1): p. 14-19.
59. American Psychiatric Association, D.S.M.T.F. and A. American Psychiatric, *Diagnostic and statistical manual of mental disorders: DSM-5*. 5. ed. 2013, Arlington, Va: American Psychiatric Association.
60. Cohen, S., T. Kamarck, and R. Mermelstein, *A global measure of perceived stress.* J Health Soc Behav, 1983. **24**(4): p. 385-96.
61. Brooks, R., *EuroQol: the current state of play.* Health Policy, 1996. **37**(1): p. 53-72.
62. Hallegraeff, J.M., et al., *Measurement of acute nonspecific low back pain perception in primary care physical therapy: reliability and validity of the brief illness perception questionnaire.* BMC Musculoskelet Disord, 2013. **14**: p. 53.
63. Kroenke, K., et al., *The PHQ-8 as a measure of current depression in the general population.* J Affect Disord, 2009. **114**(1-3): p. 163-73.
64. Von Korff, M., et al., *Grading the severity of chronic pain.* Pain, 1992. **50**(2): p. 133-49.
65. Verwoerd, A.J., et al., *A single question was as predictive of outcome as the Tampa Scale for Kinesiophobia in people with sciatica: an observational study.* J Physiother, 2012. **58**(4): p. 249-54.
66. Nicholas, M.K., B.E. McGuire, and A. Asghari, *A 2-item short form of the Pain Self-efficacy Questionnaire: development and psychometric evaluation of PSEQ-2.* J Pain, 2015. **16**(2): p. 153-63.
67. Khan, K.A., et al., *Mapping between the Roland Morris Questionnaire and generic preference-based measures.* Value Health, 2014. **17**(6): p. 686-95.

68. Hill, J.C., et al., *Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial.* Lancet, 2011. **378**(9802): p. 1560-71.
69. Konstantinou, K., et al., *Characteristics of patients with low back and leg pain seeking treatment in primary care: baseline results from the ATLAS cohort study.* BMC Musculoskelet Disord, 2015. **16**: p. 332.
70. da, C.M.C.L., et al., *The prognosis of acute and persistent low-back pain: a meta-analysis.* CMAJ, 2012. **184**(11): p. E613-24.
71. Hestbaek, L., et al., *Low back pain in primary care: a description of 1250 patients with low back pain in danish general and chiropractic practice.* Int J Family Med, 2014. **2014**: p. 106102.
72. Lauridsen, H.H., et al., *Danish version of the Oswestry disability index for patients with low back pain. Part 2: Sensitivity, specificity and clinically significant improvement in two low back pain populations.* Eur Spine J, 2006. **15**(11): p. 1717-28.
73. Fitzmaurice, G.M., N.M. Laird, and J.H. Ware, *Linear Mixed Effects Models*, in *Applied Longitudinal Analysis*. 2004, John Wilet & Sons, Inc. : USA, New Jersey. p. 187-237.
74. Kahan, B.C. and T.P. Morris, *Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis.* BMJ, 2012. **345**: p. e5840.
75. Ranstam, J., et al., *Alternative analyses for handling incomplete follow-up in the intention-to-treat analysis: the randomized controlled trial of balloon kyphoplasty versus non-surgical care for vertebral compression fracture (FREE).* BMC Med Res Methodol, 2012. **12**: p. 35.
76. Jarvinen, T.L., et al., *Blinded interpretation of study results can feasibly and effectively diminish interpretation bias.* J Clin Epidemiol, 2014. **67**(7): p. 769-72.
77. *RE-AIM*. [cited 2018; Available from: www.re-aim.org.
78. Smit, E.S., et al., *The Virtual Care Climate Questionnaire: Development and Validation of a Questionnaire Measuring Perceived Support for Autonomy in a Virtual Care Setting.* J Med Internet Res, 2017. **19**(5): p. e155.
79. May, C. and T. Finch, *Implementing, Embedding, and Integrating Practices: An Outline of Normalization Process Theory.* Sociology, 2009. **43**(3): p. 535-554.
80. May, C.R., et al., *Using Normalization Process Theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review.* Implement Sci, 2018. **13**(1): p. 80.
81. Eysenbach, G., *CONSORT-EHEALTH: implementation of a checklist for authors and editors to improve reporting of web-based and mobile randomized controlled trials.* Stud Health Technol Inform, 2013. **192**: p. 657-61.