Statistical analysis plan (SAP) for:

Cost-effectiveness of the SELFBACK app in addition to usual care for people with low back pain: statistical analyses plan (SAP) (working title)

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Section 1: Administrative information

SAP Version 1.0 (January 2023)

This SAP is for cost-effectiveness analyses based on the SELFBACK randomised controlled trial (RCT) data. The current document supplements the SELFBACK protocol registered in ClinicalTrials.gov (NCT03798288). The paper reporting primary results from the SELFBACK trial was published in JAMA Internal Medicine[1] with its SAP as a supplementary file, while the protocol paper was published in JMIR Research Protocols[2]. The SAP content for the main trial was adapted from the Guidelines for the Content of Statistical Analyses Plans in Clinical Trials[3]. The SAP for this cost-effectiveness analysis incorporates elements from the method section in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[4] and recommendations from Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report[5]. It was written after completion of the SELFBACK trial but registered in ClinicalTrials.gov before retrieving data from Danish national registry-based resources for cost-effectiveness analyses.

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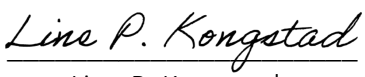

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Section 2: Introduction

Background and rationale

Digital health interventions (DHIs) have immense potential as accessible, personalised tools for managing health conditions[6]. DHIs may be important for overcoming future challenges of limited resources in the healthcare sector and are part of Denmark's digital health strategy to ensure individuals' involvement in self-management of their health conditions[7]. Despite the potential usefulness of DHIs, there is only limited research to support the claims of cost-effectiveness. The economic value of interventions is, alongside clinical efficacy, important information for decision-makers making resource allocation decisions[5]. Consequently, there is a need to assess the health-economic impact of their use.

One example of a DHI is the SELFBACK system[2,8]. Using a self-management support system delivered through an artificial intelligence-based app, persons with low back pain (LBP) were offered individually tailored self-management concordant with national and international clinical LBP guidelines[9,10]. A pragmatic RCT conducted in Denmark and Norway tested the effectiveness of the SELFBACK system as an add-on to usual care showing a small but statistically significant reduction in the primary outcomes of LBP-related disability compared to usual care at 3 months. Secondary outcomes favoured the intervention also with small effect sizes, but there were sustained results for both primary and secondary outcomes at 9 months[1]. Danish participants in the trial consented to cross-reference their information with Danish national register data. Therefore, the data available from the SELFBACK trial makes it possible to evaluate cost-effectiveness in relation to the Danish participants.

Objectives

The current health-economic analysis is based on a subset of participants in the SELFBACK RCT and aims to evaluate the 9 months' cost-effectiveness and cost-utility of the SELFBACK system in addition to usual care versus usual care alone.

The specific objectives are:

(1) to assess mean per-patient additional costs associated with the SELFBACK system compared to usual care
(2) to assess the incremental effectiveness of the SELFBACK system compared to usual care, in terms of quality of life, LBP-related disability and self-efficacy
(3) estimate the incremental cost-effectiveness/utility of the SELFBACK system compared to usual care

Section 3: Study Methods

Study Design

This study is a cost-effectiveness analysis based on data from the SELFBACK trial and cost data from registers. The design, methods and results of the RCT have been reported in detail elsewhere[1,2]. Still, we provide a brief overview of the RCT here.

Settings and Participants

We recruited adults who were 18 years or older, had nonspecific LBP within the preceding 8 weeks, scored 6 points or higher on the Roland-Morris Disability Questionnaire (RMDQ) at the time of screening, had consulted a clinician (general practitioner, physiotherapist, or

chiropractor) in the region of Southern Denmark or the Trondheim municipality in Norway or had undergone a clinical examination at an outpatient spine clinic (Spine Centre of Southern Denmark) from March 8 to December 14, 2019.

A total of 461 participants were included, whereby 317 participants from Denmark and 144 from Norway. The current study is based on the data from the 300 Danish participants that provided their unique personal identification numbers, consented to the project, and further research-related use of their data beyond the RCT and are thus eligible for inclusion in this cost-effectiveness analysis. Using the personal identification numbers, data from the RCT were merged with healthcare costs and other relevant register data from Statistics Denmark and from The Danish Health Data Authority.

Randomisation

We used a web-based trial management system for randomisation. The trial management system concealed group allocation until the randomisation was performed. Participants were randomised in a 1:1 ratio using permuted blocks with random sizes from 4 to 20 and stratified by country (Denmark or Norway) and clinician (general practitioner, physiotherapist, chiropractor, or outpatient clinic).

Intervention

The SELFBACK intervention is an app-delivered, evidence-based decision support system that, guided by case-based reasoning, provides weekly, individually tailored self-management recommendations for three main components that are endorsed by clinical guidelines: (1) physical activity (number of steps), (2) strength and flexibility exercises, and (3) daily educational messages. In addition, the app provides general information about LBP and access to several tools (goal setting, mindfulness audios, pain-relieving exercises, and sleep reminders) that participants could use at their convenience in addition to usual care[8].

Randomised to receive usual care, participants were instructed to manage their LBP according to the advice or treatment offered by their clinician. No restrictions or limitations were put on usual care. Having a common practice comparator (usual care) and inclusion of people with co-occurring musculoskeletal pain and multimorbidity[11] together with no upper age limit makes the setting more naturalistic, which improves generalizability and hence makes the data more suitable for cost-effectiveness evaluation[5].

The SELFBACK system and user involvement

The SELFBACK system was developed through the involvement of key stakeholders (care-seekers and healthcare professionals) to ensure face validity[8]. The content of the SELFBACK system was established using an intervention mapping process, and the app was tested in a pilot and a feasibility study before the RCT[8,12].

Patient self-reported data

Data on self-reported measures were collected in the SELFBACK trial using an online tool at baseline, 6 weeks and 3, 6 and 9 months after the inclusion in the trial. Data used from the questionnaires for this current analysis are socio-demographic characteristics, quality of life measured by EQ5D-5L, Roland-Morris disability questionnaire for LBP-related disability, self-efficacy by the Pain Self Efficacy Questionnaire and variables adjusted for in the main trial

(clinical setting of recruitment [General Practitioner, Physiotherapist, Chiropractor, Outpatient back clinic], age [years], sex [female, male], education [<10 years, 10-12 years, >12 years], duration of current pain episode at baseline [≤ 4 weeks, 5-12 weeks, > 12 weeks] and average pain intensity in the preceding week at baseline [0-10 scale]).

Economic evaluation

This cost-effectiveness analysis will be conducted from a national healthcare perspective and a limited societal perspective including effects on formal productivity. We merge individual self-reported patient data with Danish national registries. An overview of databases and costs is provided in Table 2.

Outcome variables

Effectiveness measures

For the cost-effectiveness analysis, we will use two clinically relevant outcomes; 1) the main outcome from the SELFBACK trial, which is LBP-related disability measured by RMDQ[13] and 2) self-efficacy reflecting people's confidence in carrying out specific activities despite their pain and indirectly how they self-manage, measured by the Pain Self-Efficacy Questionnaire (PSEQ)[14].

Utility measure

For the cost-utility analysis, we will use quality-adjusted life years (QALYs) as the primary outcome. QALYs are calculated based on the EuroQol-5L Dimension questionnaire (EQ-5D) and weighted according to the Danish value set status[15]. EQ-5D is the most common instrument for cost-effectiveness analyses[16]. The 9-month QALYs will be calculated by multiplying the utilities by the amount of time a patient spent in a particular health state. Transitions between health states are linearly interpolated.

Measures of resource use and costs

In Denmark, the Danish National Health Service primarily finance the cost of healthcare utilisation in primary and secondary healthcare. Exceptions to this are chiropractic, physiotherapy, and psychology consultations in primary care, which incur additional out-of-pocket expenses the patient pays.

Individual patient data on primary sector healthcare utilisation and related cost are retrieved from the National Health Service Registry (Sygesikringsregisteret)[17] with services provided by General practitioners, Chiropractors, Physiotherapists, and Medical specialists. Use of secondary sector care utilisation will be retrieved from the National Patient Registry (Landspatientregisteret)[18], including assessments, tests and procedures at Spine centers and rheumatology, neurology, orthopaedic and neurosurgery departments and redeemed prescriptive medication from the National Prescription Registry (Lægemiddeldatabasen)[19].

Costs of prescription medication will be calculated based on prices charged by the pharmacies (excluding VAT). Primary healthcare costs will be valued according to the prevailing fee schedules agreed upon between the providers and the Danish Regions. Hospital treatment costs will be valued with official hospital Diagnosis Related Group (DRG) tariffs provided by the National Health Data Authority. All monetary values will be presented in euros at 2022

cost levels. Therefore, costs will be uplifted to 2022 price levels using the Net Price Index maintained by Statistics Denmark.

Formal productivity costs

Data on lost formal production, measured in terms of long-term (>4 weeks) sickness absence, will be retrieved from the Danish Register for Evaluation of Marginalization (DREAM)[20]. Productivity loss was estimated using the Human Capital method based on weeks of absence from work for participants who were not retired. The value of forgone earnings is assessed by the average gross wage.

Intervention costs

Valuation of the SELFBACK intervention will be based on average marked values of similar apps. Since all costs and outcomes occur within 1 year, discounting will not be applied.

Sample size

Based on sample size and drop-out calculations (power of 90% to detect a 2-point mean group difference in RMDQ score at 3 months and a 30% drop-out rate during follow-up), the main trial aimed for 350 participants but included as many as 461 participants (ref protocol and main), with 300 of these participants from Denmark eligible for this analysis. The SELFBACK trial was powered for the clinical outcome but not the cost-effectiveness analysis.

Section 4: Statistical analysis

The statistical analyses will be performed based on the intention-to-treat principle; patients are analysed in the group they were allocated. All costs consumed and effects gained within the 9 months of the trial will be calculated for both the SELFBACK intervention group and the usual care group.

Costs

Parametric and non-parametric methods appropriate for the data will be used to report descriptive statistics (i.e., mean, standard deviation [SD], lower and upper quartiles, minimum and maximum values) for all resource variables and total costs by trial arm. Binary and categorical variables will be represented in terms of percentages.

Multivariable regression analyses will be used to estimate incremental costs. Because costs are normally right-skewed, general linear models are considered. Two models are estimated; a base-case model, adjusting only for health care costs during the 12-month pre-baseline period, and a model that in addition includes the variables adjusted for in the main trial[1]. The base-case model is estimated both using missing values being imputed and using complete cases.

Effectiveness measures

Effectiveness measures applied in the cost-effectiveness analyses correspond to the clinical endpoints in the trial. These statistical analyses are described in the clinical trial protocol[2].

For the EQ-5D-5L index values, central tendency and dispersion measures will be presented for both groups at baseline, 6 weeks, 3, 6, and 9 months after the inclusion in the trial. These

will be presented along with median values and the 25th and the 75th percentiles, as recommended by the EuroQoL Group[21].

Multivariable regression analyses will be used to estimate incremental QALYs. Because QALYs are normally left-skewed, general linear models are considered. Two models are estimated; a base-case model, adjusting for baseline utility values[22], and a model that, in addition, includes the variables adjusted for in the main trial[1]. The base-case model is estimated both using missing values being imputed and using complete cases.

Baseline characteristics will be reported as percentages for binary variables and mean values and SDs for continuous variables.

Cost-effectiveness

The economic evaluation is conducted as a within-trial analysis. The incremental cost-effectiveness ratio (ICER) between the two groups, will be calculated as the mean difference in cost between the two groups divided by the mean difference in effect.

Conventional methods to examine the sensitivity of the cost-effectiveness analysis will be applied, such as Cost-effectiveness plans using bias-corrected bootstrapping with 1000 repetitions and cost-effectiveness acceptability curves. Deterministic sensitivity analyses will be performed on the valuation of the app.

Analyses will be performed using STATA (depending on the analyser's preference).

Missing data

Multiple imputations based on fully conditional specifications will impute missing outcome data at follow-up. For each analysis, the imputations will be based on a model that includes the outcome variables at all time points and group allocation. By multiple imputations, five imputed data sets will be created, each of which will be analysed separately. The results of the five analyses will be pooled using Rubin's rules. Table 3 shows the number of missing observations for the chosen outcome measure variables of the Danish participants (n=317).

Table 3. Missing data for the chosen outcome measures (n=300, Danish cohort)

	Baseline	6 weeks	3 months	6 months	9 months
EQ5D	0	68	47	63	68
RMDQ	0	63	41	60	66
PSEQ	1	67	47	63	68

Section 5: Ethical considerations

Participation in this study was voluntary. All patients received written and oral information about the study before accepting the invitation and signed written consent forms.
Approval for data collection, management, and storage in accordance with the EU General Data Protection Regulation (GDPR) was granted in 2019 by the legal office at the University of Denmark under the umbrella agreement with Danish Data Protection Agency (201-57-0008, RIO number 10.408 and O_10255). Ethical approval was granted by the Danish ethics committee (S-20182000-24). The SELFBACK trial was registered ClinicalTrials.gov [NCT03798288].

Section 6: Study Funding

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