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Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

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Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

ABSTRACT

Introduction: Chronic pain affects about 20-40% of the population and is linked to mental health outcomes and impaired daily functioning. Pharmacological interventions are commonly insufficient for producing relief and recovery of functioning. Behavioural health treatment is key to generate lasting benefits across outcome domains. However, most people with chronic pain cannot easily access evidence-based behavioural interventions. The overall aim of the DAHLIA project is to develop, evaluate, and implement a widely accessible digital behavioural health treatment to improve well-being in individuals with chronic pain.

Methods and analysis: The project follows the four phases of the mHealth Agile Development and Evaluation Lifecycle: (i) *development and pre-implementation surveillance* using focus groups, stakeholder interviews, and a business model; (ii) iterative *optimisation studies* applying single case experimental design (SCED) method in 4-6 iterations with n=10 patients and their health care professionals per iteration; (iii) a two-armed *clinical randomized controlled trial* enhanced with SCED (n=180 patients per arm); (iv) and interview-based *post-market surveillance*. Data analyses include multilevel modelling, cost-utility, and indicative analyses.

In October 2021, inter-sectorial partners are engaged and funding is secured for four years. The treatment content is compiled and the first treatment prototype is in preparation. Clinical sites in three Swedish regions are informed and recruitment for phase one will start in autumn 2021. To facilitate long-term impact and accessibility, the treatment will be integrated into a Swedish health platform (www.1177.se), which is used on a national level as a hub for advice, information, guidance, and e-services for health and healthcare.

Ethics and dissemination: The study plan has been reviewed and approved by Swedish Ethical Review Authorities. Findings will be actively disseminated through peer-reviewed journals, conference presentations, social media, and outreach activities for the wider public.

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Keywords: chronic pain; digital; behavioral health; protocol; intervention; single case experimental design; diary; implementation; randomized controlled trial

Strength and limitations of the study

- An agile, iterative, and data-driven process is ideally suited to navigate the complex challenges faced during the development, evaluation, and implementation of a digital behavioural treatment.
- Executing the project with a multi-disciplinary, inter-sectorial, and international team brings expertise and insights from complementary views together.
- Patients and different stakeholders, such as health care professionals, managers and digital developers, are involved in the project from the start, thus ensuring that individual needs to use and/ or promote the treatment can be met.
- The richness of methodologies combining traditional clinical trial evaluations on the population level, fine-graded momentary data collection on the individual level, explicit focus on cost-effectiveness, and determinants of implementation allows for a treatment evaluation from all angles.
- Due to the complexity and step-wise approach of this project, problems (e.g., delays in recruitment) in earlier phases might negatively affect the execution of later phases, thus calling for mitigation strategies to address potential delays.

INTRODUCTION

Chronic pain (CP) affects 20 to 40 % of the adult population[1]. Due to the COVID-19 pandemic, prevalence rates may increase further since CP can develop as a post-viral syndrome, from insufficient risk factor management during lockdown (e.g., inactivity, stress), or from accumulated unmet rehabilitation needs in overburdened rehab services[2 3]. Chronic pain impacts not only individuals' daily activities and overall quality of life, but also social and working contexts[4]. Thus, considerable direct and indirect health-related costs are associated with CP[5] and it represents a major issue for health care services and society at large.

A consensus exists regarding the importance of a holistic perspective integrating social, psychological, and biological factors of CP to accommodate this condition and its implications, and to guide interventions aimed at providing support[6]. Considering the typical complexity of CP, pharmacological treatment alone is usually insufficient in producing sustained relief and recovery of functioning[7]. Instead, management plans should target key behavioural, emotional, cognitive, and social factors in everyday functioning and quality of life[8].

To generate general and lasting benefits across outcome domains, person-centred, behavioural health interventions are critical. The necessity to match the pain treatment with specific needs of each patient has been the focus of discussion for the past decades[9]. Existing evidence supports methods that stem from cognitive behavioural frameworks[10], including the fear-avoidance model of pain and disability[11] and the psychological flexibility model, the model underlying acceptance and commitment therapy (ACT)[12 13]. In this type of treatment, the objective is to optimize effects by individualising treatment through evidence-based therapeutic procedures[14]. In clinical practice, face-to-face therapy dominates in effectively promoting well-being in patients with CP[7 15]. Modes of treatment delivery are evolving, however, as new models of care emerge.

Until now and despite the empirical support, interdisciplinary treatment, including behavioural interventions, are commonly not available or difficult to access for most individuals with CP[16 17]. Digital solutions aiming at promoting health, also known as eHealth, appear promising to bridge this gap as they appear cost-effective, can be tailored to individual needs, applied in everyday life, and used at the patients' convenience[18]. Particularly in light of the COVID-19 pandemic, distance approaches are gaining more attention in the management of CP[19]. However, the development and implementation of evidence-based digital interventions face challenges.

Innovative digital treatments require an accurate scientific evaluation to ensure clinical effectiveness. As it is still seen as the "gold standard", digital interventions for CP are often assessed through research-led randomized controlled trials (RCTs)[18 20 21]. However, a call for real-world and n-of-1 evaluations of efficacy and safety of individual assessment and treatment approaches is also being heard[22]. Compared to RCTs, n-of-1 study designs utilise repeated measurements to provide a more fine-graded, time- and context-sensitive picture of individual trajectories and pattern, thus allowing to evaluate effects at the within-person level[23].

Moreover, it has been shown that eHealth innovations purely originated from an academic context are rarely sustainably implemented into health care practice due to a lack of infrastructure, funding, and time[24]. To avoid research waste when creating new eHealth solutions, a strong user-centred design and focus on implementation is suggested[25]. A framework that combines the scientific rigor of traditional research methods with a rapid and iterative digital product development approach is needed. Then, the development of an evidence-based and user-friendly digital behavioural treatment is facilitated that is implementation-ready for applied health care.

The 'mHealth agile development and evaluation lifecycle' (Figure 1) is a framework created to promote the development of evidence-based, effective, and sustainable digital solutions[26]. This framework emphasises practicality, flexibility, rapid evaluation, and the possibility to adjust protocols to meet technological changes and insights that emerge as part of the process. Therefore, Wilson, et al. [26]'s framework will guide the present project with the ultimate goal to develop, evaluate, and implement an effective and accessible behavioural treatment to improve health in individuals with CP across Sweden.

--- FIGURE 1 NEAR HERE---

Research objectives

The overall aim of this project is to develop, evaluate, and implement a digital behavioural health treatment to improve well-being in individuals with CP. The treatment will be integrated into a nationally available health care web-platform, which facilitates large scale evaluations, further development, dissemination, and long-term use in clinical practice across Sweden. Within the project, we will (i) develop a prototype of the digital treatment matching the needs of individuals with CP, using focus groups to assess user demands, and discuss possible treatment structures and content, (ii) pilot the treatment in several iterations to evaluate its feasibility and acceptability, efficacy, and individual change processes by combining intensive (Single case experimental design (SCED)) and extensive methods; (iii) conduct a two-armed

RCT enhanced with SCED to assess the clinical effectiveness, cost-effectiveness, and long-term effects compared to treatment as usual (TAU) on a between- and within-person level; and (iv) identify barriers and facilitators, and monitor the implementation process of the treatment, through a business model and stakeholder interviews.

METHODS AND ANALYSIS

Following the mHealth agile lifecycle[26], the DAHLIA (Acronym: Digital beaviourAl HeaLth for chronIc pAin) project consists of an identification phase 0 and four main phases: Development, optimisation, clinical trial evaluation, and post-market surveillance (See overview of the DAHLIA project in Figure 2). Phase 1 includes two studies: focus groups with patients and health care professionals (HCPs) to develop the treatment prototype (Study 1), and stakeholder interviews to prepare for the implementation process by creating a business model and identifying of barriers and facilitators (Study 2). Phase 2 (Optimisation) aims at optimising the treatment and entails 4-6 iterations to test and gradually improve the prototype in a data-driven manner (Study 3). Phase 3 consists of a large-scale clinical trial to evaluate the digital treatment in comparison to TAU in a two-armed RCT enhanced with SCED (Study 4). Finally in phase 4, a post-market surveillance is conducted using interviews with stakeholders from different Swedish regions, also presenting lessons-learned (Study 5). Each phase may inform and alter subsequent phases, in line with the agile approach. Details of the studies are described in the following paragraphs.

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Project Identification

Involvement of inter-sectorial partners and international collaborators

This project is a collaboration between academia, health care, and industry. The academic partners come from seven universities in four countries (Sweden, Belgium, the Netherlands, and the U.S.). The researchers contribute to the project with their scientific and clinical experience in developing and evaluating digital treatments, implementation sciences, cost-utilisation analysis, CP and related health issues, and the SCED method. The DAHLIA treatment will be designed within the 1177.se platform in collaboration with health care developers and digital designers in Region Kalmar and supported by the industry partner Inera, who is responsible for the maintenance of the platform. The health care partners currently represent three of the 21 regions in Sweden, and include primary care centres in Region Kalmar, the Pain Clinic at Capio St. Göran Hospital, Region Stockholm, and the Rehabilitation centre in Region Örebro.

Personas as early user research

Personas are typical patient- or user-profiles illustrating the target group of a treatment or product and can be useful in the development of digital interventions to communicate user

needs to the development team[27 28]. By giving a narrative and name, personas facilitate a more concrete discussion of patient needs, and to what extent the treatment might match those needs[29]. In the DAHLIA project, three distinct patient personas evolved in an online workshop and were edited over several months until the project partners were developed in a stepwise manner. The personas originated from patient interviews in a previous study[27], and discussed in an online workshop to assess the relevance for the DAHLIA project. The personas were then adjusted based on factors identified in research[30-32], other personas used in digital development projects region Kalmar, and input from the clinical researchers (RW, IF, KB, LMcC, SP). The personas were continuously edited over several months until the project partners agreed on the final versions. The categories for each persona are: (i) *personal information*, including employment, education, family, background and social context, social support, and living area; (ii) *patient pain profile*, including pain problem, consequences, pain behaviour, and attitude to treatment; (iii) *health care and treatment*, including contact with health care, comorbidities, and medicine; and (iv) *personal needs and goals*, specifically related to the treatment. Figure 3 illustrates one of the personas used in the DAHLIA project.

--- FIGURE 3 NEAR HERE ---

During the early development of the DAHLIA treatment prototype (version 1.0), and prior to patient involvement, personas were used to ensure that relevant characteristics and contextual factors were considered[33]. The personas were presented at the start of treatment workshops to discuss, for instance, if and how the treatment content and structure fit the personas' characteristics and met their needs. Potential problems for a persona in relation to treatment elements were identified, resulting in further discussions and consensus-based adjustments.

Guiding principles in the development process of the DAHLIA treatment

Four three-hour online workshops took place between June 2020 and June 2021 to discuss the theoretical framework, conceptual model, and treatment components. Project partners presented their previous work related to behavioural treatment approaches and conferred on the guiding principles for the prototype development. The group reached consensus on using learning theory[34] as the theoretical framework for assessment and treatment. Furthermore, it was agreed that the fear-avoidance model[11] and psychological flexibility model[10 14 35] should be used as conceptual models for the DAHLIA treatment. Conclusively, the primary objective of the treatment is to increase resilience to pain and distress by promoting and training behavioural skills of relevance to the individual's functioning and well-being. Furthermore, a

self-guided micro-learning format[36] was chosen, including brief and frequent sessions (micro-sessions), delivered digitally and accessible via a smartphone or desktop computer (www.1177.se; details see 'Stakeholder interviews (Study 2)).

Based on the theoretical framework and conceptual models, values-oriented exposure is considered to be the core procedure. Exposure implies the use of systematic contact with negative experience such as pain and feelings of emotional distress that promotes avoidance, in a way that reduces their adverse influence and produces more flexible, varied, and engaged patterns of behaviour. Essentially, the function of exposure is to reduce negatively reinforced behaviour focused on alleviating unwanted experiences, in favour of positively reinforced behaviour focused on approaching goals in daily life. Exposure is enabled by several behavioural processes, such as identifying life values and noticing own thoughts and emotions, known as defusion (OPEN), flexible attention to the present (AWARE), and the building of extended habits of engagement (ACTIVE)[10].

At the end of Phase 0, the following is envisioned: The DAHLIA treatment will run over six weeks and includes four self-guided micro-sessions per week. Each session will include a set of key elements (see Figure 4). The extent to which each of these elements will be included in the session can vary. It should be noted that due to the agile process, data-driven decisions might result in changes to this suggested structure.

--- FIGURE 4 NEAR HERE---

A chat function will enable patients to connect with their health care professionals (HCPs, see details section 'participants and recruitment') for additional guidance, asynchronous feedback, and further instructions. The role of the HCP is to encourage and motivate patients to remain in the program and intervene in case the individual situation worsens. At the start of the treatment, a specific weekday will be agreed on, during which the HCP replies to the patient's message. Potentially, the reply could also be a chat message, a phone call, or a video call. The contact with the HCP will take place once a week, with a minimum of six individual interactions between the HCP and patient. HCPs will receive training, a manual, and supervision to provide the treatment.

Furthermore, patients will be prompted to fill in a pre-scheduled digital diary twice a day. The digital diary has the purpose to enable self-monitoring for increased self-awareness of own behaviours, emotions, and routines, and thus enhanced orientation towards values and goals[37], and data collection to gain insight into the individual change processes and effects of the treatment in the context of the SCED. The full list of the daily diary items can be found in the 'Individual change processes' section.

After the main six-week intervention period, the treatment also entails booster-sessions delivered through the 1177 web-platform after two and four months. The participants get invited via SMS or emails to revisit the web-platform where they can engage in short behavioural exercises. Booster sessions are suggested in other contexts to support long-term behavioural changes[38] and reinforce patients learned coping strategies. Figure 5 summarises the DAHLIA treatment components.

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Participants and recruitment

In the DAHLIA project, participants will be people who either use or deliver the digital treatment, or who facilitate the treatment implementation. Thus, study participants are (i) patients with CP, (ii) HCPs treating patients with CP, (iii) health care managers, (iv) developers of the 1177.se web platform, (v) other stakeholders identified in the process (e.g., policy makers, representatives from patient organisations). Health care professionals will be licensed psychologists or psychotherapists trained in cognitive behavioural therapy. Health care managers, developers, and other stakeholders need to be directly or indirectly connected with the treatment (e.g., decision-making on an organisational level; technical support etc.), but no other requirements apply.

Patients are eligible for inclusion if they: are older than 18 years of age; report a pain duration of ≥ 3 months; are able to communicate in Swedish; and have access to a computer, smartphone, and internet in their home environment. The exclusion criteria are: injury or illness that require immediate assessment and treatment, or is expected to progress significantly during the next 6 months; unstable medication (based on self-report: changes in medication during the past 3 months or expected within the next 3 months that could influence well-being and functioning substantially, such as opioids, anti-epileptic drugs, antidepressants); previous CBT treatment (including ACT) during the past 6 months; severe psychiatric co-morbidity (for instance, high risk of suicide).

Information regarding the DAHLIA project and specific sub-studies will be provided to the clinics, including detailed instructions for eligibility. Regions recruiting patients are Kalmar, Stockholm, and Örebro. Additional regions have expressed interest in participating and recruitment might be extended. Patients will be approached via their health care centres and once patients have expressed interest in study participation, a formal eligibility check will be conducted. Potential participants will be screened at their respective clinic via a face-to-face or online meeting by their treating care professionals, including psychologist and pain

physicians. A short interview will be conducted to confirm eligibility and ensure that none of the exclusion criteria are met. Informed consent is then obtained from all participants prior to enrolment in the study. Sociodemographic and pain-descriptive information will be collected from all participants including age, sex, level of education, occupation, location, level, and duration of pain, pain diagnosis (if applicable), and approaches to relief pain (e.g., medication, heat, physiotherapy).

Phase 1: Development

Focus groups (Study 1)

The aim of this study is to (i) identify the needs of patients and HCPs and (ii) match the treatment content to their needs. At least three focus groups will be conducted in autumn 2021, one with HCPs (i.e., psychologists/ psychotherapists trained in CBT) and two with patients. Per focus group, 6-8 participants will join[39]. An attempt will be made to recruit a heterogeneous group of patients in terms of such characteristics as pain condition, sex, and socio-economic background. The focus groups will be held online and take 90-120 minutes. A semi-structured guide inspired by Gruters, et al. [40] will be followed. In addition to a general discussion around health and individual needs at the start, the focus group leader (i.e., research assistant and clinical coordinator) will ask participants to reflect on the design, set-up, content, and prospective feasibility of the DAHLIA treatment (details see Appendix 1). The group conversations will be audio- and video-taped. Field notes will provide further insight into relevant cues and observations.

The recordings will be transcribed verbatim and the data analysis will be performed by two independent researchers. The information for the patient groups and HCP group will be analysed separately. A combination of inductive and deductive content analysis will be used. First, the deductive approach will determine the themes emerging from the semi-structured guide: (i) health needs and determinants to live well with CP, and (ii) feedback on the DAHLIA treatment. Then, an indicative analysis will be performed to identify categories within the themes. The transcript will be read carefully and open coding will be used. A consensus meeting with a third researcher will be conducted as a final step. This approach has been described previously and appears valid to answer the research question[40 41]. The results from the focus groups will be integrated into the treatment prototype (version 2.0).

Stakeholder interviews (Study 2)

The aim of this study is to develop a preliminary business model for the digital behavioural treatment and identify barriers and facilitators of the prospective implementation process. An explicit focus on implementation early during treatment development has been recommended[42]. Particularly, business modelling in the context of eHealth technologies can help to create a set of success factors that will influence sustainability and effectiveness[43]. To build the knowledge base across the multiple studies and settings, the consolidated framework for implementation research (CFIR)[44] will be used. The CFIR has five major domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation. It is utilized as part of the analysis, as explained below.

As a first step, a preliminary version of the business model canvas was filled in by the research team (SB, SJ, RW, HC). As suggested by Osterwalder and Pigneur [45] 'a business model describes the rationale of how an organization creates, delivers, and captures value' (p.14) and demonstrates the logic of how a company or organisation intends to generate profit for a service or product. The nine blocks of the business model cover four areas of a business: customers, offers, infrastructure, and financial viability. Figure 6 presents the template of the business model canvas and short definitions for each segment, including example aspects relevant for the DAHLIA project.

--- FIGURE 6 NEAR HERE---

In the present study, the treatment will be integrated into the national public health care website (www.1177.se), using the digital platform for behavioural health ('Stöd och Behandling'). This digital platform is free from commercial interests, maintained by Inera, which is owned by the county councils and regions. The general aim of this national website is to increase access to healthcare, strengthen the position of the patient, and contribute to improved public health. The website (www.1177.se) contains health care information, inspiration, and e-services. Each of the 21 regions in Sweden is responsible for coordinating activities and services provided on www.1177.se, which are conducted by own staff or contracted providers. Through a national network, providers and regions can cooperate and share licenses for services.

The business model will be discussed and refined as part of the stakeholder interviews. Currently identified stakeholders are software developers, HCPs, and health care managers. A semi-structured guide inspired by a previous study on eHealth implementation[46] will structure the interviews and gather information on gatekeepers, barriers, and facilitators for prospective

dissemination and use. Questions are tailored to the different stakeholders and include, for example, '*If/how is the interventions' content updated?*', '*Who is responsible/ involved in the maintenance of the intervention?*', '*What could facilitate/ hinder the implementation process?*', and '*Do you think this intervention has the potential to become successful in your care facility?*'. The full guide can be seen in Appendix 2. As part of the agile process, the guide may be adjusted based on information collected during the interviews and tailored to additional stakeholders including policy makers or representatives from patient organisations.

A minimum of eight interviews will be conducted and snow-ball sampling will identify additional participants that can inform the process. Interviews will be conducted until data saturation is achieved and no new topics seem to emerge. The interviews will be recorded, and the qualitative data will be transcribed. Then, a qualitative thematic analysis will be performed[47] with statements related to potential barriers and facilitators. An inductive approach to group the information will applied in order to best scope the replies and map categories onto the CFIR domains[44] as previously described.

Finally, implementation strategies matching the emerging topics will be formulated[48]. Together with the business model, these two elements represent the implementation plan for the DAHLIA project. Findings from this study may furthermore influence the post- market surveillance (Study 5, see details below).

Phase 2: Optimisation (Study 3)

The aim of the optimisation phase is to pilot the treatment and improve it through an iterative data-driven process using small patient cohorts. The primary objective is to determine the treatment feasibility and acceptability, and the secondary objectives are to examine individual change processes, and efficacy across iterations on a group-level. The general procedures include the eligibility check, and four assessment periods: baseline, main treatment period, post-intervention, and 3- and 6-months follow-ups. Results from each iteration will be integrated into the subsequent iteration, then tested again, until satisfaction is reached and no new major issues seem to emerge. In the optimisation studies, different methodologies will be combined namely momentary data collection using digital diaries, retrospective questionnaires, and semi-structured interviews. The latter will be conducted by a research assistant, while the diaries and questionnaires will be completed online. Figure 7 provides an overview of the procedure in relation to the research objectives.

--- FIGURE 7 NEAR HERE ----

In total, 40 to 60 patients and their treating HCPs will be included, with n=10 patient-HCP dyads each iteration. Four iterations have been seen as sufficient in a previous study to optimise a digital treatment[49], therefore, a minimum of four iterations will be conducted in the DAHLIA project. In accordance with the agile approach, additional iterations may be performed if deemed necessary. The rationales for the approaches and methodological details are described below.

Feasibility and acceptability

The procedure to evaluate the feasibility and acceptability of the treatment includes self-reports, interviews, and technical data. Short self-reports will be collected after each micro- and booster-session. Specifically, patients will be asked to rate the micro-session on its usefulness, enjoyment, and comprehension (‘*I experienced today’s session as helpful/ enjoyable/ understandable.*’, rated on a 7-point numerical scale from 1=not at all, to 7=very much).

Furthermore, at the end of the main intervention period, interviews will be conducted following a semi-structured guide to assess the participants’ general experience and different treatment components, specifically the diary, micro-sessions, and chat function. Questions are first rated on a 7-point numeric scale and participants are then encouraged to elaborate on their response with further details, if possible. Examples of questions are ‘*Did the intervention hinder your daily occupation?*’, ‘*Were the micro-sessions difficult or unclear?*’, ‘*Did you experience the digital diary as burdensome?*’, or ‘*Would you recommend the treatment to a friend?*’ (details see Appendix 3). This guide is based on other feasibility studies[49 50] and tailored to the DAHLIA treatment components. The HCPs will also be interviewed using a guide that follows the same structure (i.e., numeric scale and open elaborations), but the specific questions will be informed by the focus groups (study 1).

Additionally, technical data generated from the 1177.se website will be collected. These data include time and frequency of log-ins, duration of engagement with the treatment, and use of components. Technical data will be used to describe the overall use and adherence, and allows mediation analyses to determine the influence of engagement rates on treatment outcomes.

Data from the feasibility assessments will be analysed using descriptive statistics and qualitative synthesis to identify trends. The results will be presented reflecting the two core variables from the Technology Acceptance Model (TAM): ‘Perceived Usefulness’ and ‘Perceived Ease of Use’[51]. After each iteration, the insight gathered will be fed back to the

developers and integrated to gradually improve the feasibility and acceptability through data-driven adjustments of the treatment.

Individual change processes

The optimisation studies implement a sequential replicated and randomized single case experimental design (SCED) to gain detailed insight into within-person behavioural changes, and to develop and test the DAHLIA intervention, which has been recommended in the context of CP[52]. In SCEDs, each case functions as their own control and changes are evaluated comparing levels of the outcome variables across different phases (e.g., baseline phase 'A' and treatment phase 'B')[53]. The methodology aims to demonstrate cause-effect relationships between the treatment (independent variable) and the target behaviour (dependent variable)[54].

When planning a SCED study, the Risk of Bias in N-of-1 Trials (RoBiNT) Scale, a critical appraisal tool that evaluates the methodological quality of intervention studies using single-case methodology, can be followed as guidance [54 55]. The design decision made in the present study were based on this appraisal tool to ensure a scientifically robust approach. Table 1 provides details on the design elements.

Table 1. Methodological SCED approach of the DAHLIA study based on the RoBiNT Scale.

Item	RoBiNT Scale	SCED details, per optimisation iteration (*anticipated points)*
INTERNAL VALIDITY SUBSCALE		
1	Design	A **replicated randomised AB-design** with 10 x A-B (total of 20 phases), providing the opportunity to observe the experimental effect 10 times. (*2 points*)
2	Randomisation	The **start of the treatment phase** and therefore length of baseline phase will be determined **randomly** for each participant, with the baseline phase lasting between 5 to 10 days. This means that the treatment phase will start on any day between the 6th and 11th assignment. (*2 points*)
3	Sampling behaviour during all phases	The baseline phase will last at least 5 days, with twice daily sampling, resulting in **10 data points** or more **(phase A)** (assuming 100% compliance to diary). The treatment phase will run over 6 weeks, with twice daily sampling on at least 4 days per week (6 weeks x 4 days x twice daily sampling), resulting in **48 data points** or more **(phase B)** (assuming 100% compliance to diary). Even if the compliance rate should be lower, the amount of data points will lie >5 data points. *(2 points)*
4	Blinding of participants and HCP delivering the treatment	**Blinding** of the participant and practitioner is **not feasible** in the DAHLIA project. The behavioural treatment is delivered through a web-platform independently of the HCP; however, the HCP provides weekly, tailored support in addition to the online treatment. Neither the participant nor the HCP are blinded. (*0 points*).
5	Blinding (masking) of assessors	Patients complete self-report diaries and are **not blinded** to treatment phase, therefore, not independent of the therapy process. *(0 point)*
6	Inter-rater agreement	The measure of the target behaviour is a **subject measure** relying on **self-reports** from the digital diaries. (*0 points*)
7	Treatment adherence	The treatment is delivered through a **web-platform** following a standardized approach. Adherence to treatment (%) is calculated using **digital log-in data**. (*2 points*)
EXTERNAL VALIDITY AND INTERPRETATION SUBSCALE		

8	Baseline characteristics	A short interview by an HCP as part of the eligibility check will be conducted. Furthermore, a **case formulation** including information on age, sex, aetiology of CP, and severity of CP will be presented when presenting the results; this information will be based on a baseline assessment (online self-report). (*2 points*)
9	Setting	Information on the **general location** (Swedish region, hospital/ pain clinic) will be provided; however, the participant will engage with the online treatment in their everyday life, and therefore, it will not be possible to include details about the specific environment. (*1 point*)
10	Dependent variable (target behaviour)	Table 2 provides an overview of all diary items, which are scores on a 7-point Likert-Scale, except from the pain level item (0-100). **Process outcome measures**: 5 items on psychological (in)flexibility (see Table 2), 2 items on pain self-efficacy, 1 item on pain avoidance. **Primary outcome measures**: 1 item on pain level, 1 item on pain interference, 1 item on pain catastrophizing. **Secondary outcome measures**: 3 items on sleep, 2 items on affect, 1 item on stress, 1 item on fatigue. (*2 points*)
11	Independent variable (treatment)	A detailed description of the DAHLIA treatment is given above, including the **treatment content**, and **number, duration, and frequency of sessions**. (*2 points*)
12	Raw data record	**Ten cases** will be recorded (4-6 iteration with n=10 participants per iteration). Raw data will be presented with a data point for each diary entry. (*2 points*)
13	Data analysis	Data will be analysed and reported for each participant individually. **Structured visual analysis, effect size measures** and a **randomization test wrapper** for **multilevel models** will be applied. (*2 points*).
14	Replication	**Ten participants** will be included (per optimisation iteration). Across all iterations, data from n=40-60 participants will be available. (*2 points*)
15	Generalization	Patients will be heterogeneous in their characteristics. Furthermore, retrospective self-reports will be completed by each participant **pre-post treatment,** including two **FUs** (details see Table 3)**.** (*1 point*)

Under the condition that all choices can be executed as intended, the internal validity of this SCED study will reach 8/14 points, and the external validity will reach 14/16 points. The total interpretation score will be 22/30 points. This score indicates a moderate methodological rigour [56].

Target behaviours will be assessed via self-reports collected through a digital diary. This diary will be prompted through the SMS function of REDCap, or a smartphone application (e.g., www.mpath.io). Both data collection methods will be piloted with participants to ensure that the diary works reliably. Participants will be prompted to complete the diary twice daily (for details see Table 2). Proposed diary items are based on traditional questionnaires and other diary studies[57], and were chosen as they assess relevant aspects in the context of CP. Furthermore, items should be short and easily to answer quickly[57]. The order of the items will be the same in each prompt to allow participants to get used to the questions, minimise time to complete the diary, and thus limit interference with their daily flow. The reliability, validity, and sensitivity of the items will be explored as part of the optimisation studies using suggested statistics (e.g., P-technique factor analysis). Idiosyncratic items might also be discussed with patients, in line with the agile approach, to improve validity and potentially patient engagement and ownership. Based on user-input, scientific evidence, and insight gained, diary items might

be optimised and adjusted, and any adjustments made will be reported in prospective publications.

Table 2. Proposed daily diary items.

LUNCH/ EVENING DIARY			
Instructions (Availability to fill out: Lunch diary 12-14h, evening diary 18-20h)		LUNCH: Hello & welcome to your digital diary! Please reflect on last night and this morning, and rate the following statements. Self-reflections can help to understand your daily routines and needs better. Let's get started. EVENING: Welcome back to your daily diary. Please take 2-3 minutes to reflect on this afternoon.	
	Construct	Item	Answering scale
		Last night, …	
1	Sleep[1]	… I generally slept well.	7-point numeric scale
2	Sleep[1]	… I had problems falling asleep.	7-point numeric scale
3	Sleep[1]	… I woke up frequently or too early.	7-point numeric scale
		During the morning/ During the afternoon…	
4	Positive affect	… I felt happy, energetic, at ease, or enthusiastic.	7-point numeric scale
5	Negative affect	… I felt down, irritated, depressed, or hopeless.	7-point numeric scale
6	Stress	… I felt stressed.	7-point numeric scale
7	Fatigue	… I felt tired.	7-point numeric scale
8	Experiential avoidance/ Acceptance[2]	… I tried to distract myself when I felt unpleasant emotions. … I opened myself to all my feelings, the good and the bad.	7-point numeric scale
9	Lack of contact with present moment/ Present moment awareness[2]	… I did most things on "automatic" with little awareness of what I was doing. … I was attentive and aware of my emotions.	7-point numeric scale
10	Self as content/ Self as context[2]	… I criticized myself for having irrational or inappropriate emotions. … I tried to see the larger picture, even when I was down, depressed, or hopeless.	7-point numeric scale
11	Fusion/ Defusion[2]	… distressing thoughts tended to spin around in my mind like a broken record. … I was able to notice my thoughts and feelings without getting overwhelmed by them.	7-point numeric scale
12	Lack of contact with values/ Values[2]	… I didn't have time to focus on things that are important to me. … I tried to connect with what is truly important to me.	7-point numeric scale
13	Inaction / Committed action[2]	… negative feelings trapped me in inaction. … I didn't quit working towards what is important even if it was though.	7-point numeric scale

14	Pain level	… my overall pain level was:	0 (no pain) to 10 (worst pain imaginable)
15	Pain interference	… my pain interfered with my…	7-point numeric scale o General activities o Mood o Walking abilities o Normal work (including housework) o Relations with others o Enjoyment of life
16	Pain catastrophizing	… I worry about whether my pain will stop or not.	7-point numeric scale
17	Pain avoidance	… I did not do things to avoid feeling my pain.	7-point numeric scale
18	Pain self-efficacy	… I could do some form of housework/ paid/ unpaid work, despite the pain.	7-point numeric scale
19	Pain self-efficacy	… I could live a normal lifestyle, despite the pain.	7-point numeric scale
20	Open question	I would also like to share this about my morning/ afternoon:	Free text
21	Treatment interaction[3]	Today, I completed a treatment module.	o Yes. o No, because it was a 'module free day'. o No, but I will do it tonight. No, because: *free text*
	Instructions	LUNCH: Thank you & have a nice afternoon! EVENING: Thank you very much for taking the time to fill in your diary. Have a nice evening!	

7-point numerical scale ranges from 1: not at all, to 7: very much.

Note: [1]Sleep items only as part of the morning questionnaire; [2]Both psychological flexibility and inflexibility items will be tested to determine with are more feasible and suitable to use; [3]Treatment interaction item only as part of the evening questionnaire.

In addition to the information in Table 1, the analysis will be executed as follows. Diary data have a multilevel structure because repeated measurements (level 1) are nested within individuals (level 2). First, structured visual analysis will be conducted for each individual separately following the four steps described in Kratochwill, et al. [53] to examine the within- and between-phase patterns in respect to the effects on level, trend, variability, immediacy,

overlap, and consistency. Additionally, effect size measures will be calculated at the individual level using standardized mean difference and Tau-U, and at a group level using the between-case standardised mean difference[58]. Finally, to avoid making distributional and random sampling assumptions, the randomization test wrapper for multilevel models will be used to synthesise the data from the whole group of cases and evaluate treatment effects[59]. Scientific advisors of this project will provide expertise and support in the SCED analyses. Results will be presented following the RoBiNT scale and SCRIBE guideline[60].

Efficacy across iterations

In the optimization studies, efficacy will be determined using both intensive (SCED) as well as extensive methods (retrospective self-reports from baseline, post-intervention and FUs; see Figure 7). The diary and questionnaire data will be aggregated across all iterations, thus include data from 40-60 participants. This approach allows to investigate the generalisability of results of the SCED and evaluate treatment effects in applied research[61]. MultiSCED will be used for the SCED data [62].

The proposed retrospective questionnaires used can be separated into process, primary, and secondary outcome measures (see Table 3). Additionally, negative treatment effects may occur in the context of internet interventions, and therefore, need to be acknowledged and systematically assessed[63]. Negative treatment effects are here assessed post-treatment using the negative effects questionnaire (NEQ), a tool with reliable and valid psychometrics[64].

Descriptive statistics of the retrospective questionnaires will summarize demographics and pre-treatment clinical characteristics of the sample. To evaluate changes in treatment outcomes over time, linear multilevel modelling (MLM) will also be used. MLM accounts for repeated measures within subjects and can handle missing data, which will be addressed per variable. Using a random intercept model, time will be treated as a categorial variable and pre-treatment values will be specified as the reference point. Therefore, results will be interpreted as a change from pre-treatment to post-treatment and, from pre-treatment to follow-up assessments. Anchor-based methods will be applied to determine clinical significance of changes in outcome measures[65]. Separate linear growth models[66] will be computed for each variable, while controlling for multiple testing. Significance level is set at Alpha (α)=0.05.

498 Table 3. Proposed outcome variables and tools used to assess efficacy using extensive methods.

Focus	Variables	Instrument	Supported psychometrics
Process outcome measures	Open/ Acceptance	Chronic Pain Acceptance Questionnaire (CPAQ)	Internal consistency and criterion validity (Swedish version) [67]
	Aware	5 items on,'acting with awareness' from the Five Facets Mindfulness Questionnaire (FFMQ)	Internal consistency, reliability, and construct validity (Swedish version) [68]
	Engaged/ committed actions	(i) Valuing questionnaire; (ii) Committed action questionnaire	(i) Internal consistency and construct validity (Swedish version) [69]; (ii) Proven validity and reliability (Swedish version) [70]
	Psychological flexibility	Swedish translation of the Multidimensional psychological flexibility inventory (MPFI)	Convergent and discriminant validities (English version) [71]
	Self-efficacy	General self-efficacy scale (S-GSE)	Reliable with high internal consistency (Swedish version) [72]
	Pain self-efficacy	Pain self-efficacy questionnaires (PSEQ-2)	Evidence for reliability and validity (English version) [73], translated into Swedish [74]
	Avoidance	Avoidance subscale of Psychological Inflexibility in Pain Scale (PIPS)	Internal validity and construct validity (Swedish version) [75]
Primary outcome measure	Catastrophizing	Subscale of coping strategies questionnaire (CSQ)	Internal consistency and sufficient test-retest reliability (Swedish version) [76 77]
	(Dis)ability/ pain screening	Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ)	Clinically reliable and valid (Swedish version) [78]
	Work ability	Work ability index (WAI)	Validated (Swedish version) [79]
	Functioning	Brief pain inventory (BPI-SF)	Reliable and valid in multiple languages (including Swedish version) [80]
Secondary outcome measure	Well-being/ depression	Patient Health Questionnaire (PHQ-9)	Satisfactory content validity and sufficient reliability (Swedish version) [81]
	Perceived stress	Perceived Stress Scale (PSS)	Internal reliability and construct validity (Swedish version) [82]
	Sleep problems	Insomnia Severity Index (ISI)	Satisfactory factor structure, internal reliability, and concurrent validity (Swedish version) [83]
	Health-related quality of life	EQ-5D	Standardised measure of health-related quality of life develop by the EuroQol Group[84]

Phase 3: Clinical evaluation (Study 4)

Randomized controlled trial enhanced by SCED

To determine the clinical effectiveness of the DAHLIA treatment, a RCT enhanced with SCED will be conducted. While RCTs provide estimates of between-subject treatment responses, differences in average scores between groups, they are unable to indicate specific within-subject responses. Simons, et al. [85] apply a similar design and argue that SCED is a valuable addition to a traditional RCT design. One reason for this combined approach is that RCTs provide information on the population level, whereas SCEDs focus on the individual level. Furthermore, heterogeneity of treatment effects might remain undetected in a traditional RCT design[86]. Additionally, the need for large cohorts of patients for adequate sub-group analysis[87], and a lack of feasibility to reach certain patient groups[88] limits the insights from a traditional RCT. Applying SCED and multilevel modelling, even group results from small and distinct cohorts can be performed on a meta-analysis level[85].

Outcome measures will be the same as in the optimisation studies, including the diary items for the SCED (see Table 2), and retrospective questionnaires (see details Table 3; including NEQ post-treatment[64]). A priori computations based on a power of .95, four questionnaire assessment points and a medium effect size shows that 360 participants (180 in each arm) are sufficient to generate stable findings in the analyses of treatment effects. With an estimated attrition rate of 18%, this implies that 295 participants will provide post-treatment data, which is considered adequate also for moderator/ predictor and cost-effectiveness evaluations. However, outcome measures and calculated sample size will be updated and might be modified based on iterations in the prior phase.

Treatment arm randomization is conducted by a research assistant following the decision on study inclusion by the HCP and after the baseline assessment (sociodemographic information, questionnaires, A-phase of SCED) is completed. Participants are randomized to the treatment arm or treatment as usual (TAU) using a block randomization strategy to ascertain equal distributions across the arms. Randomization is conducted by a local project manager who is not involved in the screening or intervention. Next, participants undergo treatment; then all participants complete the post-intervention assessment (questionnaires and 5-day digital diary). Booster-sessions will be sent to the participants in the intervention group at 2- and 4-months. Finally, at the 3- and 6-month follow-ups (FUs), all participants complete the questionnaires and 5-day digital diary period. In case participants decide to discontinue the study at any point in time, they might choose to provide a reason.

To examine changes in process, primary and secondary outcome measures (Table 3), linear mixed models will be conducted comparing the DAHLIA treatment to TAU. Analysis will be performed using group as a fixed between-person factor (two levels: DAHLIA treatment and TAU), and time as a fixed within-person variable (four levels: baseline, post-treatment, 3-month FU, 6-month FU). The linear mixed model will estimate fixed effects (regression slopes) for change in the intervals during (baseline to post-treatment assessment), and after (post-treatment to 3- and 6-month FU) the treatment period. The intervals will be entered as a categorical dummy variable (three levels). Potential confounders will be added to the model as covariates (i.e., age, gender, pain diagnosis, pain duration). Data will be analysed with the support of a statistician and using the latest version of SPSS. Mean change will be reported and test of significance will be two-sided with a set alpha level of 0.05.

Health economic evaluation

A short-term health economic evaluation will compare the DAHLIA treatment and the TAU at the primary endpoint (post-treatment). Additionally, an equivalent long-term evaluation will be performed at the end of the FU period using cumulative data collected up to that assessment point. Costs in both trial arms will be estimated from a societal perspective for each participant in the trial based on resource items and associated relevant unit costs. The use of societal resources comprises information on the use of resources related to healthcare contacts and medication (medical records and register data), and productivity losses related to absence from work (the LISA database). Costs to deliver the digital intervention will be estimated based on, for instance, HCPs' time spent on treatment. Total costs will be aggregated by trial arm.

The self-report tool EQ5D[84] will be completed by the participants at pre-, post-treatment and FUs and used to measure changes in health-related quality of life (HRQoL), to calculate quality adjusted life years (QALYs). Total QALY gains for participants over the trial will be estimated using the area under the curve method[89]. Cost data and QALYs will be analysed using generalized linear models to account for non-normal distributions[90]. Data will be analysed controlling for the influence of covariates, and by adjusting for baseline data. Cost-utility analysis (CUA) will be conducted with QALYs gained as primary outcome, comparing incremental costs with incremental changes in QALYs for digital treatment and TAU. Results will be presented as an incremental cost-effectiveness ratio (ICER), representing the ratio between the difference in costs and the difference in QALY gained between the digital treatment and TAU. Incremental cost-effectiveness ration will be expressed as cost per additional QALY, which is the most common approach in health economics[91]. Uncertainty

around the cost and outcome data will be explored and presented on cost-effectiveness plans, representing the distribution of the cost and outcome differences between both conditions. The probability of digital treatment being cost-effective compared to TAU will be presented across a range of price values a decision-maker would be willing to pay, represented by a cost-effectiveness acceptability curve[92].

Phase 4: Post-market surveillance (Study 5)

Similar to the development phase (Study 2), interviews with stakeholders will be conducted, recorded, and transcribed. The stakeholders participating in study 2 will be approached, along with additional key stakeholders identified during the implementation process. Appendix 4 provides the full overview of the interview questions. Questions reflect on the process so far (e.g., '*What kind and how many resources were needed to bring this intervention into practice?*'), on the current status (e.g., '*What issues are you currently facing?'*), and prospective adjustments (e.g., *'What will the prospective maintenance and upkeep look like?'*). These questions are preliminary and may be adjusted based on findings of Phase 1-3. Even though the 1177.se website is free for the end users (i.e., patients and HCPs), special attention may also be paid to financing, as a lack thereof can be a barrier for long-term implementation of eHealth interventions[93].

The qualitative data will be analysed following the same process as that used in Phase 1. Specifically, an inductive analysis to identify and summarise themes will be performed, and information will be mapped onto the domains of the CFIR[44]. The implementation strategy and plan will be reviewed, and lessons-learned will be presented to inform prospective implementation studies.

Patient and public involvement

This is a study protocol and due to ethical and practical reasons, no patients were directly involved in the project yet. However, the Personas originated from interviews with patients, as described above, and patients and other stakeholders will be involved in all planned phases of the DAHLIA project. Dissemination to patients and the public is described in more detail the section 'Ethics and Dissemination'.

DISCUSSION

Chronic pain is a huge public health problem, in suffering, disability, and costs for individuals and society. Widely accessible and sustainable behavioural treatment options could help to address this problem. An agile and user-centred development integrating a data-driven decision-making process and scientific evaluation of effects is essential to produce an evidence-based intervention of this type for individuals with CP. To our knowledge, this is the first project utilizing the mHealth agile development framework[26] to systematically build a digital behavioural treatment within a nationally used health care hub. The purpose of this project is to improve the standard of care for individuals with CP by applying the innovative development framework, thus providing an accessible, user-friendly, and empirically supported behavioural treatment to maintain or improve resilience, functioning, and well-being in this population.

Strengths include (i) the execution of the project by a multi-disciplinary, inter-sectorial, and international research team, (ii) the overall agile, iterative, and data-driven process, and (iii) the involvement of patients and different stakeholders early and throughout the development. Furthermore, (iv) the richness of methodologies using mixed methods, combining a traditional clinical trial evaluation on the population level (RCT), fine-graded data collection (SCED) on the level of the individual, and (v) an explicit focus on cost-effectiveness and determinants of implementation will be highlighted. The project is (vi) based on innovative strategies in the field of eHealth and digital treatments, and (vii) key gatekeepers such as regional leaders support the initiative.

Due to the ambitious and multifaceted nature of the project, several inherent challenges and risks should also be acknowledged. In case a sub-study should be delayed, e.g., due to recruitment difficulties or technical development issues, this delay could affect the whole project. Subsequently, adjustments following the agile approach could be discussed to balance the practical feasibility of executing the study and limiting the impact on its robustness.

Furthermore, the multidisciplinary, inter-sectorial approach is certainly a strength of the DAHLIA project, however, it might also have inherent challenges. For example, interests of stakeholders might differ, which needs to be considered and addressed. Here, communication is key, but compromises might be needed to ascertain satisfactory benefits for all parties involved.

Regarding the DAHLIA treatment itself, a high level of patient engagement (e.g., four micro-session per week combined with frequent diary assessments) will be required. These

demands might be perceived as burdensome by some individual. However, contact with HCPs will support participants' motivation and engagement. Furthermore, the focus groups and optimisation studies will provide insight into the perceived intensity, thus feasibility of the intervention set-up, and the agile process allows to adjust it accordingly. Specially, tailoring of the length of the micro-sessions and frequency of diary prompts will be explored.

Furthermore, the DAHLIA treatment may not be suitable for all people with CP and the question of "what fits for whom" will be continuously discussed. The website (www.1177.se) is a national health care hub in Sweden, but research shows that older adults, people with cognitive problems, or disabilities are less likely to use technologies[94], which could result in a bias in recruitment and usability. To improve inclusivity, the possibility to provide additional training for certain populations, such as older adults[95], will be explored. An additional issue is that the project is currently executed in Swedish, which excludes people with limited proficiency in Swedish. Therefore, translation into other languages and further cultural adaptations will be considered.

The DALHIA treatment may have the potential to become a widely implemented first line of treatment. However, some CP groups will likely benefit form an alternative treatment format (e.g., face-to-face), or complementary interventions. Thus, additional studies may explore if and how physiotherapists, general practitioners, or occupational therapists can deliver the DAHLIA treatment.

Finally, the treatment could prospectively be scaled and adjusted for other groups of patients with CP, e.g., children and adolescents, people with disabilities, and/or other medical conditions such as individuals with severe mental or physical co-morbidities. In addition, support offered as part of the DAHLIA treatment can be extended to significant others and family members of people living with CP. Thus, by using an agile development approach, the DAHLIA project might grow to support the heterogeneous group of individuals with CP and their complex health needs.

Ethics and Dissemination

The study received approval from Swedish ethical review authorities (Dnr 2021-02437). All participants will receive a detailed patient information sheet, have one week time to consider participation, and sign informed consent prior to participation. Each study participant will receive a unique study code to ensure anonymity and confidentiality. Data will be stored confirm Swedish privacy regulations on secure servers at Karolinska Institutet.

The project is announced on the Karolinska Institutet website (Rikard Wicksell's research group), and on social media, primarily twitter. The general outline of the project has been presented at online conferences. Next to the study protocol paper, the intention is to publish a number of peer-reviewed manuscripts, in which any protocol modifications will also be communicated. The results will be presented at (inter-)national conferences and networking events. Popular science articles, podcasts, radio interviews, and animated videos are additionally planned to disseminate the results to the wider public.

Author's contribution

SB, SJ, KB, LMcC, IFl, SP, and RW were involved in the conception and design of this project. RW acquired the funding. RW received the funding. HC provided specific input on the topic of implementation, IFe contributed with her expertise on health economy, and LS, PO, and JV added valuable knowledge on the single-case experimental design aspects of the project. SB drafted the manuscript, and all authors revised the manuscript and checked the intellectual content. All authors gave final approval and agree to be accountable for all aspects of the work.

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Completing interests

None declared.

Access to data and protocol details

Only the research team will have access to the raw data and participant code. Anonymised data will be made available as part of publications, whenever possible. Researchers from other universities may request to receive access to other information (e.g., informed consent sheets, data management plan).

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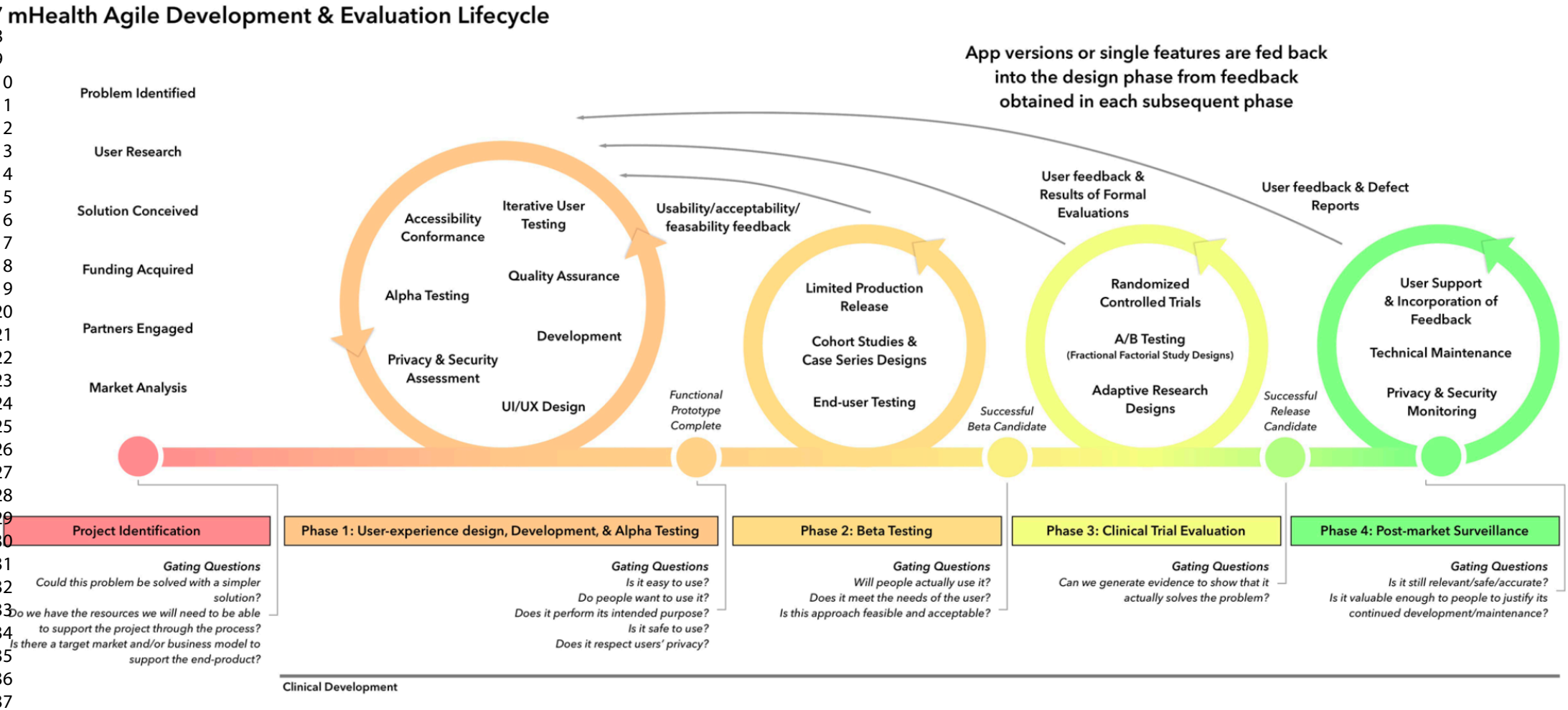
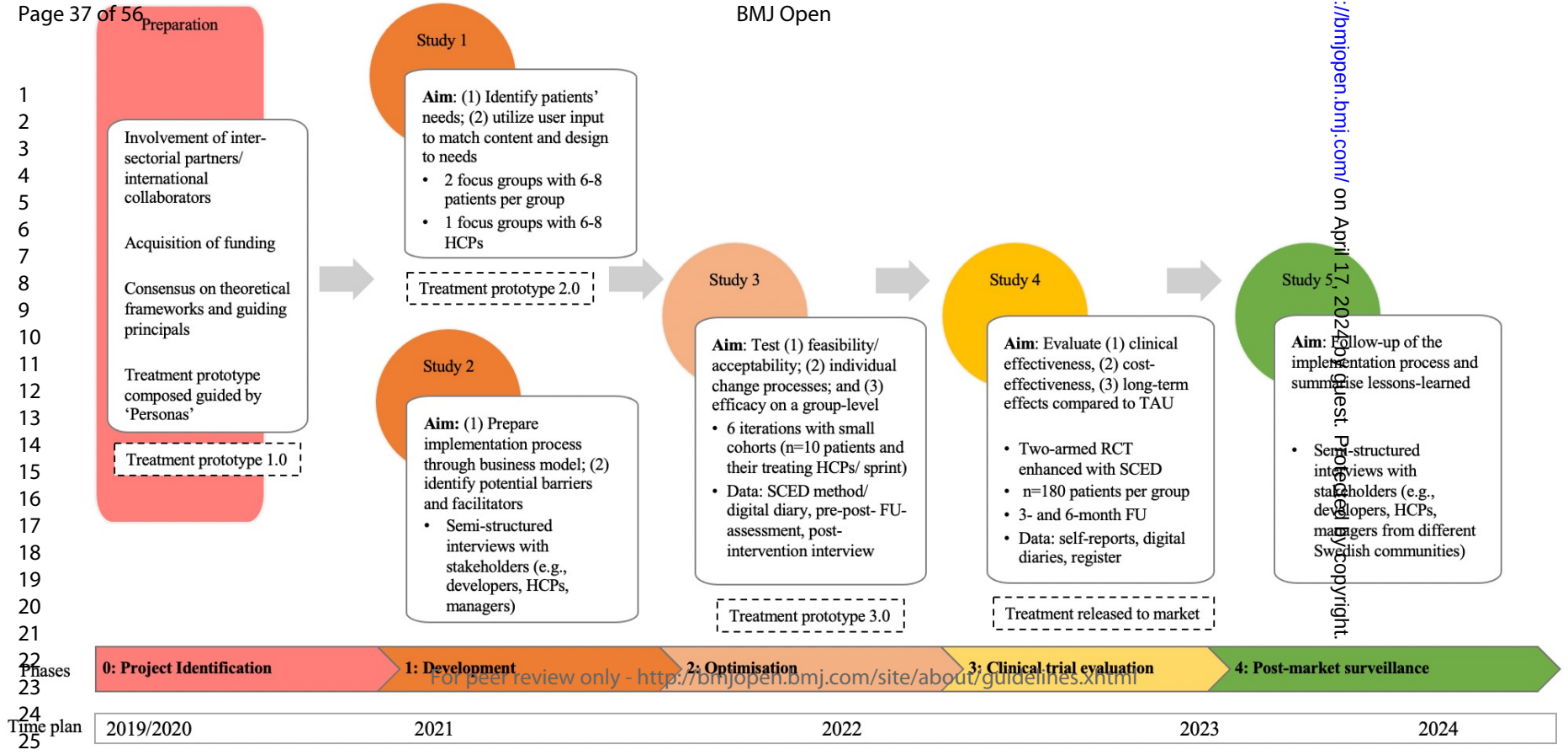
Figure legend

- Figure 1. mHealth Agile Development & Evaluation Lifecycle (Wilson et al., 2018).
- Figure 2. DAHLIA project overview including highlights of each study and time plan. HCP= health care professional; SCED= single case experimental design; TAU= treatment as usual; RCT= randomised controlled trial; FU= follow-up.
- Figure 3. Example of a DAHLIA Persona with chronic pain.
- Figure 4. DAHLIA treatment micro-session elements. HCP= health care professional. Note: The name "DAHLIA treatment" is mainly for academic settings; in the 1177 web-platform, a more intuitive treatment name will be chosen.
- Figure 5. The DAHLIA treatment components.
- Figure 6. Template of business model canvas (based on Osterwald & Pigneur, 2010). Grey boxes: Example aspects of the DAHLIA business model; the final model will be a result of the stakeholder interviews.
- Figure 7. General overview of the optimisation studies and specific procedure in each iteration. SCED= Single-case experimental design. FU= Follow-up. HCP= Health care professional.





AIDA
18 yrs. old

Employment:
N/A, high school student.

Education:
Primary school
Ongoing high school education.

Family:
Mother and father with foreign background, four younger siblings.

Background and social context:
Born in Pakistan, moved to Sweden when she was four years old. Leads an active life with hobbies and after-school activities. Frequently works out at the gym, pushing herself.
Aida has many friends and it is important for her to be popular. She is ambitious in school with high demands from her home-environment. She often feels stressed and does not think she is performing as expected. Aida carries a lot of responsibility at home. She has a high level of technological literacy and uses her smartphone for everything.

Social support (related to pain): Despite her family and many friends, Aida feels lonely in her pain. She feels that no one understands or takes it seriously. Her parents are constantly nagging, stressing that the health services should be able to help. Aida finds it strange that she is in so much pain even though she works out a lot and does everything she is "supposed to". Despite her efforts, there are days when she is paralyzed by pain and the feeling of being under pressure.

City/countryside: Apartment in large city.

PATIENT PAIN PROFILE

Pain problems:
- No clinical diagnosis.
- Recurrent headaches.
- Tensions in shoulders and neck.
- Stomach ache.

Consequences:
- Difficult to concentrate when in pain.
- Although Aida really wants to go to school, she is increasingly staying at home as she cannot manage.
- "Jojo behavior" – some days she keeps active and works out, while other days she is completely exhausted.

Pain behavior:
- Wants a "quick fix" and prefers to continue pushing rather than taking a step back and think.
- Exercises to get in better shape to handle the pain.
- Keeps on going to alleviate anxiety despite feeling the need to rest.

Attitude to treatment:
- Wants to be a "good patient" and do everything she is told (and then some).
- Happy to visit doctors but does not see herself as someone who needs mental health support or treatment.

HEALTH CARE & TREATMENT

Contact with health care:
- Checked vision and has gone through a variety of investigations for the recurrent headaches.
- Visited dentist focusing on temporomandibular joints (jaw region).
- Sought care due to various somatic disorders (head, neck, stomach).

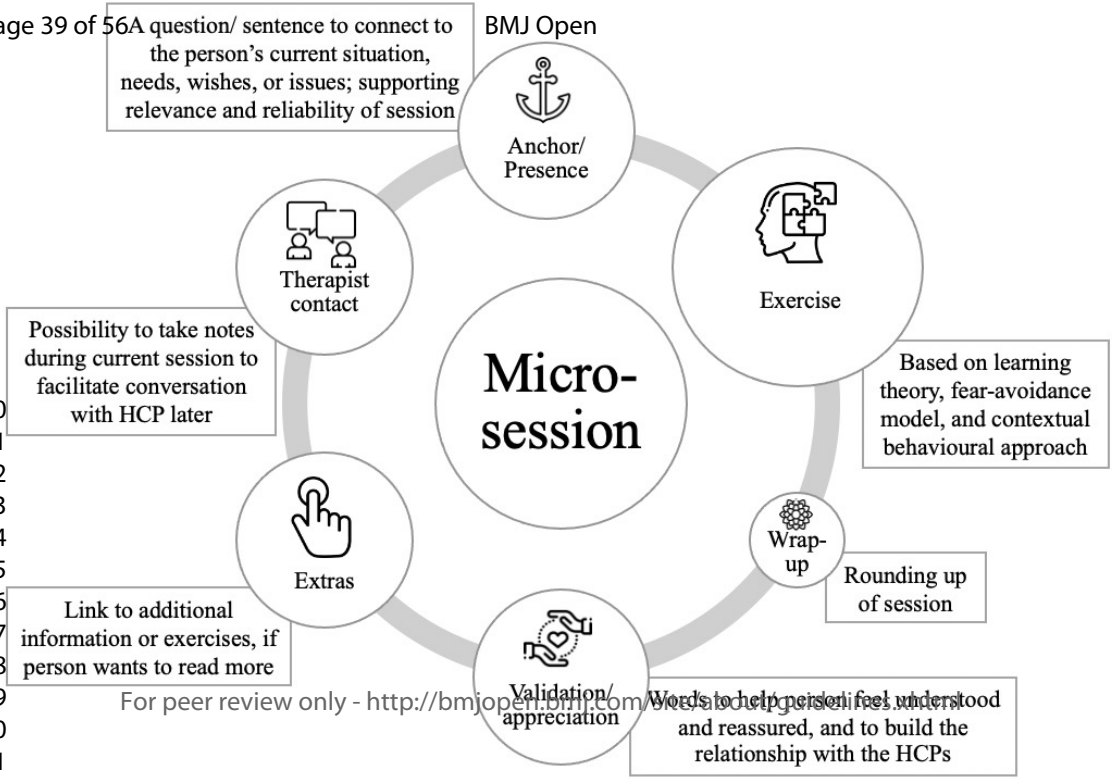
Comorbidities:
- Stress
- Anxiety
- Sleeping problems

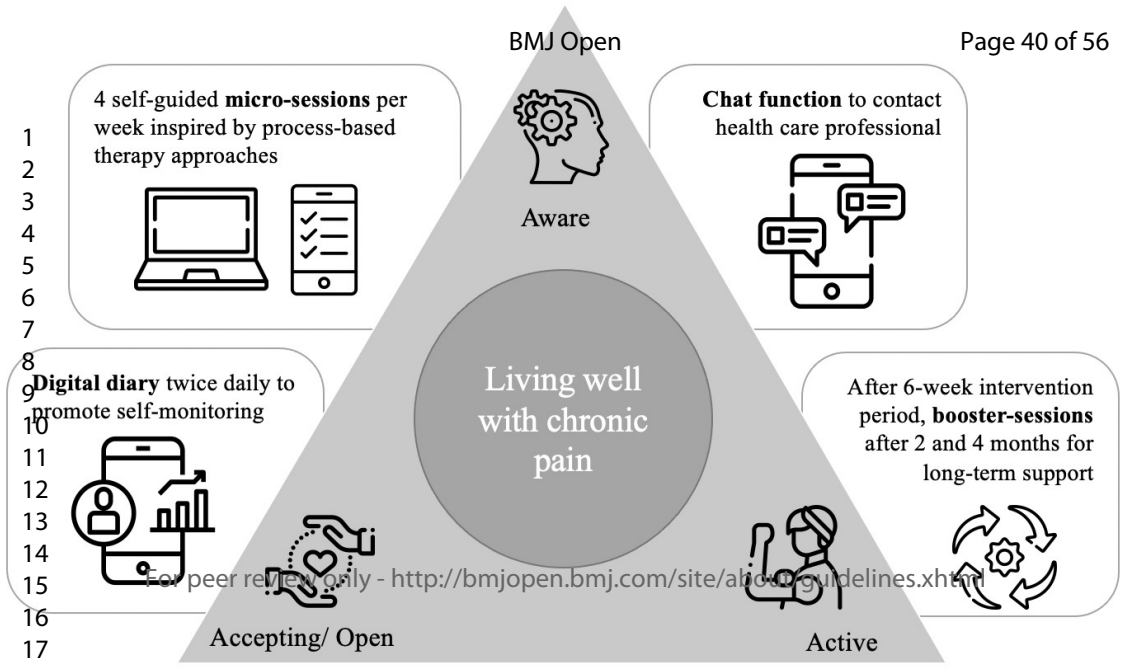
Medicine:
- Pain killers

PERSONAL NEEDS & GOALS

Treatment needs:
- Wants to be independent and take an active part in her treatment. Needs to feel that she can influence her situation.
- Wants to follow/have an overview of own progress.

Goals:
- To live an active and productive life without pain.
- To learn how to maintain a balanced lifestyle without guilt when resting.





Key Partners

(8) Describes the network of suppliers and partners that make the business model work, e.g.:

- Optimization and economy of scale
- Reduction of risks and uncertainty
- Acquisition of particular resources and activities

➢ *Soft ware partners*
➢ *Health care*

Key Activities

(7) Describes the most important things a company must do to make its business model work, e.g.:

- Production
- Problem solving
- Platform/ Network

➢ *Developing content*
➢ *IT support and development*

Key Resources

(6) Describes the most important assets required to make a business model work, e.g.:

- Physical
- Intellectual
- Human
- Financial

➢ *IT upkeep*

Value Propositions

(2) Describes the bundle of products and services that create value for a specific customer segment, e.g.:

- Newness
- Performance
- Customisation
- "Getting the job done" Design
- Brand/Status
- Price
- Cost reduction
- Risk reduction
- Accessibility
- Convenience/Usability

➢ *Usable, effective, evidence-based treatment*
➢ *Accessible and free for patients*

Customer Relationships

(4) Describes the types of relationships a company establishes with specific customer segments, e.g.:

- Personal assistance
- Self-service
- Automated services
- Communities
- Co-creation

➢ *Personal assistance*
➢ *Co-creation*

Channels

(3) Describes how a company communicates with and reaches its customer segments to deliver a value proposition (direct/indirect), e.g.:

- Sales Force
- Web sale
- Own stores
- Partner stores
- Wholesaler

➢ *Information on 1177*

Customer Segments

(1) Defines the different groups of people or organizations an enterprise aims to reach and serve. e.g.:

- Mass market
- Niche market
- Segmented
- Diversified
- Multi-sided platforms (multi-sided markets)

➢ *Patients with chronic pain*
➢ *Health care organisations*

Cost Structure

(9) Describes all costs incurred to operate a business model, e.g.:

- Cost-driven
- Value-driven
- Fixed costs
- Variable costs
- Economies of scale
- Economies of scope

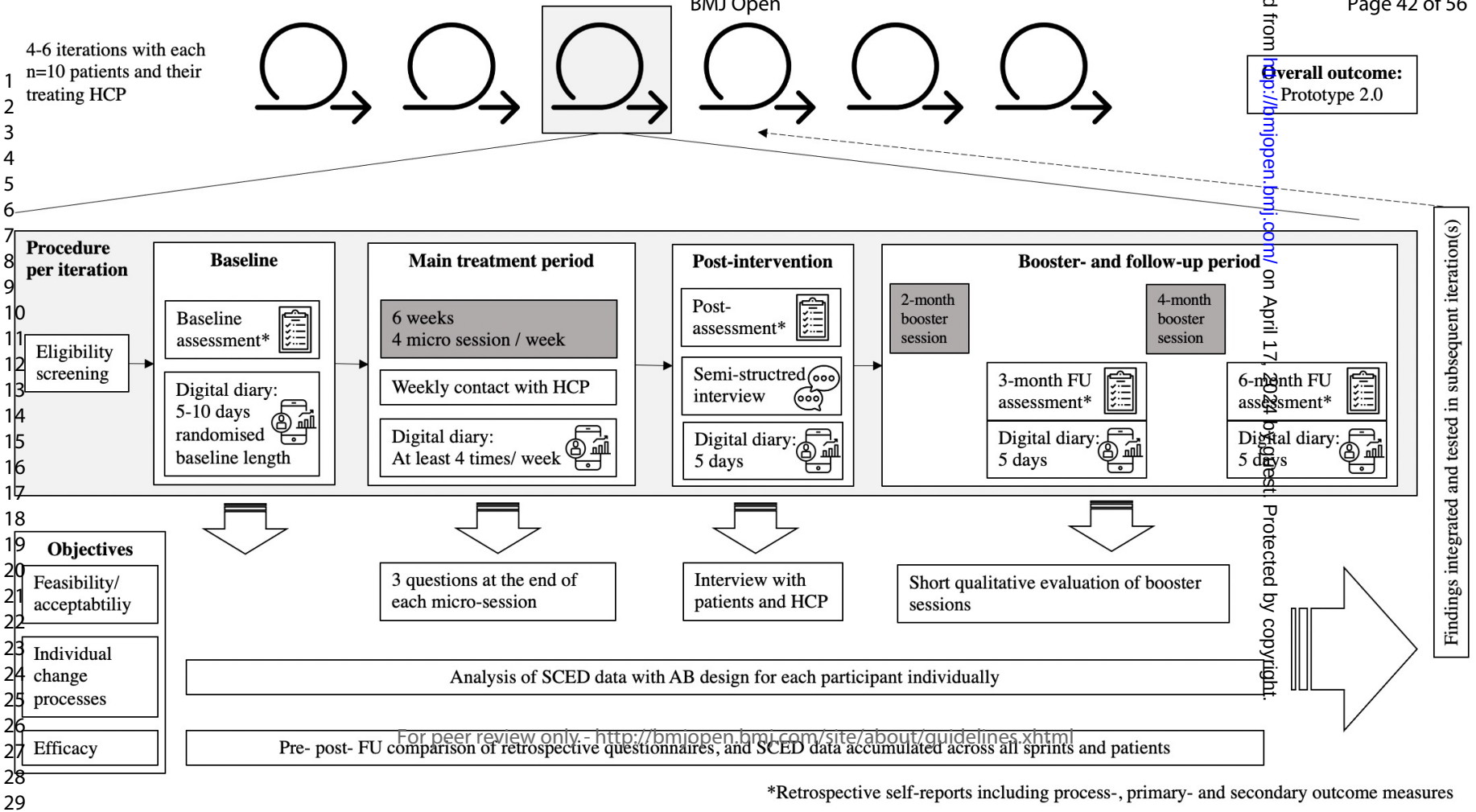
➢ *Platform and content development/ upkeep*

Revenue Streams

(5) Represents the cash a company generates from each customer segment (costs must be subtracted from revenues to create earnings), e.g.:

- Asset sale
- Usage fee
- Subscription fees
- Lending/ renting/ leasing
- Licensing
- Brokerage fees
- Advertising

➢ *Free for patients*
➢ *Licensing for regions*



*Retrospective self-reports including process-, primary- and secondary outcome measures

Appendix 1:

Semi-structured focus group guide
6-8 participants per focus group

FOR PATIENTS (*2 focus groups; heterogenic in terms of age, gender, pain condition, pain history, etc.*):

1. General introduction, informed consent, collect sociodemographic details (10min.)
2. Short introduction round (10min.)

3. Core question 1: **Living with chronic pain** (30min.)
   It would be amazing to have a magic pill to just take all the pain away, so you could live without it. But unfortunately, we don't have that magic pill. Instead, we want to help you and other people with chronic pain to find a way to live well with the pain. (*Presentation on definition of health (Huber et al., 2011): ability to adapt and self-manage physical, mental and social aspects of health, and examples*).
   a. Based on this definition of health, can you describe your own health needs? Which (aspects of your) needs are currently unmet?
   b. In which moments of your life do you feel happiest/ most engaged/ most satisfied?
   c. What helps you to engage in these 'happy moments'?
   d. What are barriers to engage in these 'happy moments'?
   e. What would you need to engage in these moments more often?

BREAK 10 Min.

4. Core question 2: **The DAHLIA treatment**
   Presentation of the proposed treatment, aim, design, theoretical background, and examples of exercises (10min); following a discussion (30min)
   a. What do you think of this treatment? What do you like, what do you dislike? (Please reflect on (1) design, (2) set-up, (3) content, (4) other (e.g., terminology: treatment, intervention, program; patient vs. person))
   b. How feasible would it be to do this treatment?
   c. Do you think this treatment meets you needs?
   d. Is there anything else you would like to add?

FOR HEALTH CARE PROFESSIONALS (*1 focus group, psychologists/ psychotherapists trained in cognitive-behavioural therapy; heterogenic in terms of age, gender, cultural background)*:

1. General introduction, informed consent, collect sociodemographic details (10min.)
2. Short introduction round (10min.)

3. Core question 1: **Supporting people with chronic pain** (30min)
   People with chronic pain have complex needs and treatment has to meet these needs. We are interested in your experiences in what works well to improve

the overall health and well-being of patients with chronic pain. (*Presentation on definition of health (Huber et al., 2011): ability to adapt and self-manage physical, mental and social aspects of health, and examples*).

a. Which (aspects of) your patient's health needs are unmet? What is needed to support chronic pain patients in the best way?
b. What barriers and facilitators to deliver support to chronic pain patients do you face? Please reflect on elements related to the patient, treatment options, and the health care in general.

BREAK 10 Min.

4. Core question 2: **The DAHLIA treatment**

Presentation of the proposed treatment, aim, design, theoretical background, and examples of exercises (10min); following a discussion (30min)

a. What do you think of this treatment? What do you like, what do you not like? (Please reflect on (1) design, (2) set-up, (3) content, (4) other (e.g., terminology: treatment, intervention, program; patient vs. person))
b. How feasible would it be for you to deliver this treatment?
c. Does the treatment meet the needs of the patients with chronic pain?
d. Is there anything else you would like to add?

Appendix 2. Baseline interviews with stakeholders

Various stakeholders will be approached, including developers, health care professionals, and managers. Through snow-ball sampling, other potential stakeholders will be identified and approached (e.g., individuals from policy making or municipality representatives).

Stakeholder: developers

I. General

Theme: Experience and development of digital interventions within the 1177 web-platform

1. What is your job description and what are your responsibilities?
2. How is the 1177 web-platform structured, in the region of Kalmar and Sweden?
3. How many digital interventions are available within 1177 in your region?
4. Who developed these interventions; who integrated them in the platform?
5. How are these interventions financed?
6. Who is responsible/ involved in the maintenance of the interventions?
7. If/ how is the interventions' content updated?
8. If/ how are the interventions used and promoted in health care?
9. If/how is user satisfaction with interventions evaluated?
10. If/how do collaborations with other regions look like?

II. Specifics (focus about DAHLIA project)

1. How would you describe the anticipated implementation process of this intervention?
2. What is needed to support the implementation process?
3. What could facilitate the implementation process?
4. What could hinder the implementation process?
5. What are benefits for you/ the 1177 web-platform when developing this intervention?
6. Are you enthusiastic about this intervention, if so, why?
7. Do you think this intervention has the potential to be successful in your region, and Sweden?
8. Where would you like to see this intervention in 5 years?

Stakeholder: health care professionals

I. General

Theme: Experience and use of digital interventions with patients

1. What is your job description and what are your responsibilities?
2. What is your experience in delivering interventions via the 1177 web-platform?
3. If/when there is a new intervention available in the 1177 web-platform, how do you usually hear about it?
4. What makes it attractive to deliver such an intervention?
5. What resources are needed for you to deliver these interventions (e.g., time, knowledge, managerial support)?
6. What hinders you to deliver these interventions?

II. Specifics (short introduction of DAHLIA project and details of digital behavioral health treatment for people with chronic pain)

1. Do you think there is a need for this intervention? Please elaborate.
2. What benefits for yourself/your work do you anticipate through this intervention?
3. What benefits for your patients do you anticipate?
4. What disadvantages or problems do you anticipate when delivering this intervention?

5. What disadvantages or problems for your patients when receiving the intervention do you anticipate?
6. What would hinder you to deliver this intervention?
7. What would facilitate you to deliver this intervention?
8. Are you enthusiastic about this intervention, if so, why?
9. Do you think this intervention has the potential to be successful in your care facility?
10. Where would you like to see this intervention in 5 years?

Stakeholder: health care managers

Theme: Experience and promotion of digital interventions in care facility

1. What is your job description and what are your responsibilities?
2. How many digital interventions are currently offered by the 1177 web-platform (and used) in your care facility?
3. What is needed to implement an intervention from the 1177 web-platform in your care facility?
4. How do digital interventions get financed in your care facility?
5. What is your involvement in digital interventions in your care facility? How do you support the use of digital interventions?
6. What hinders the implementation of these interventions, in your eyes?
7. If/ how does your care facility collaborate with other regions regarding digital interventions from the 1177 web-platform?

II. Specifics (short introduction of DAHLIA project and details of digital behavioral health treatment for people with chronic pain)

1. Do you think there is a need for this intervention? Please elaborate.
2. What kind of benefits do you anticipate for employees through this intervention?
3. What kind of benefits do you anticipate for patients through this intervention?
4. What kind of disadvantages or problems for employees do you anticipate through this intervention?
5. What kind of disadvantages or problems for patients do you anticipate through this intervention?
6. Are you enthusiastic about this intervention, and if so, why?
7. How will you promote this intervention in your care facility?
8. Do you think this intervention has the potential to be successful in your care facility?
9. Where would you like to see this intervention in 5 years?

Final question for all participants:

The main points I take away from this interview are [summary]. I appreciate the time you took for this interview. Who else should we talk about regarding the implementation of this intervention? Is there anything else you think would be helpful for me to know?

Appendix 3. Feasibility/ acceptability; questionnaire.

Table 1. Semi-structured interview guide to evaluate the general feasibility and acceptability of the treatment.

Topics	**Questions**	**Answering scores**	**Open question**
You recently completed the 6-week treatment. For us, it is very important to hear how you experienced it so that we can improve the content, design, and other aspects further. Thank you for taking the time to provide us with your input. First, we would like to ask you to reflect on and rate the **past weeks and treatment** in general.			
General	Were the past 6 weeks usual weeks for you?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Did special events occur?		
	Were you able to read the text in the treatment well?		
	Was the text understandable?		
	Did the intervention hinder your daily occupations?		
	Did technical issues occur?		
	Would you recommend this treatment to a friend?		
Secondly, we would like to ask you to reflect on and rate the four short **sessions** that were offered each week.			
Micro-sessions	Did you like doing the sessions?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Were the sessions difficult or unclear?		
	Did you experience the sessions as helpful?		
	Have the sessions influenced your behavior?		
	Have the sessions influenced your emotions?		
	Have the sessions influenced your thoughts?		
	Did you experience the sessions as time consuming?		
	Did you experience the sessions as boring?		
Third, we would like to ask you to reflect and rate the **messenger function** with which you could communicate with your health care professional.			
Messenger function/ health care professional	Was the messenger function overall helpful?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Did you experience the weekly messages sent by your health care professional as motivating?		
	Did you feel supported by your health care professional?		
Fourth, we would like to ask you to reflect on and rate the **daily diary**.			
Digital diary	Did you experience the daily diaries as burdensome?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Was it enjoyable to complete the digital diary?		
	Did you become more aware of your thoughts using the digital diary?		
	Did you become more aware of your behavior using the digital diary?		
	Did you become more aware of your emotions using the digital diary?		
Is there anything else you would like to add?			Free text

Appendix 4: Follow-up interviews with stakeholders

The stakeholders from the baseline assessment will be approached again. Furthermore, through snow-ball sampling, potential new stakeholders will be identified and also approached.

Stakeholder: developers

Process so far:

1. When reflecting on the overall development, evaluation, and implementation process, what went well?
2. When reflecting on the overall development, evaluation, and implementation process, what did not go well?
3. What factors supported the process of bringing this intervention into practice?
4. What factors hindered the process of bringing this intervention into practice?
5. What kind and how much resources were needed?
6. Did the process go as anticipated? If not, what was surprising?
7. How satisfied are you with the process so far?
8. What was most challenging during the implementation process?

Current use:

1. What are you currently doing to keep the intervention implemented?
2. Do you have sufficient resources? Please elaborate.
3. What issues are you currently facing? What solutions for these issues do you have?

Prospective adjustments:

1. What will the prospective maintenance and upkeep look like?
2. Who is responsible for that?
3. If there should be a change in employment, who ensures that the intervention remains updated?

Stakeholder: health care professionals

Process so far:

1. How often did you deliver the digital intervention?
2. What kind of benefits for yourself, your work, and/or your patients did you experience?
3. What kind of disadvantages for yourself, your work, and/or your patients did you experience?
4. What kind of support for delivering the intervention (e.g., training, technical guidance when issues arose) did you receive?
5. What hindered you in delivering the intervention?
6. What facilitated you to deliver the intervention?

Current use:

1. How satisfied are you with the intervention overall?
2. Which elements of the intervention need improvement?

Prospective adjustments:

1. Do you plan on delivering the intervention in the future? If not, please elaborate.
2. Would you recommend the intervention to a colleague?
3. What kind of problems do you anticipate in the future; and do you have potential solutions for them?

Stakeholder: health care managers

Process so far:

1. How would you describe your involvement in implementing the intervention?
2. How many resources were needed for the implementation?
3. Did the implementation process go as expected? If not, what was surprising?
4. How did you support your employees to deliver the intervention?

Current use:

1. How satisfied are you currently with the intervention (e.g., reflecting on use, content, promotion, required resources, (technical) issues)?
2. What aspects of the current implementation/ practical use need improvements?

Prospective adjustments:

1. Do you plan to offer the intervention in your region in the future? Please elaborate.
2. Would you recommend this intervention to another region/ other health care organizations? Please elaborate.
3. What kind of problems do you anticipate in the future?

Final question for all participants:

The main points I take away from this interview are [summary]. I appreciate the time you took for this interview. Who else should we talk about regarding the implementation of this intervention? Is there anything else you think would be helpful for me to know?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	28
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,28
Roles and	#5b	Name and contact information for the trial sponsor	1

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	6-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8, Fig. 2
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11,12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	11

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11, Fig 4, Fig 5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12, 14,15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Fig 7, Tab 2, Tab 3, and related sections
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, Fig 7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12, 13, 14, 21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11,12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for	21, Tabl. 1

		stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21, Fig 7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14, 21
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a (Tab 1)
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Described for each sub-study
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in	26, 28

		the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Tab 1, 19-21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-14, 21, 22,
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19, 20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	28
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21 (NEQ)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3, 27
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	27

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11-12, 27
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	27, 28
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	28
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	27
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	28
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	28
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

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Title: Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

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Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

ABSTRACT

Introduction: Chronic pain affects about 20-40% of the population and is linked to mental health outcomes and impaired daily functioning. Pharmacological interventions are commonly insufficient for producing relief and recovery of functioning. Behavioural health treatment is key to generate lasting benefits across outcome domains. However, most people with chronic pain cannot easily access evidence-based behavioural interventions. The overall aim of the DAHLIA project is to develop, evaluate, and implement a widely accessible digital behavioural health treatment to improve well-being in individuals with chronic pain.

Methods and analysis: The project follows the four phases of the mHealth Agile Development and Evaluation Lifecycle: (i) *development and pre-implementation surveillance* using focus groups, stakeholder interviews, and a business model; (ii) iterative *optimisation studies* applying single case experimental design (SCED) method in 4-6 iterations with n=10 patients and their health care professionals per iteration; (iii) a two-armed *clinical randomized controlled trial* enhanced with SCED (n=180 patients per arm); (iv) and interview-based *post-market surveillance*. Data analyses include multilevel modelling, cost-utility, and indicative analyses.

In October 2021, inter-sectorial partners are engaged and funding is secured for four years. The treatment content is compiled and the first treatment prototype is in preparation. Clinical sites in three Swedish regions are informed and recruitment for phase one will start in autumn 2021. To facilitate long-term impact and accessibility, the treatment will be integrated into a Swedish health platform (www.1177.se), which is used on a national level as a hub for advice, information, guidance, and e-services for health and healthcare.

Ethics and dissemination: The study plan has been reviewed and approved by Swedish Ethical Review Authorities. Findings will be actively disseminated through peer-reviewed journals, conference presentations, social media, and outreach activities for the wider public.

Trial Registration number: ClinicalTrials.gov Identifier: NCT05066087; Karolinska Institutet Protocol Record Dnr 2021-02437.

Keywords: chronic pain; digital; behavioral health; protocol; intervention; single case experimental design; diary; implementation; randomized controlled trial

Strength and limitations of the study

- An agile, iterative, and data-driven process is ideally suited to navigate the complex challenges faced during the development, evaluation, and implementation of a digital behavioural treatment.
- Executing the project with a multi-disciplinary, inter-sectorial, and international team brings expertise and insights from complementary views together.
- Patients and different stakeholders, such as health care professionals, managers and digital developers, are involved in the project from the start, thus ensuring that individual needs to use and/ or promote the treatment can be met.
- The richness of methodologies combining traditional clinical trial evaluations on the population level, fine-graded momentary data collection on the individual level, explicit focus on cost-effectiveness, and determinants of implementation allows for a treatment evaluation from all angles.
- Due to the complexity and step-wise approach of this project, problems (e.g., delays in recruitment) in earlier phases might negatively affect the execution of later phases, thus calling for mitigation strategies to address potential delays.

INTRODUCTION

Chronic pain (CP) affects 20 to 40 % of the adult population[1]. Due to the COVID-19 pandemic, prevalence rates may increase further since CP can develop as a post-viral syndrome, from insufficient risk factor management during lockdown (e.g., inactivity, stress), or from accumulated unmet rehabilitation needs in overburdened rehab services[2 3]. Chronic pain impacts not only individuals' daily activities and overall quality of life, but also social and working contexts[4]. Thus, considerable direct and indirect health-related costs are associated with CP[5] and it represents a major issue for health care services and society at large.

A consensus exists regarding the importance of a holistic perspective integrating social, psychological, and biological factors of CP to accommodate this condition and its implications, and to guide interventions aimed at providing support[6]. Considering the typical complexity of CP, pharmacological treatment alone is usually insufficient in producing sustained relief and recovery of functioning[7]. Instead, management plans should target key behavioural, emotional, cognitive, and social factors in everyday functioning and quality of life[8].

To generate general and lasting benefits across outcome domains, person-centred, behavioural health interventions are critical. The necessity to match the pain treatment with specific needs of each patient has been the focus of discussion for the past decades[9]. Existing evidence supports methods that stem from cognitive behavioural frameworks[10], including the fear-avoidance model of pain and disability[11] and the psychological flexibility model, the model underlying acceptance and commitment therapy (ACT)[12 13]. In this type of treatment, the objective is to optimize effects by individualising treatment through evidence-based therapeutic procedures[14]. In clinical practice, face-to-face therapy dominates in effectively promoting well-being in patients with CP[7 15]. Modes of treatment delivery are evolving, however, as new models of care emerge.

Until now and despite the empirical support, interdisciplinary treatment, including behavioural interventions, are commonly not available or difficult to access for most individuals with CP[16 17]. Digital solutions aiming at promoting health, also known as eHealth, appear promising to bridge this gap as they appear cost-effective, can be tailored to individual needs, applied in everyday life, and used at the patients' convenience[18]. Particularly in light of the COVID-19 pandemic, distance approaches are gaining more attention in the management of CP[19]. However, the development and implementation of evidence-based digital interventions face challenges.

Innovative digital treatments require an accurate scientific evaluation to ensure clinical effectiveness. As it is still seen as the "gold standard", digital interventions for CP are often assessed through research-led randomized controlled trials (RCTs)[18 20 21]. However, a call for real-world and n-of-1 evaluations of efficacy and safety of individual assessment and treatment approaches is also being heard[22]. Compared to RCTs, n-of-1 study designs utilise repeated measurements to provide a more fine-graded, time- and context-sensitive picture of individual trajectories and pattern, thus allowing to evaluate effects at the within-person level[23].

Moreover, it has been shown that eHealth innovations purely originated from an academic context are rarely sustainably implemented into health care practice due to a lack of infrastructure, funding, and time[24]. To avoid research waste when creating new eHealth solutions, a strong user-centred design and focus on implementation is suggested[25 26]. A framework that combines the scientific rigor of traditional research methods with a rapid and iterative digital product development approach is needed. Then, the development of an evidence-based and user-friendly digital behavioural treatment is facilitated that is implementation-ready for applied health care.

The 'mHealth agile development and evaluation lifecycle' (Figure 1) is a framework created to promote the development of evidence-based, effective, and sustainable digital solutions[27]. This framework emphasises practicality, flexibility, rapid evaluation, and the possibility to adjust protocols to meet technological changes and insights that emerge as part of the process. Therefore, Wilson, et al. [27]'s framework will guide the present project. Additionally, the Medical Research Council guidance for developing and evaluating complex interventions will inform the processes[26 28]. By applying these perspectives, the ultimate goal to develop, evaluate, and implement an effective and accessible behavioural treatment will be reached, thus improving health in individuals with CP across Sweden.

--- FIGURE 1 NEAR HERE---

Research objectives

The overall aim of this project is to develop, evaluate, and implement a digital behavioural health treatment to improve well-being in individuals with CP. The treatment will be integrated into a nationally available health care web-platform, which facilitates large scale evaluations, further development, dissemination, and long-term use in clinical practice across Sweden. Within the project, we will (i) develop a prototype of the digital treatment matching the needs of individuals with CP, using focus groups to assess user demands, and discuss possible treatment structures and content, (ii) pilot the treatment in several iterations to evaluate its

feasibility and acceptability, efficacy, and individual change processes by combining intensive (Single case experimental design (SCED)) and extensive methods; (iii) conduct a two-armed RCT enhanced with SCED to assess the clinical effectiveness, cost-effectiveness, and long-term effects compared to treatment as usual (TAU) on a between- and within-person level; and (iv) identify barriers and facilitators, and monitor the implementation process of the treatment, through a business model and stakeholder interviews.

METHODS AND ANALYSIS

Following the mHealth agile lifecycle[27], the DAHLIA (Acronym: Digital behaviourAl HeaLth for chronIc pAin) project consists of an identification phase 0 and four main phases: Development, optimisation, clinical trial evaluation, and post-market surveillance (See overview of the DAHLIA project in Figure 2). Phase 1 includes two studies: focus groups with patients and health care professionals (HCPs) to develop the treatment prototype (Study 1), and stakeholder interviews to prepare for the implementation process by creating a business model and identifying of barriers and facilitators (Study 2). Phase 2 (Optimisation) aims at optimising the treatment and entails 4-6 iterations to test and gradually improve the prototype in a data-driven manner (Study 3). Phase 3 consists of a large-scale clinical trial to evaluate the digital treatment in comparison to TAU in a two-armed RCT enhanced with SCED (Study 4). Finally in phase 4, a post-market surveillance is conducted using interviews with stakeholders from different Swedish regions, also presenting lessons-learned (Study 5). Each phase may inform and alter subsequent phases, in line with the agile approach. Details of the studies are described in the following paragraphs.

--- FIGURE 2 NEAR HERE ---

Project Identification

Involvement of inter-sectorial partners and international collaborators

This project is a collaboration between academia, health care, and industry. The academic partners come from seven universities in four countries (Sweden, Belgium, the Netherlands, and the U.S.). The researchers contribute to the project with their scientific and clinical experience in developing and evaluating digital treatments, implementation sciences, cost-utilisation analysis, CP and related health issues, and the SCED method. The DAHLIA treatment will be designed within the www.1177.se platform in collaboration with health care developers and digital designers in Region Kalmar and supported by the industry partner Inera, who is responsible for the maintenance of the platform. The health care partners currently represent three of the 21 regions in Sweden, and include primary care centres in Region Kalmar, the Pain Clinic at Capio St. Göran Hospital, Region Stockholm, and the Rehabilitation centre in Region Örebro.

Personas as early user research

Personas are typical patient- or user-profiles illustrating the target group of a treatment or product and can be useful in the development of digital interventions to communicate user

needs to the development team[29 30]. By giving a narrative and name, personas facilitate a more concrete discussion of patient needs, and to what extent the treatment might match those needs[31]. In the DAHLIA project, three distinct patient personas evolved in an online workshop and were edited over several months until the project partners were developed in a stepwise manner. The personas originated from patient interviews in a previous study[29], and discussed in an online workshop to assess the relevance for the DAHLIA project. The personas were then adjusted based on factors identified in research[32-34], other personas used in digital development projects region Kalmar, and input from the clinical researchers (RW, IF, KB, LMcC, SP). The personas were continuously edited over several months until the project partners agreed on the final versions. The categories for each persona are: (i) *personal information*, including employment, education, family, background and social context, social support, and living area; (ii) *patient pain profile*, including pain problem, consequences, pain behaviour, and attitude to treatment; (iii) *health care and treatment*, including contact with health care, comorbidities, and medicine; and (iv) *personal needs and goals*, specifically related to the treatment. Figure 3 illustrates one of the personas used in the DAHLIA project.

--- FIGURE 3 NEAR HERE ---

During the early development of the DAHLIA treatment prototype (version 1.0), and prior to patient involvement, personas were used to ensure that relevant characteristics and contextual factors were considered[35]. The personas were presented at the start of treatment workshops to discuss, for instance, if and how the treatment content and structure fit the personas' characteristics and met their needs. Potential problems for a persona in relation to treatment elements were identified, resulting in further discussions and consensus-based adjustments.

Guiding principles in the development process of the DAHLIA treatment

When developing and evaluating complex interventions, one might either rely on already existing treatments or adapt these to the context, or chose to build a new treatment based on research evidence and theory of the problem[26]. In the present project, the latter was chosen for the following reasons. Firstly, the initiative for this project originated from the Swedish Region Kalmar identifying the need for a digital treatment for chronic pain patients, which resulted in a collaboration with the research team. Furthermore, contextual factors such as organisational aspects, technical systems, and licencing agreements define the conditions for in this project. Finally, by creating a new treatment together with stakeholders (i.e., managers, regional

developers, therapists, patients) and building on an existing digital structure (www.1177.se), the digital treatment can accommodate all identified requirements.

The following process was therefore followed to create the new treatment: Four three-hour online workshops took place between June 2020 and June 2021 to discuss the theoretical framework, conceptual model, and treatment components. Project partners presented their previous work related to behavioural treatment approaches and conferred on the guiding principles for the prototype development. The group reached consensus on using learning theory[36] as the theoretical framework for assessment and treatment. Furthermore, it was agreed that the fear-avoidance model[11] and psychological flexibility model[10 14 37] should be used as conceptual models for the DAHLIA treatment. Conclusively, the primary objective of the treatment is to increase resilience to pain and distress by promoting and training behavioural skills of relevance to the individual's functioning and well-being. Furthermore, a self-guided micro-learning format[38] was chosen, including brief and frequent sessions (micro-sessions), delivered digitally and accessible via a smartphone or desktop computer (www.1177.se; details see 'Stakeholder interviews (Study 2)).

Based on the theoretical framework and conceptual models, values-oriented exposure is considered to be the core procedure. Exposure implies the use of systematic contact with negative experience such as pain and feelings of emotional distress that promotes avoidance, in a way that reduces their adverse influence and produces more flexible, varied, and engaged patterns of behaviour. Essentially, the function of exposure is to reduce negatively reinforced behaviour focused on alleviating unwanted experiences, in favour of positively reinforced behaviour focused on approaching goals in daily life. Exposure is enabled by several behavioural processes, such as identifying life values and noticing own thoughts and emotions, known as defusion (OPEN), flexible attention to the present (AWARE), and the building of extended habits of engagement (ACTIVE)[10].

At the end of Phase 0, the following is envisioned: The DAHLIA treatment will run over six weeks and includes four self-guided micro-sessions per week. Each session will include a set of key elements (see Figure 4). The extent to which each of these elements will be included in the session can vary. It should be noted that due to the agile process, data-driven decisions might result in changes to this suggested structure.

--- FIGURE 4 NEAR HERE---

A chat function will enable patients to connect with their health care professionals (HCPs, see details section 'participants and recruitment') for additional guidance, asynchronous feedback, and further instructions. The role of the HCP is to encourage and

motivate patients to remain in the program and intervene in case the individual situation worsens. At the start of the treatment, a specific weekday will be agreed on, during which the HCP replies to the patient's message. Potentially, the reply could also be a chat message, a phone call, or a video call. The contact with the HCP will take place once a week, with a minimum of six individual interactions between the HCP and patient. HCPs will receive training, a manual, and supervision to provide the treatment.

Furthermore, patients will be prompted to fill in a pre-scheduled digital diary twice a day. The digital diary has the purpose to enable self-monitoring for increased self-awareness of own behaviours, emotions, and routines, and thus enhanced orientation towards values and goals[39], and data collection to gain insight into the individual change processes and effects of the treatment in the context of the SCED. The full list of the daily diary items can be found in the 'Individual change processes' section.

After the main six-week intervention period, the treatment also entails booster-sessions delivered through the www.1177.se web-platform after two and four months. The participants get invited via SMS or emails to revisit the web-platform where they can engage in short behavioural exercises. Booster sessions are suggested in other contexts to support long-term behavioural changes[40] and reinforce patients learned coping strategies. Figure 5 summarises the DAHLIA treatment components.

--- FIGURE 5 NEAR HERE ---

Participants and recruitment

In the DAHLIA project, participants will be people who either use or deliver the digital treatment, or who facilitate the treatment implementation. Thus, study participants are (i) patients with CP, (ii) HCPs treating patients with CP, (iii) health care managers, (iv) developers of the www.1177.se web platform, (v) other stakeholders identified in the process (e.g., policy makers, representatives from patient organisations). Health care professionals will be licensed psychologists or psychotherapists trained in cognitive behavioural therapy. Health care managers, developers, and other stakeholders need to be directly or indirectly connected with the treatment (e.g., decision-making on an organisational level; technical support etc.), but no other requirements apply.

Patients are eligible for inclusion if they: are older than 18 years of age; report a pain duration of ≥ 3 months; are able to communicate in Swedish; and have access to a computer, smartphone, and internet in their home environment. The exclusion criteria are: injury or illness that require immediate assessment and treatment, or is expected to progress significantly during

the next 6 months; unstable medication (based on self-report: changes in medication during the past 3 months or expected within the next 3 months that could influence well-being and functioning substantially, such as opioids, anti-epileptic drugs, antidepressants); previous CBT treatment (including ACT) during the past 6 months; severe psychiatric co-morbidity (for instance, high risk of suicide). For study 1 (focus groups), only the exclusion criteria "severe psychiatric co-morbidity (for instance, high risk of suicide) will be applied as long-term health aspects are not expected to cause practical or ethical issues.

Information regarding the DAHLIA project and specific sub-studies will be provided to the clinics, including detailed instructions for eligibility. Regions recruiting patients are Kalmar, Stockholm, and Örebro. Additional regions have expressed interest in participating and recruitment might be extended. Patients will be approached via their health care centres and once patients have expressed interest in study participation, a formal eligibility check will be conducted. Potential participants will be screened at their respective clinic via a face-to-face or online meeting by their treating care professionals, including psychologist and pain physicians. A short interview will be conducted to confirm eligibility and ensure that none of the exclusion criteria are met. Informed consent is then obtained from all participants prior to enrolment in the study. Sociodemographic and pain-descriptive information will be collected from all participants including age, sex, level of education, occupation, location, level, and duration of pain, pain diagnosis (if applicable), and approaches to relief pain (e.g., medication, heat, physiotherapy).

Phase 1: Development

Focus groups (Study 1)

The aim of this study is to (i) identify the needs of patients and HCPs and (ii) match the treatment content to their needs. At least three focus groups will be conducted in autumn 2021, one with HCPs (i.e., psychologists/ psychotherapists trained in CBT) and two with patients. Per focus group, 6-8 participants will join[41]. An attempt will be made to recruit a heterogeneous group of patients in terms of such characteristics as pain condition, sex, and socio-economic background. The focus groups will be held online and take 90-120 minutes. A semi-structured guide inspired by Gruters, et al. [42] will be followed. In addition to a general discussion around health and individual needs at the start, the focus group leader (i.e., research assistant and clinical coordinator) will ask participants to reflect on the design, set-up, content, and prospective feasibility of the DAHLIA treatment (details see Appendix 1). The group

conversations will be audio- and video-taped. Field notes will provide further insight into relevant cues and observations.

The recordings will be transcribed verbatim and the data analysis will be performed by two independent researchers. The information for the patient groups and HCP group will be analysed separately. A combination of inductive and deductive content analysis will be used. First, the deductive approach will determine the themes emerging from the semi-structured guide: (i) health needs and determinants to live well with CP, and (ii) feedback on the DAHLIA treatment. Then, an indicative analysis will be performed to identify categories within the themes. The transcript will be read carefully and open coding will be used. A consensus meeting with a third researcher will be conducted as a final step. This approach has been described previously and appears valid to answer the research question[42 43]. The results from the focus groups will be integrated into the treatment prototype (version 2.0).

Stakeholder interviews (Study 2)

The aim of this study is to develop a preliminary business model for the digital behavioural treatment and identify barriers and facilitators of the prospective implementation process. An explicit focus on implementation and economic aspects early during treatment development has been recommended[44 45]. Particularly, business modelling in the context of eHealth technologies can help to create a set of success factors that will influence uptake, sustainability, and effectiveness[46]. A business model is part of the implementation strategy and also presented a foundation for conversations with users and stakeholders regarding the value and purpose of an eHealth technology[46]. Moreover, to build the knowledge base across the multiple studies and settings, the consolidated framework for implementation research (CFIR)[47] will be used. The CFIR has five major domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation. It is utilized as part of the analysis, as explained below.

As a first step, a preliminary version of the business model canvas was filled in by the research team (SB, SJ, RW, HC). As suggested by Osterwalder and Pigneur [48] 'a business model describes the rationale of how an organization creates, delivers, and captures value' (p.14) and demonstrates the logic of how a company or organisation intends to generate profit for a service or product. The nine blocks of the business model cover four areas of a business: customers, offers, infrastructure, and financial viability. Figure 6 presents the template of the business model canvas and short definitions for each segment, including example aspects relevant for the DAHLIA project.

--- FIGURE 6 NEAR HERE---

In the present study, the treatment will be integrated into the national public health care website (www.1177.se), using the digital platform for behavioural health ('Stöd och Behandling'). This digital platform is free from commercial interests, maintained by Inera, which is owned by the county councils and regions. The general aim of this national website is to increase access to healthcare, strengthen the position of the patient, and contribute to improved public health. The website (www.1177.se) contains health care information, inspiration, and e-services. Each of the 21 regions in Sweden is responsible for coordinating activities and services provided on www.1177.se, which are conducted by own staff or contracted providers. Through a national network, providers and regions can cooperate and share licenses for services.

The business model will be discussed and refined as part of the stakeholder interviews. Currently identified stakeholders are software developers, HCPs, and health care managers. A semi-structured guide inspired by a previous study on eHealth implementation[49] will structure the interviews and gather information on gatekeepers, barriers, and facilitators for prospective dissemination and use. Questions are tailored to the different stakeholders and include, for example, '*If/how is the interventions' content updated?*', '*Who is responsible/ involved in the maintenance of the intervention?*', '*What could facilitate/ hinder the implementation process?*', and '*Do you think this intervention has the potential to become successful in your care facility?*'. The full guide can be seen in Appendix 2. As part of the agile process, the guide may be adjusted based on information collected during the interviews and tailored to additional stakeholders including policy makers or representatives from patient organisations.

A minimum of eight interviews will be conducted and snow-ball sampling will identify additional participants that can inform the process. Interviews will be conducted until data saturation is achieved and no new topics seem to emerge. The interviews will be executed online, take 60-90 min, and the conversation will be recorded. The qualitative data will be transcribed. Then, a qualitative thematic analysis will be performed[50] with statements related to potential barriers and facilitators. An inductive approach to group the information will applied in order to best scope the replies and map categories onto the CFIR domains[47] as previously described.

Finally, implementation strategies matching the emerging topics will be formulated[51]. Together with the business model, these two elements represent the implementation plan for the DAHLIA project. Findings from this study may furthermore influence the post- market surveillance (Study 5, see details below).

Phase 2: Optimisation (Study 3)

The aim of the optimisation phase is to pilot the treatment and improve it through an iterative data-driven process using small patient cohorts. The primary objective is to determine the treatment feasibility and acceptability, and the secondary objectives are to examine individual change processes, and efficacy across iterations on a group-level. The general procedures include the eligibility check, and four assessment periods: baseline, main treatment period, post-intervention, and 3- and 6-months follow-ups. Results from each iteration will be integrated into the subsequent iteration, then tested again, until satisfaction is reached and no new major issues seem to emerge. In the optimisation studies, different methodologies will be combined namely momentary data collection using digital diaries, retrospective questionnaires, and semi-structured interviews. The latter will be conducted by a research assistant, while the diaries and questionnaires will be completed online. Figure 7 provides an overview of the procedure in relation to the research objectives.

--- FIGURE 7 NEAR HERE ----

In total, 40 to 60 patients and their treating HCPs will be included, with n=10 patient-HCP dyads each iteration. Four iterations have been seen as sufficient in a previous study to optimise a digital treatment[52], therefore, a minimum of four iterations will be conducted in the DAHLIA project. In accordance with the agile approach, additional iterations may be performed if deemed necessary. The rationales for the approaches and methodological details are described below.

Feasibility and acceptability

The mixed-method procedure to evaluate the feasibility and acceptability of the treatment includes self-reports, interviews, and technical data. Short self-reports will be collected after each micro- and booster-session. Specifically, patients will be asked to rate the micro-session on its usefulness, enjoyment, and comprehension ('*I experienced today's session as helpful/ enjoyable/ understandable.*', rated on a 7-point numerical scale from 1=not at all, to 7=very much).

Furthermore, at the end of the main intervention period, interviews will be conducted following a semi-structured guide to assess the participants' general experience and different treatment components, specifically the diary, micro-sessions, and chat function. Questions are first rated on a 7-point numeric scale and participants are then encouraged to elaborate on their response with further details, if possible. Examples of questions are '*Did the intervention hinder your daily occupation?*', '*Were the micro-sessions difficult or unclear?*', '*Did you*

experience the digital diary as burdensome?', or '*Would you recommend the treatment to a friend?*' (details see Appendix 3). This guide is based on other feasibility studies[52 53] and tailored to the DAHLIA treatment components. The HCPs will also be interviewed using a guide that follows the same structure (i.e., numeric scale and open elaborations), but the specific questions will be informed by the focus groups (study 1).

Additionally, technical data generated from the www.1177.se website will be collected. These data include time and frequency of log-ins, duration of engagement with the treatment, and use of components. Technical data will be used to describe the overall use and adherence, and allows mediation analyses to determine the influence of engagement rates on treatment outcomes.

Data from the feasibility assessments will be analysed using descriptive statistics and qualitative synthesis to identify trends. The results will be presented reflecting the two core variables from the Technology Acceptance Model (TAM): 'Perceived Usefulness' and 'Perceived Ease of Use'[54]. After each iteration, the insight gathered will be fed back to the developers and integrated to gradually improve the feasibility and acceptability through data-driven adjustments of the treatment. Next to the qualitative self-report, quantitative ratings of the treatment components, and technical usage data, outcome measure to determine the feasibility and acceptability also include flow of participant recruitment and retention (i.e., number of participants that were approached, signed informed consent, and started/ completed the treatment), treatment-fidelity rates (i.e., post-treatment therapist self-report "*Was the treatment delivered as planned?"*), treatment compliance (i.e., indicated through log-in data, self-report from patients and therapists), and (reasons for) dropouts in each iteration.

Individual change processes

The optimisation studies implement a sequential replicated and randomized single case experimental design (SCED) to gain detailed insight into within-person behavioural changes, and to develop and test the DAHLIA intervention, which has been recommended in the context of CP[55]. In SCEDs, each case functions as their own control and changes are evaluated comparing levels of the outcome variables across different phases (e.g., baseline phase 'A' and treatment phase 'B')[56]. The methodology aims to demonstrate cause-effect relationships between the treatment (independent variable) and the target behaviour (dependent variable)[57].

When planning a SCED study, the Risk of Bias in N-of-1 Trials (RoBiNT) Scale, a critical appraisal tool that evaluates the methodological quality of intervention studies using single-case methodology, can be followed as guidance [57 58]. The design decision made in the

present study were based on this appraisal tool to ensure a scientifically robust approach. Table 1 provides details on the design elements.

Table 1. Methodological SCED approach of the DAHLIA study based on the RoBiNT Scale.

Item	RoBiNT Scale	SCED details, per optimisation iteration (*anticipated points)*
INTERNAL VALIDITY SUBSCALE		
1	Design	A **replicated randomised AB-design** with 10 x A-B (total of 20 phases), providing the opportunity to observe the experimental effect 10 times. (*2 points*)
2	Randomisation	The **start of the treatment phase** and therefore length of baseline phase will be determined **randomly** for each participant, with the baseline phase lasting between 5 to 10 days. This means that the treatment phase will start on any day between the 6th and 11th assignment. (*2 points*)
3	Sampling behaviour during all phases	The baseline phase will last at least 5 days, with twice daily sampling, resulting in **10 data points** or more **(phase A)** (assuming 100% compliance to diary). The treatment phase will run over 6 weeks, with twice daily sampling on at least 4 days per week (6 weeks x 4 days x twice daily sampling), resulting in **48 data points** or more **(phase B)** (assuming 100% compliance to diary). Even if the compliance rate should be lower, the amount of data points will lie >5 data points. *(2 points)*
4	Blinding of participants and HCP delivering the treatment	**Blinding** of the participant and practitioner is **not feasible** in the DAHLIA project. The behavioural treatment is delivered through a web-platform independently of the HCP; however, the HCP provides weekly, tailored support in addition to the online treatment. Neither the participant nor the HCP are blinded. (*0 points*).
5	Blinding (masking) of assessors	Patients complete self-report diaries and are **not blinded** to treatment phase, therefore, not independent of the therapy process. *(0 point)*
6	Inter-rater agreement	The measure of the target behaviour is a **subject measure** relying on **self-reports** from the digital diaries. (*0 points*)
7	Treatment adherence	The treatment is delivered through a **web-platform** following a standardized approach. Adherence to treatment (%) is calculated using **digital log-in data**. (*2 points*)
EXTERNAL VALIDITY AND INTERPRETATION SUBSCALE		
8	Baseline characteristics	A short interview by an HCP as part of the eligibility check will be conducted. Furthermore, a **case formulation** including information on age, sex, aetiology of CP, and severity of CP will be presented when presenting the results; this information will be based on a baseline assessment (online self-report). (*2 points*)
9	Setting	Information on the **general location** (Swedish region, hospital/ pain clinic) will be provided; however, the participant will engage with the online treatment in their everyday life, and therefore, it will not be possible to include details about the specific environment. (*1 point*)
10	Dependent variable (target behaviour)	Table 2 provides an overview of all diary items, which are scores on a 7-point Likert-Scale, except from the pain level item (0-100). **Process outcome measures**: 5 items on psychological (in)flexibility (see Table 2), 2 items on pain self-efficacy, 1 item on pain avoidance. **Primary outcome measures**: 1 item on pain level, 1 item on pain interference, 1 item on pain catastrophizing. **Secondary outcome measures**: 3 items on sleep, 2 items on affect, 1 item on stress, 1 item on fatigue. (*2 points*)
11	Independent variable (treatment)	A detailed description of the DAHLIA treatment is given above, including the **treatment content**, and **number, duration, and frequency of sessions**. (*2 points*)
12	Raw data record	**Ten cases** will be recorded (4-6 iteration with n=10 participants per iteration). Raw data will be presented with a data point for each diary entry. (*2 points*)
13	Data analysis	Data will be analysed and reported for each participant individually. **Structured visual analysis, effect size measures** and a **randomization test wrapper** for **multilevel models** will be applied. (*2 points*).

14	Replication	**Ten participants** will be included (per optimisation iteration). Across all iterations, data from n=40-60 participants will be available. (*2 points*)
15	Generalization	Patients will be heterogeneous in their characteristics. Furthermore, retrospective self-reports will be completed by each participant **pre-post treatment,** including two **FUs** (details see Table 3)**.** (*1 point*)

Under the condition that all choices can be executed as intended, the internal validity of this SCED study will reach 8/14 points, and the external validity will reach 14/16 points. The total interpretation score will be 22/30 points. This score indicates a moderate methodological rigour [59].

Target behaviours will be assessed via self-reports collected through a digital diary. This diary will be prompted through the SMS function of REDCap, or a smartphone application (e.g., www.mpath.io). Both data collection methods will be piloted with participants to ensure that the diary works reliably. Participants will be prompted to complete the diary twice daily (for details see Table 2). Proposed diary items are based on traditional questionnaires and diary studies[60], and were chosen as they assess relevant aspects in the context of CP. More specifically, sleep items are based on the Insomnia Severity Index[61], mood, stress, and fatigue items are adapted from previous digital diaries studies[60], psychological (in-) flexibility items (experiential avoidance/ acceptance; lack of contact with present moment/ present moment awareness; self as context/ context; (de-)fusion; (lack of contact with) values); inaction/ committed action) are based on Multidimensional psychological flexibility inventory[62], the pain level item is based on a Pain Rating Scale[63], pain catastrophizing item are based on the Pain Catastrophizing Scale[64], the pain avoidance item is based on the Psychological Inflexibility in Pain Scale[65], pain interference categories are based on the Brief Pain Inventory Scale[66], and pain self-efficacy items are is based on the Pain Self-Efficacy Questionnaire[67].

Generally, items should be short and easily to answer quickly[60]. The order of the items will be the same in each prompt to allow participants to get used to the questions, minimise time to complete the diary, and thus limit interference with their daily flow. The reliability, validity, and sensitivity of the items will be explored through pilot studies and as part of the optimisation studies using suggested statistics (e.g., P-technique factor analysis). Idiosyncratic items might also be discussed with patients, in line with the agile approach, to improve validity and potentially patient engagement and ownership. Based on user-input, scientific evidence, and insight gained, diary items might be optimised and adjusted, and any adjustments made will be reported in prospective publications.

Table 2. Proposed daily diary items.

LUNCH/ EVENING DIARY			
Instructions (Availability to fill out: Lunch diary 12-14h, evening diary 18-20h)		LUNCH: Hello & welcome to your digital diary! Please reflect on last night and this morning, and rate the following statements. Self-reflections can help to understand your daily routines and needs better. Let's get started. EVENING: Welcome back to your daily diary. Please take 2-3 minutes to reflect on this afternoon.	
	Construct	Item	Answering scale
		Last night, …	
1	Sleep[1]	… I had problems falling asleep.	7-point numeric scale
2	Sleep[1]	… I had problems sleeping.	7-point numeric scale
3	Sleep[1]	… I woke up too early.	7-point numeric scale
		During the morning/ During the afternoon…	
4	Positive affect	… I felt happy, energetic, at ease, or enthusiastic.	7-point numeric scale
5	Negative affect	… I felt down, irritated, depressed, or hopeless.	7-point numeric scale
6	Stress	… I felt stressed.	7-point numeric scale
7	Fatigue	… I felt tired.	7-point numeric scale
8	Experiential avoidance/ Acceptance[2]	… I tried to distract myself when I felt unpleasant emotions. … I opened myself to all my feelings, the good and the bad.	7-point numeric scale
9	Lack of contact with present moment/ Present moment awareness[2]	… I did most things on "automatic" with little awareness of what I was doing. … I was attentive and aware of my emotions.	7-point numeric scale
10	Self as content/ Self as context[2]	… I criticized myself for having irrational or inappropriate emotions. … I tried to see the larger picture, even when I was down, depressed, or hopeless.	7-point numeric scale
11	Fusion/ Defusion[2]	… distressing thoughts tended to spin around in my mind like a broken record. … I was able to notice my thoughts and feelings without getting overwhelmed by them.	7-point numeric scale
12	Lack of contact with values/ Values[2]	… I didn't have time to focus on things that are important to me. … I tried to connect with what is truly important to me.	7-point numeric scale
13	Inaction / Committed action[2]	… negative feelings trapped me in inaction. … I didn't quit working towards what is important even if it was though.	7-point numeric scale
14	Pain level	… my overall pain level was:	0 (no pain) to 10 (worst pain imaginable)
15	Pain interference	… my pain interfered with my…	7-point numeric scale ○ General activities ○ Mood ○ Walking abilities

			○ Normal work (including housework) ○ Relations with others ○ Enjoyment of life
16	Pain catastrophizing (rumination)	… I kept thinking about how much I hurt.	7-point numeric scale
17	Pain catastrophizing (magnification)	… I felt my pain overwhelmed me.	7-point numeric scale
18	Pain catastrophizing (Helplessness)	… I was afraid that my pain would get worse.	7-point numeric scale
19	Pain avoidance	… I avoided planning activities because of my pain.	7-point numeric scale
20	Pain self-efficacy	… I could do some form of housework/ paid/ unpaid work, despite the pain.	7-point numeric scale
21	Pain self-efficacy	… I could live a normal lifestyle, despite the pain.	7-point numeric scale
22	Open question	I would also like to share this about my morning/ afternoon:	Free text
23	Treatment interaction[3]	Today, I completed a treatment module.	○ Yes. ○ No, because it was a 'module free day'. ○ No, but I will do it tonight. No, because: *free text*
	Instructions	LUNCH: Thank you & have a nice afternoon! EVENING: Thank you very much for taking the time to fill in your diary. Have a nice evening!	

7-point numerical scale ranges from 1: not at all, to 7: very much; alternatively, based on user input, a visual analogue slider scale from 0: not at all, to 100: very much might be used. Note: [1]Sleep items only as part of the morning questionnaire; [2]Both psychological flexibility and inflexibility items will be tested to determine with are more feasible and suitable to use; [3]Treatment interaction item only as part of the evening questionnaire.

In addition to the information in Table 1, the analysis will be executed as follows. Diary data have a multilevel structure because repeated measurements (level 1) are nested within individuals (level 2). First, structured visual analysis will be conducted for each individual separately following the four steps described in Kratochwill, et al. [56] to examine the within- and between-phase patterns in respect to the effects on level, trend, variability, immediacy, overlap, and consistency. Additionally, effect size measures will be calculated at the individual

level using standardized mean difference and Tau-U, and at a group level using the between-case standardised mean difference[68]. Finally, to avoid making distributional and random sampling assumptions, the randomization test wrapper for multilevel models will be used to synthesise the data from the whole group of cases and evaluate treatment effects[69]. Scientific advisors of this project will provide expertise and support in the SCED analyses. Results will be presented following the RoBiNT scale and SCRIBE guideline[70].

Efficacy across iterations

In the optimization studies, efficacy will be determined using both intensive (SCED) as well as extensive methods (retrospective self-reports from baseline, post-intervention and FUs; see Figure 7). The diary and questionnaire data will be aggregated across all iterations, thus include data from 40-60 participants. This approach allows to investigate the generalisability of results of the SCED and evaluate treatment effects in applied research[71]. MultiSCED will be used for the SCED data [72].

The proposed retrospective questionnaires used can be separated into process, primary, and secondary outcome measures (see Table 3). Additionally, negative treatment effects may occur in the context of internet interventions, and therefore, need to be acknowledged and systematically assessed[73]. Negative treatment effects are here assessed post-treatment using the negative effects questionnaire (NEQ), a tool with reliable and valid psychometrics[74].

Descriptive statistics of the retrospective questionnaires will summarize demographics and pre-treatment clinical characteristics of the sample. To evaluate changes in treatment outcomes over time, linear multilevel modelling (MLM) will also be used. MLM accounts for repeated measures within subjects and can handle missing data, which will be addressed per variable. Using a random intercept model, time will be treated as a categorial variable and pre-treatment values will be specified as the reference point. Therefore, results will be interpreted as a change from pre-treatment to post-treatment and, from pre-treatment to follow-up assessments. Anchor-based methods will be applied to determine clinical significance of changes in outcome measures[75]. Separate linear growth models[76] will be computed for each variable, while controlling for multiple testing. Significance level is set at Alpha (α)=0.05.

Table 3. Proposed outcome variables and tools used to assess efficacy using extensive methods.

Focus	Variables	Instrument	Supported psychometrics
Process outcome measures	Open/ Acceptance	Chronic Pain Acceptance Questionnaire (CPAQ)	Internal consistency and criterion validity (Swedish version) [77]
	Aware	5 items on,'acting with awareness' from the Five Facets Mindfulness Questionnaire (FFMQ)	Internal consistency, reliability, and construct validity (Swedish version) [78]
	Engaged/ committed actions	(i) Valuing questionnaire; (ii) Committed action questionnaire	(i) Internal consistency and construct validity (Swedish version) [79]; (ii) Proven validity and reliability (Swedish version) [80]
	Psychological flexibility	Swedish translation of the Multidimensional psychological flexibility inventory (MPFI)	Convergent and discriminant validities (English version) [62]
	Self-efficacy	General self-efficacy scale (S-GSE)	Reliable with high internal consistency (Swedish version) [81]
	Pain self-efficacy	Pain self-efficacy questionnaires (PSEQ-2)	Evidence for reliability and validity (English version) [67], translated into Swedish [82]
	Avoidance	Avoidance subscale of Psychological Inflexibility in Pain Scale (PIPS)	Internal validity and construct validity (Swedish version) [65]
Primary outcome measure	Catastrophizing	3-Item Daily Pain Catastrophizing Scale (PCS)	Recommended instrument to understand mechanims[64]
	(Dis)ability/ pain screening	Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ)	Clinically reliable and valid (Swedish version) [83]
	Work ability	Work ability index (WAI)	Validated (Swedish version) [84]
	Functioning	Brief pain inventory (BPI-SF)	Reliable and valid in multiple languages (including Swedish version) [66]
Secondary outcome measure	Well-being/ depression	Patient Health Questionnaire (PHQ-9)	Satisfactory content validity and sufficient reliability (Swedish version) [85]
	Perceived stress	Perceived Stress Scale (PSS)	Internal reliability and construct validity (Swedish version) [86]
	Sleep problems	Insomnia Severity Index (ISI)	Satisfactory factor structure, internal reliability, and concurrent validity (Swedish version) [61]
	Health-related quality of life	EQ-5D	Standardised measure of health-related quality of life develop by the EuroQol Group[87]

Phase 3: Clinical evaluation (Study 4)

Randomized controlled trial enhanced by SCED

To determine the clinical effectiveness of the DAHLIA treatment, a RCT enhanced with SCED will be conducted. While RCTs provide estimates of between-subject treatment responses,

differences in average scores between groups, they are unable to indicate specific within-subject responses. Simons, et al. [88] apply a similar design and argue that SCED is a valuable addition to a traditional RCT design. One reason for this combined approach is that RCTs provide information on the population level, whereas SCEDs focus on the individual level. Furthermore, heterogeneity of treatment effects might remain undetected in a traditional RCT design[89]. Additionally, the need for large cohorts of patients for adequate sub-group analysis[90], and a lack of feasibility to reach certain patient groups[91] limits the insights from a traditional RCT. Applying SCED and multilevel modelling, even group results from small and distinct cohorts can be performed on a meta-analysis level[88].

Outcome measures will be the same as in the optimisation studies, including the diary items for the SCED (see Table 2), and retrospective questionnaires (see details Table 3; including NEQ post-treatment[74]). A priori computations based on a power of .95, four questionnaire assessment points and a medium effect size shows that 360 participants (180 in each arm) are sufficient to generate stable findings in the analyses of treatment effects. With an estimated attrition rate of 18%, this implies that 295 participants will provide post-treatment data, which is considered adequate also for moderator/ predictor and cost-effectiveness evaluations. However, outcome measures and calculated sample size will be updated and might be modified based on iterations in the prior phase.

Treatment arm randomization is conducted by a research assistant following the decision on study inclusion by the HCP and after the baseline assessment (sociodemographic information, questionnaires, A-phase of SCED) is completed. Participants are randomized to the treatment arm or treatment as usual (TAU) using a block randomization strategy to ascertain equal distributions across the arms. Randomization is conducted by a local project manager who is not involved in the screening or intervention. Next, participants undergo treatment; then all participants complete the post-intervention assessment (questionnaires and 5-day digital diary). Booster-sessions will be sent to the participants in the intervention group at 2- and 4-months. Finally, at the 3- and 6-month follow-ups (FUs), all participants complete the questionnaires and 5-day digital diary period. In case participants decide to discontinue the study at any point in time, they might choose to provide a reason.

To examine changes in process, primary and secondary outcome measures (Table 3), linear mixed models will be conducted comparing the DAHLIA treatment to TAU. Analysis will be performed using group as a fixed between-person factor (two levels: DAHLIA treatment and TAU), and time as a fixed within-person variable (four levels: baseline, post-treatment, 3-month FU, 6-month FU). The linear mixed model will estimate fixed effects

(regression slopes) for change in the intervals during (baseline to post-treatment assessment), and after (post-treatment to 3- and 6-month FU) the treatment period. The intervals will be entered as a categorical dummy variable (three levels). Potential confounders will be added to the model as covariates (i.e., age, gender, pain diagnosis, pain duration). Data will be analysed with the support of a statistician and using the latest version of SPSS. Mean change will be reported and test of significance will be two-sided with a set alpha level of 0.05.

Health economic evaluation

A short-term health economic evaluation will compare the DAHLIA treatment and the TAU at the primary endpoint (post-treatment). Additionally, an equivalent long-term evaluation will be performed at the end of the FU period using cumulative data collected up to that assessment point. Costs in both trial arms will be estimated from a societal perspective for each participant in the trial based on resource items and associated relevant unit costs. The use of societal resources comprises information on the use of resources related to healthcare contacts and medication (medical records and register data), and productivity losses related to absence from work (the LISA database). Costs to deliver the digital intervention will be estimated based on, for instance, HCPs' time spent on treatment. Total costs will be aggregated by trial arm.

The self-report tool EQ5D[87] will be completed by the participants at pre-, post-treatment and FUs and used to measure changes in health-related quality of life (HRQoL), to calculate quality adjusted life years (QALYs). Total QALY gains for participants over the trial will be estimated using the area under the curve method[92]. Cost data and QALYs will be analysed using generalized linear models to account for non-normal distributions[93]. Data will be analysed controlling for the influence of covariates, and by adjusting for baseline data. Cost-utility analysis (CUA) will be conducted with QALYs gained as primary outcome, comparing incremental costs with incremental changes in QALYs for digital treatment and TAU. Results will be presented as an incremental cost-effectiveness ratio (ICER), representing the ratio between the difference in costs and the difference in QALY gained between the digital treatment and TAU. Incremental cost-effectiveness ratio will be expressed as cost per additional QALY, which is the most common approach in health economics[94]. Uncertainty around the cost and outcome data will be explored and presented on cost-effectiveness plans, representing the distribution of the cost and outcome differences between both conditions. The probability of digital treatment being cost-effective compared to TAU will be presented across a range of price values a decision-maker would be willing to pay, represented by a cost-effectiveness acceptability curve[95].

Phase 4: Post-market surveillance (Study 5)

Similar to the development phase (Study 2), interviews with stakeholders will be conducted, recorded, and transcribed. The stakeholders participating in study 2 will be approached, along with additional key stakeholders identified during the implementation process. Appendix 4 provides the full overview of the interview questions. Questions reflect on the process so far (e.g., '*What kind and how many resources were needed to bring this intervention into practice?*'), on the current status (e.g., '*What issues are you currently facing?'*), and prospective adjustments (e.g., *'What will the prospective maintenance and upkeep look like?'*). These questions are preliminary and may be adjusted based on findings of Phase 1-3. Even though the www.1177.se website is free for the end users (i.e., patients and HCPs), special attention may also be paid to financing, as a lack thereof can be a barrier for long-term implementation of eHealth interventions[96].

The qualitative data will be analysed following the same process as that used in Phase 1. Specifically, an inductive analysis to identify and summarise themes will be performed, and information will be mapped onto the domains of the CFIR[47]. The implementation strategy and plan will be reviewed, and lessons-learned will be presented to inform prospective implementation studies.

Patient and public involvement

This is a study protocol and due to ethical and practical reasons, no patients were directly involved in the project yet. However, the Personas originated from interviews with patients, as described above, and patients and other stakeholders will be involved in all planned phases of the DAHLIA project. Dissemination to patients and the public is described in more detail the section 'Ethics and Dissemination'.

DISCUSSION

Chronic pain is a huge public health problem, in suffering, disability, and costs for individuals and society. Widely accessible and sustainable behavioural treatment options could help to address this problem. An agile and user-centred development integrating a data-driven decision-making process and scientific evaluation of effects is essential to produce an evidence-based intervention of this type for individuals with CP. To our knowledge, this is the first project utilizing the mHealth agile development framework[27] to systematically build a digital behavioural treatment within a nationally used health care hub. The purpose of this project is to improve the standard of care for individuals with CP by applying the innovative development framework, thus providing an accessible, user-friendly, and empirically supported behavioural treatment to maintain or improve resilience, functioning, and well-being in this population.

Strengths include (i) the execution of the project by a multi-disciplinary, inter-sectorial, and international research team, (ii) the overall agile, iterative, and data-driven process, and (iii) the involvement of patients and different stakeholders early and throughout the development. Furthermore, (iv) the richness of methodologies using mixed methods, combining a traditional clinical trial evaluation on the population level (RCT), fine-graded data collection (SCED) on the level of the individual, and (v) an explicit focus on cost-effectiveness and determinants of implementation will be highlighted. The project is (vi) based on innovative strategies in the field of eHealth and digital treatments, and (vii) key gatekeepers such as regional leaders support the initiative. The DAHLIA approach is also in line with the widely used MRC framework by considering contextual and economical aspects, building on theory, involving stakeholders, and refining the intervention[45].

Due to the ambitious and multifaceted nature of the project, several inherent challenges and risks should also be acknowledged. In case a sub-study should be delayed, e.g., due to recruitment difficulties or technical development issues, this delay could affect the whole project. Subsequently, adjustments following the agile approach could be discussed to balance the practical feasibility of executing the study and limiting the impact on its robustness.

Furthermore, the multidisciplinary, inter-sectorial approach is certainly a strength of the DAHLIA project, however, it might also have inherent challenges. For example, interests of stakeholders might differ, which needs to be considered and addressed. Here, communication is key, but compromises might be needed to ascertain satisfactory benefits for all parties involved.

Regarding the DAHLIA treatment itself, a high level of patient engagement (e.g., four micro-session per week combined with frequent diary assessments) will be required. These demands might be perceived as burdensome by some individual. However, contact with HCPs will support participants' motivation and engagement. Furthermore, the focus groups and optimisation studies will provide insight into the perceived intensity, thus feasibility of the intervention set-up, and the agile process allows to adjust it accordingly. Specially, tailoring of the length of the micro-sessions and frequency of diary prompts will be explored.

Furthermore, the DAHLIA treatment may not be suitable for all people with CP and the question of "what fits for whom" will be continuously discussed. The website (www.1177.se) is a national health care hub in Sweden, but research shows that older adults, people with cognitive problems, or disabilities are less likely to use technologies[97], which could result in a bias in recruitment and usability. To improve inclusivity, the possibility to provide additional training for certain populations, such as older adults[98], will be explored. An additional issue is that the project is currently executed in Swedish, which excludes people with limited proficiency in Swedish. Therefore, translation into other languages and further cultural adaptations will be considered.

The DALHIA treatment may have the potential to become a widely implemented first line of treatment. However, some CP groups will likely benefit from an alternative treatment format (e.g., face-to-face), or complementary interventions. Thus, additional studies may explore if and how physiotherapists, general practitioners, or occupational therapists can deliver the DAHLIA treatment.

Finally, the treatment could prospectively be scaled and adjusted for other groups of patients with CP, e.g., children and adolescents, people with disabilities, and/or other medical conditions such as individuals with severe mental or physical co-morbidities. In addition, support offered as part of the DAHLIA treatment can be extended to significant others and family members of people living with CP. Thus, by using an agile development approach, the DAHLIA project might grow to support the heterogeneous group of individuals with CP and their complex health needs.

Ethics and Dissemination

The study received approval from Swedish ethical review authorities (Dnr 2021-02437). All participants will receive a detailed patient information sheet, have one week time to consider participation, and sign informed consent prior to participation. Each study participant will receive a unique study code to ensure anonymity and confidentiality. Data will be stored in accordance with Swedish regulations on secure servers at Karolinska Institutet.

The project is announced on the Karolinska Institutet website (Rikard Wicksell's research group), and on social media, primarily twitter. The general outline of the project has been presented at online conferences. Next to the study protocol paper, the intention is to publish a number of peer-reviewed manuscripts, in which any protocol modifications will also be communicated. The results will be presented at (inter-)national conferences and networking events. Popular science articles, podcasts, radio interviews, and animated videos are additionally planned to disseminate the results to the wider public.

Author's contribution

SB, SJ, KB, LMcC, IFl, SP, and RW were involved in the conception and design of this project. RW acquired and received the funding. HC provided specific input on the topic of implementation, IFe contributed with her expertise on health economy, and LS, PO, and JV added valuable knowledge on the single-case experimental design aspects of the project. SB drafted the manuscript, and all authors revised the manuscript and checked the intellectual content. All authors gave final approval and agree to be accountable for all aspects of the work.

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Completing interests

None declared.

Access to data and protocol details

Only the research team will have access to the raw data and participant code. Anonymised data will be made available as part of publications, whenever possible. Researchers from other universities may request to receive access to other information (e.g., informed consent sheets, data management plan).

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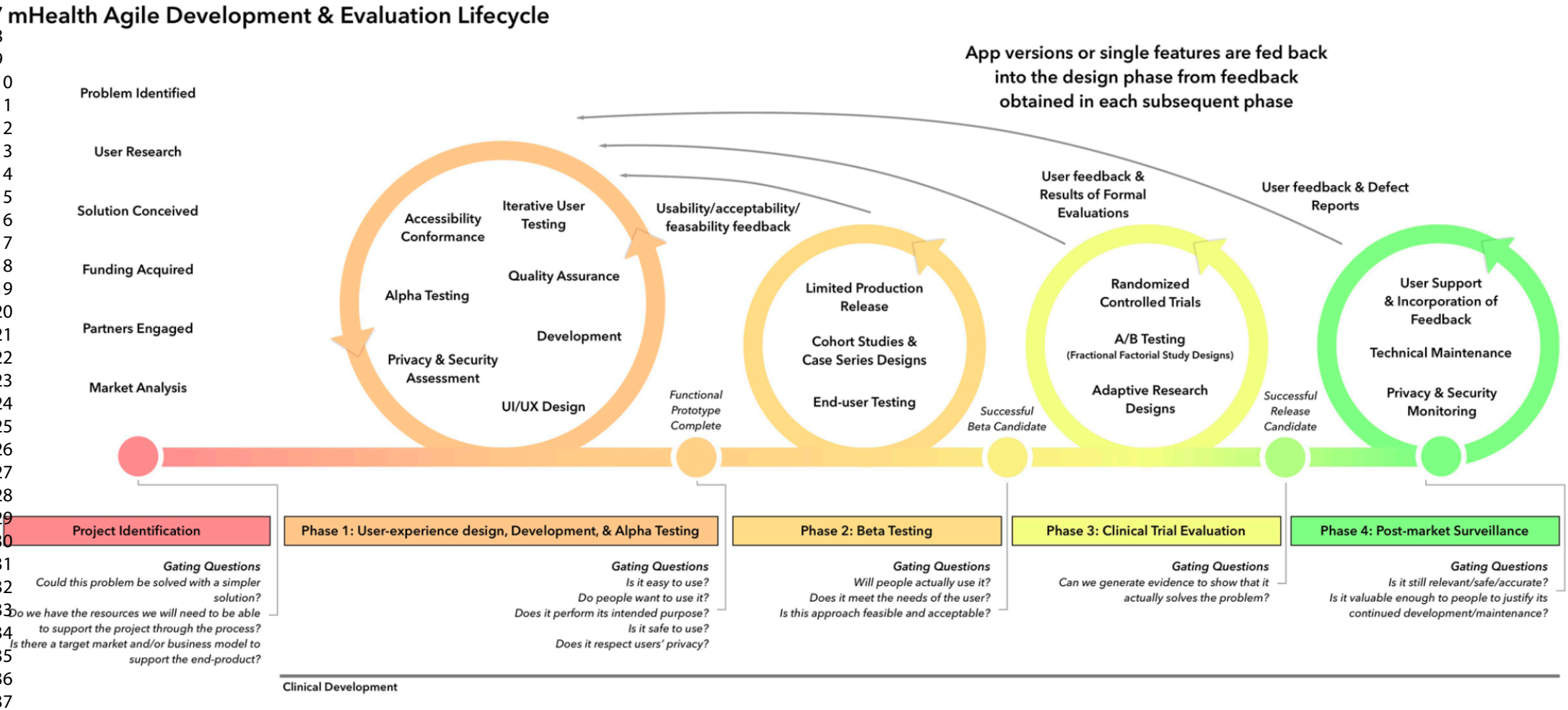
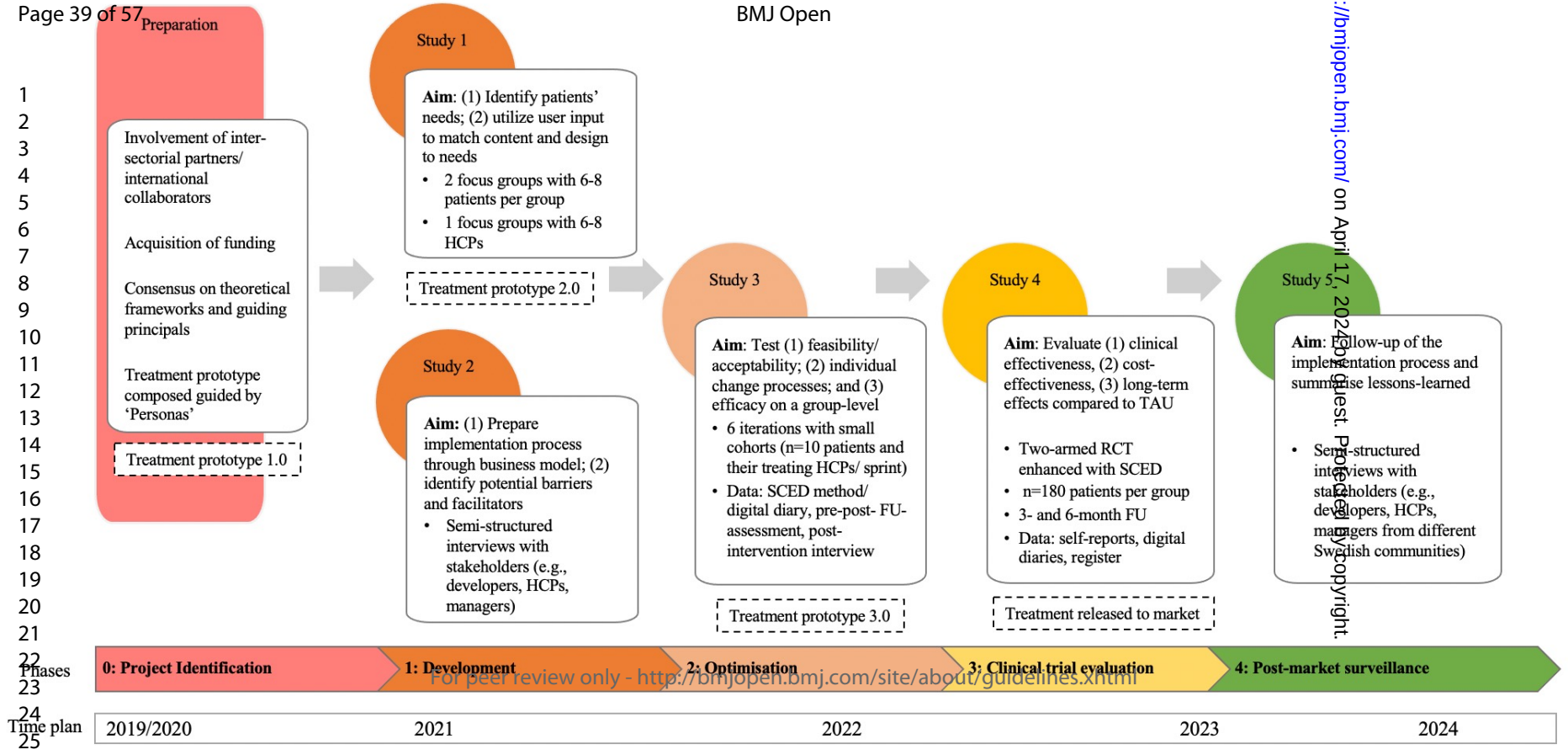
Figure legend

- Figure 1. mHealth Agile Development & Evaluation Lifecycle (Wilson et al., 2018).
- Figure 2. DAHLIA project overview including highlights of each study and time plan. HCP= health care professional; SCED= single case experimental design; TAU= treatment as usual; RCT= randomised controlled trial; FU= follow-up.
- Figure 3. Example of a DAHLIA Persona with chronic pain.
- Figure 4. DAHLIA treatment micro-session elements. HCP= health care professional. Note: The name "DAHLIA treatment" is mainly for academic settings; in the www.1177.se web-platform, a more intuitive treatment name will be chosen.
- Figure 5. The DAHLIA treatment components.
- Figure 6. Template of business model canvas (based on Osterwald & Pigneur, 2010). Grey boxes: Example aspects of the DAHLIA business model; the final model will be a result of the stakeholder interviews.
- Figure 7. General overview of the optimisation studies and specific procedure in each iteration. SCED= Single-case experimental design. FU= Follow-up. HCP= Health care professional.





AIDA
18 yrs. old

Employment:
N/A, high school student.

Education:
Primary school
Upper secondary school (ongoing).

Family:
Mother and father with foreign background, four younger siblings.

Background and social context:
Born in Pakistan, moved to Sweden when she was four years old. Leads an active life with hobbies and after-school activities. Frequently works out at the gym, pushing herself.
Aida has many friends and it is important for her to be popular. She is ambitious in school with high demands from her home-environment. She often feels stressed and does not think she is performing as expected. Aida carries a lot of responsibility at home. She has a high level of technological literacy and uses her smartphone for everything.

Social support (related to pain): Despite her family and many friends, Aida feels lonely with her pain. She feels that no one understands or takes it seriously. Her parents are constantly nagging, stressing that the health services should be able to help. Aida finds it strange that she is in so much pain even though she works out a lot and does everything she is "supposed to". Despite her efforts, there are days when she is paralyzed by pain and the feeling of being under pressure.

City/ countryside: Apartment in large city.

PATIENT PAIN PROFILE

Pain problems:
- No clinical diagnosis.
- Recurrent headaches.
- Tensions in shoulders and neck.
- Stomach ache.

Consequences:
- Difficult to concentrate when in pain.
- Although Aida really wants to go to school, she is increasingly staying at home as she cannot manage.
- "Yoyo behaviour" – some days she keeps active and works out, while other days she is completely exhausted.

Pain behaviour:
- Wants a "quick fix" and prefers to continue pushing rather than taking a step back and think.
- Exercises to get in better shape to handle the pain.
- Keeps on going to alleviate anxiety despite feeling the need to rest.

Attitude to treatment:
- Wants to be a "good patient" and do everything she is told (and then some).
- Happy to visit doctors but does not see herself as someone who needs mental health support or treatment.

HEALTH CARE & TREATMENT

Contact with health care:
- Undertaken eye test and has gone through various investigations for the recurrent headaches.
- Visited dentist focusing on temporomandibular joints (jaw region).
- Sought care due to various somatic disorders (head, neck, stomach).

Comorbidities:
- Stress
- Anxiety
- Sleeping difficulties

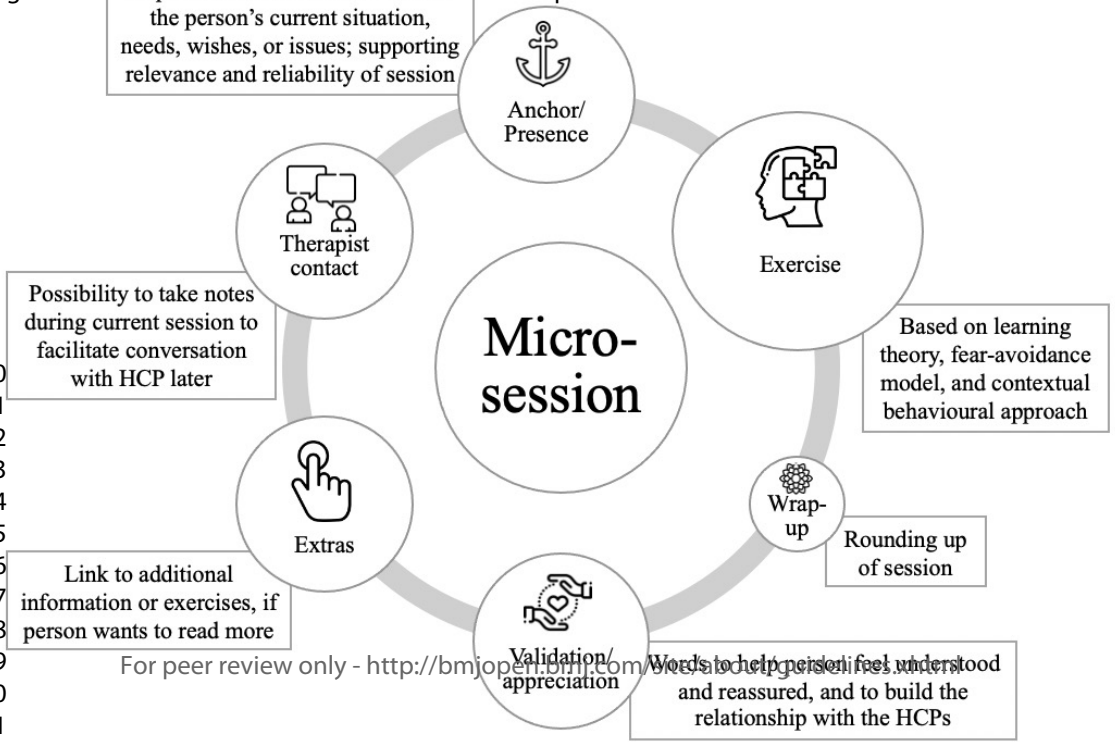
Medicine:
- Pain killers

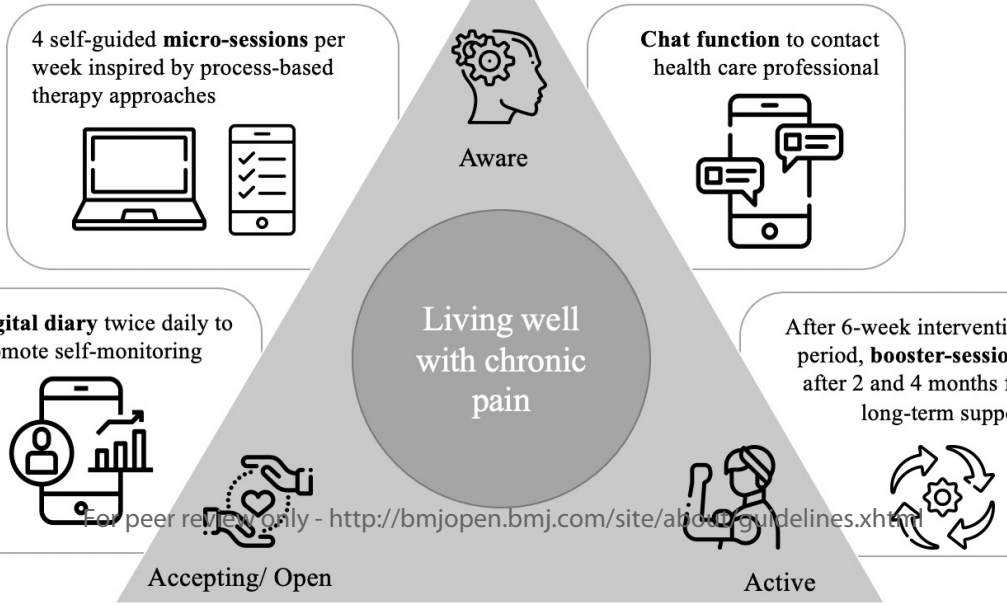
PERSONAL NEEDS & GOALS

Treatment needs:
- Wants to be independent and take an active part in her treatment. Needs to feel that she can influence her situation.
- Wants to follow/have an overview of own progress.

Goals:
- To live an active and productive life without pain.
- To learn how to maintain a balanced lifestyle without guilt when resting.

Figure 3. Example of a DAHLIA Persona with chronic pain.





Key Partners

(8) Describes the network of suppliers and partners that make the business model work, e.g.:

- Optimization and economy of scale
- Reduction of risks and uncertainty
- Acquisition of particular resources and activities

➢ *Soft ware partners*
➢ *Health care*

Key Activities

(7) Describes the most important things a company must do to make its business model work, e.g.:

- Production
- Problem solving
- Platform/ Network

➢ *Developing content*
➢ *IT support and development*

Key Resources

(6) Describes the most important assets required to make a business model work, e.g.:

- Physical
- Intellectual
- Human
- Financial

➢ *IT upkeep*

Value Propositions

(2) Describes the bundle of products and services that create value for a specific customer segment, e.g.:

- Newness
- Performance
- Customisation
- "Getting the job done" Design
- Brand/Status
- Price
- Cost reduction
- Risk reduction
- Accessibility
- Convenience/Usability

➢ *Usable, effective, evidence-based treatment*
➢ *Accessible and free for patients*

Customer Relationships

(4) Describes the types of relationships a company establishes with specific customer segments, e.g.:

- Personal assistance
- Self-service
- Automated services
- Communities
- Co-creation

➢ *Personal assistance*
➢ *Co-creation*

Channels

(3) Describes how a company communicates with and reaches its customer segments to deliver a value proposition (direct/indirect), e.g.:

- Sales Force
- Web sale
- Own stores
- Partner stores
- Wholesaler

➢ *Information on 1177*

Customer Segments

(1) Defines the different groups of people or organizations an enterprise aims to reach and serve. e.g.:

- Mass market
- Niche market
- Segmented
- Diversified
- Multi-sided platforms (multi-sided markets)

➢ *Patients with chronic pain*
➢ *Health care organisations*

Cost Structure

(9) Describes all costs incurred to operate a business model, e.g.:

- Cost-driven
- Value-driven
- Fixed costs
- Variable costs
- Economies of scale
- Economies of scope

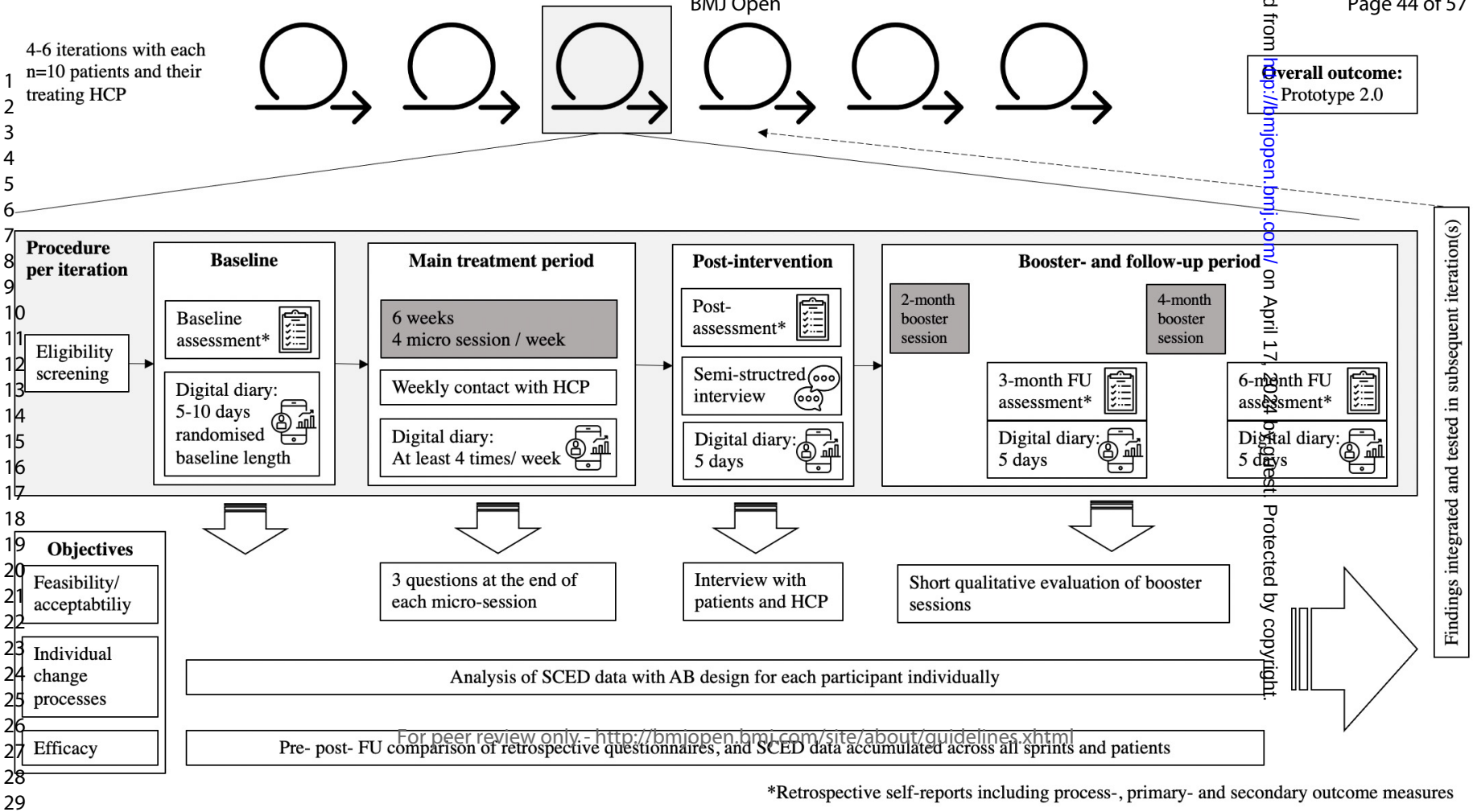
➢ *Platform and content development/ upkeep*

Revenue Streams

(5) Represents the cash a company generates from each customer segment (costs must be subtracted from revenues to create earnings), e.g.:

- Asset sale
- Usage fee
- Subscription fees
- Lending/ renting/ leasing
- Licensing
- Brokerage fees
- Advertising

➢ *Free for patients*
➢ *Licensing for regions*



*Retrospective self-reports including process-, primary- and secondary outcome measures

Appendix 1:

Semi-structured focus group guide
6-8 participants per focus group

FOR PATIENTS (*2 focus groups; heterogenic in terms of age, gender, pain condition, pain history, etc.*):

1. General introduction, informed consent, collect sociodemographic details (10min.)
2. Short introduction round (10min.)

3. Core question 1: **Living with chronic pain** (30min.)
   It would be amazing to have a magic pill to just take all the pain away, so you could live without it. But unfortunately, we don't have that magic pill. Instead, we want to help you and other people with chronic pain to find a way to live well with the pain. (*Presentation on definition of health (Huber et al., 2011): ability to adapt and self-manage physical, mental and social aspects of health, and examples*).
   a. Based on this definition of health, can you describe your own health needs? Which (aspects of your) needs are currently unmet?
   b. In which moments of your life do you feel happiest/ most engaged/ most satisfied?
   c. What helps you to engage in these 'happy moments'?
   d. What are barriers to engage in these 'happy moments'?
   e. What would you need to engage in these moments more often?

BREAK 10 Min.

4. Core question 2: **The DAHLIA treatment**
   Presentation of the proposed treatment, aim, design, theoretical background, and examples of exercises (10min); following a discussion (30min)
   a. What do you think of this treatment? What do you like, what do you dislike? (Please reflect on (1) design, (2) set-up, (3) content, (4) other (e.g., terminology: treatment, intervention, program; patient vs. person))
   b. How feasible would it be to do this treatment?
   c. Do you think this treatment meets you needs?
   d. Is there anything else you would like to add?

FOR HEALTH CARE PROFESSIONALS (*1 focus group, psychologists/ psychotherapists trained in cognitive-behavioural therapy; heterogenic in terms of age, gender, cultural background)*:

1. General introduction, informed consent, collect sociodemographic details (10min.)
2. Short introduction round (10min.)

3. Core question 1: **Supporting people with chronic pain** (30min)
   People with chronic pain have complex needs and treatment has to meet these needs. We are interested in your experiences in what works well to improve

the overall health and well-being of patients with chronic pain. (*Presentation on definition of health (Huber et al., 2011): ability to adapt and self-manage physical, mental and social aspects of health, and examples*).

a. Which (aspects of) your patient's health needs are unmet? What is needed to support chronic pain patients in the best way?
b. What barriers and facilitators to deliver support to chronic pain patients do you face? Please reflect on elements related to the patient, treatment options, and the health care in general.

BREAK 10 Min.

4. Core question 2: **The DAHLIA treatment**

Presentation of the proposed treatment, aim, design, theoretical background, and examples of exercises (10min); following a discussion (30min)

a. What do you think of this treatment? What do you like, what do you not like? (Please reflect on (1) design, (2) set-up, (3) content, (4) other (e.g., terminology: treatment, intervention, program; patient vs. person))
b. How feasible would it be for you to deliver this treatment?
c. Does the treatment meet the needs of the patients with chronic pain?
d. Is there anything else you would like to add?

Appendix 2. Baseline interviews with stakeholders

Various stakeholders will be approached, including developers, health care professionals, and managers. Through snow-ball sampling, other potential stakeholders will be identified and approached (e.g., individuals from policy making or municipality representatives).

Stakeholder: developers

I. General

Theme: Experience and development of digital interventions within the 1177 web-platform

1. What is your job description and what are your responsibilities?
2. How is the 1177 web-platform structured, in the region of Kalmar and Sweden?
3. How many digital interventions are available within 1177 in your region?
4. Who developed these interventions; who integrated them in the platform?
5. How are these interventions financed?
6. Who is responsible/ involved in the maintenance of the interventions?
7. If/ how is the interventions' content updated?
8. If/ how are the interventions used and promoted in health care?
9. If/how is user satisfaction with interventions evaluated?
10. If/how do collaborations with other regions look like?

II. Specifics (focus about DAHLIA project)

1. How would you describe the anticipated implementation process of this intervention?
2. What is needed to support the implementation process?
3. What could facilitate the implementation process?
4. What could hinder the implementation process?
5. What are benefits for you/ the 1177 web-platform when developing this intervention?
6. Are you enthusiastic about this intervention, if so, why?
7. Do you think this intervention has the potential to be successful in your region, and Sweden?
8. Where would you like to see this intervention in 5 years?

Stakeholder: health care professionals

I. General

Theme: Experience and use of digital interventions with patients

1. What is your job description and what are your responsibilities?
2. What is your experience in delivering interventions via the 1177 web-platform?
3. If/when there is a new intervention available in the 1177 web-platform, how do you usually hear about it?
4. What makes it attractive to deliver such an intervention?
5. What resources are needed for you to deliver these interventions (e.g., time, knowledge, managerial support)?
6. What hinders you to deliver these interventions?

II. Specifics (short introduction of DAHLIA project and details of digital behavioral health treatment for people with chronic pain)

1. Do you think there is a need for this intervention? Please elaborate.
2. What benefits for yourself/your work do you anticipate through this intervention?
3. What benefits for your patients do you anticipate?
4. What disadvantages or problems do you anticipate when delivering this intervention?

5. What disadvantages or problems for your patients when receiving the intervention do you anticipate?
6. What would hinder you to deliver this intervention?
7. What would facilitate you to deliver this intervention?
8. Are you enthusiastic about this intervention, if so, why?
9. Do you think this intervention has the potential to be successful in your care facility?
10. Where would you like to see this intervention in 5 years?

Stakeholder: health care managers

Theme: Experience and promotion of digital interventions in care facility

1. What is your job description and what are your responsibilities?
2. How many digital interventions are currently offered by the 1177 web-platform (and used) in your care facility?
3. What is needed to implement an intervention from the 1177 web-platform in your care facility?
4. How do digital interventions get financed in your care facility?
5. What is your involvement in digital interventions in your care facility? How do you support the use of digital interventions?
6. What hinders the implementation of these interventions, in your eyes?
7. If/ how does your care facility collaborate with other regions regarding digital interventions from the 1177 web-platform?

II. Specifics (short introduction of DAHLIA project and details of digital behavioral health treatment for people with chronic pain)

1. Do you think there is a need for this intervention? Please elaborate.
2. What kind of benefits do you anticipate for employees through this intervention?
3. What kind of benefits do you anticipate for patients through this intervention?
4. What kind of disadvantages or problems for employees do you anticipate through this intervention?
5. What kind of disadvantages or problems for patients do you anticipate through this intervention?
6. Are you enthusiastic about this intervention, and if so, why?
7. How will you promote this intervention in your care facility?
8. Do you think this intervention has the potential to be successful in your care facility?
9. Where would you like to see this intervention in 5 years?

Final question for all participants:

The main points I take away from this interview are [summary]. I appreciate the time you took for this interview. Who else should we talk about regarding the implementation of this intervention? Is there anything else you think would be helpful for me to know?

Appendix 3. Feasibility/ acceptability; questionnaire.

Table 1. Semi-structured interview guide to evaluate the general feasibility and acceptability of the treatment.

Topics	**Questions**	**Answering scores**	**Open question**
You recently completed the 6-week treatment. For us, it is very important to hear how you experienced it so that we can improve the content, design, and other aspects further. Thank you for taking the time to provide us with your input. First, we would like to ask you to reflect on and rate the **past weeks and treatment** in general.			
General	Were the past 6 weeks usual weeks for you?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Did special events occur?		
	Were you able to read the text in the treatment well?		
	Was the text understandable?		
	Did the intervention hinder your daily occupations?		
	Did technical issues occur?		
	Would you recommend this treatment to a friend?		
Secondly, we would like to ask you to reflect on and rate the four short **sessions** that were offered each week.			
Micro-sessions	Did you like doing the sessions?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Were the sessions difficult or unclear?		
	Did you experience the sessions as helpful?		
	Have the sessions influenced your behavior?		
	Have the sessions influenced your emotions?		
	Have the sessions influenced your thoughts?		
	Did you experience the sessions as time consuming?		
	Did you experience the sessions as boring?		
Third, we would like to ask you to reflect and rate the **messenger function** with which you could communicate with your health care professional.			
Messenger function/ health care professional	Was the messenger function overall helpful?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Did you experience the weekly messages sent by your health care professional as motivating?		
	Did you feel supported by your health care professional?		
Fourth, we would like to ask you to reflect on and rate the **daily diary**.			
Digital diary	Did you experience the daily diaries as burdensome?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Was it enjoyable to complete the digital diary?		
	Did you become more aware of your thoughts using the digital diary?		
	Did you become more aware of your behavior using the digital diary?		
	Did you become more aware of your emotions using the digital diary?		
Is there anything else you would like to add?			Free text

Appendix 4: Follow-up interviews with stakeholders

The stakeholders from the baseline assessment will be approached again. Furthermore, through snow-ball sampling, potential new stakeholders will be identified and also approached.

Stakeholder: developers

Process so far:

1. When reflecting on the overall development, evaluation, and implementation process, what went well?
2. When reflecting on the overall development, evaluation, and implementation process, what did not go well?
3. What factors supported the process of bringing this intervention into practice?
4. What factors hindered the process of bringing this intervention into practice?
5. What kind and how much resources were needed?
6. Did the process go as anticipated? If not, what was surprising?
7. How satisfied are you with the process so far?
8. What was most challenging during the implementation process?

Current use:

1. What are you currently doing to keep the intervention implemented?
2. Do you have sufficient resources? Please elaborate.
3. What issues are you currently facing? What solutions for these issues do you have?

Prospective adjustments:

1. What will the prospective maintenance and upkeep look like?
2. Who is responsible for that?
3. If there should be a change in employment, who ensures that the intervention remains updated?

Stakeholder: health care professionals

Process so far:

1. How often did you deliver the digital intervention?
2. What kind of benefits for yourself, your work, and/or your patients did you experience?
3. What kind of disadvantages for yourself, your work, and/or your patients did you experience?
4. What kind of support for delivering the intervention (e.g., training, technical guidance when issues arose) did you receive?
5. What hindered you in delivering the intervention?
6. What facilitated you to deliver the intervention?

Current use:

1. How satisfied are you with the intervention overall?
2. Which elements of the intervention need improvement?

Prospective adjustments:

1. Do you plan on delivering the intervention in the future? If not, please elaborate.
2. Would you recommend the intervention to a colleague?
3. What kind of problems do you anticipate in the future; and do you have potential solutions for them?

Stakeholder: health care managers

Process so far:

1. How would you describe your involvement in implementing the intervention?
2. How many resources were needed for the implementation?
3. Did the implementation process go as expected? If not, what was surprising?
4. How did you support your employees to deliver the intervention?

Current use:

1. How satisfied are you currently with the intervention (e.g., reflecting on use, content, promotion, required resources, (technical) issues)?
2. What aspects of the current implementation/ practical use need improvements?

Prospective adjustments:

1. Do you plan to offer the intervention in your region in the future? Please elaborate.
2. Would you recommend this intervention to another region/ other health care organizations? Please elaborate.
3. What kind of problems do you anticipate in the future?

Final question for all participants:

The main points I take away from this interview are [summary]. I appreciate the time you took for this interview. Who else should we talk about regarding the implementation of this intervention? Is there anything else you think would be helpful for me to know?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	28
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,28
Roles and	#5b	Name and contact information for the trial sponsor	1

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	6-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8, Fig. 2
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11,12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	11

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11, Fig 4, Fig 5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12, 14,15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Fig 7, Tab 2, Tab 3, and related sections
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, Fig 7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12, 13, 14, 21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11,12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for	21, Tabl. 1

		stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21, Fig 7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14, 21
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a (Tab 1)
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Described for each sub-study
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in	26, 28

		the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Tab 1, 19-21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-14, 21, 22,
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19, 20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	28
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21 (NEQ)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3, 27
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	27

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11-12, 27
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	27, 28
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	28
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	27
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	28
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	28
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

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Title: Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

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Development, evaluation, and implementation of a digital behavioural health treatment for chronic pain: Study protocol of the multi-phase DAHLIA project

ABSTRACT

Introduction: Chronic pain affects about 20-40% of the population and is linked to mental health outcomes and impaired daily functioning. Pharmacological interventions are commonly insufficient for producing relief and recovery of functioning. Behavioural health treatment is key to generate lasting benefits across outcome domains. However, most people with chronic pain cannot easily access evidence-based behavioural interventions. The overall aim of the DAHLIA project is to develop, evaluate, and implement a widely accessible digital behavioural health treatment to improve well-being in individuals with chronic pain.

Methods and analysis: The project follows the four phases of the mHealth Agile Development and Evaluation Lifecycle: (i) *development and pre-implementation surveillance* using focus groups, stakeholder interviews, and a business model; (ii) iterative *optimisation studies* applying single case experimental design (SCED) method in 4-6 iterations with n=10 patients and their health care professionals per iteration; (iii) a two-armed *clinical randomized controlled trial* enhanced with SCED (n=180 patients per arm); (iv) and interview-based *post-market surveillance*. Data analyses include multilevel modelling, cost-utility, and indicative analyses.

In October 2021, inter-sectorial partners are engaged and funding is secured for four years. The treatment content is compiled and the first treatment prototype is in preparation. Clinical sites in three Swedish regions are informed and recruitment for phase one will start in autumn 2021. To facilitate long-term impact and accessibility, the treatment will be integrated into a Swedish health platform (www.1177.se), which is used on a national level as a hub for advice, information, guidance, and e-services for health and healthcare.

Ethics and dissemination: The study plan has been reviewed and approved by Swedish Ethical Review Authorities. Findings will be actively disseminated through peer-reviewed journals, conference presentations, social media, and outreach activities for the wider public.

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Keywords: chronic pain; digital; behavioral health; protocol; intervention; single case experimental design; diary; implementation; randomized controlled trial

Strength and limitations of the study

- An agile, iterative, and data-driven process is ideally suited to navigate the complex challenges faced during the development, evaluation, and implementation of a digital behavioural treatment.
- Executing the project with a multi-disciplinary, inter-sectorial, and international team brings expertise and insights from complementary views together.
- Patients and different stakeholders, such as health care professionals, managers and digital developers, are involved in the project from the start, thus ensuring that individual needs to use and/ or promote the treatment can be met.
- The richness of methodologies combining traditional clinical trial evaluations on the population level, fine-graded momentary data collection on the individual level, explicit focus on cost-effectiveness, and determinants of implementation allows for a treatment evaluation from all angles.
- Due to the complexity and step-wise approach of this project, problems (e.g., delays in recruitment) in earlier phases might negatively affect the execution of later phases, thus calling for mitigation strategies to address potential delays.

INTRODUCTION

Chronic pain (CP) affects 20 to 40 % of the adult population[1]. Due to the COVID-19 pandemic, prevalence rates may increase further since CP can develop as a post-viral syndrome, from insufficient risk factor management during lockdown (e.g., inactivity, stress), or from accumulated unmet rehabilitation needs in overburdened rehab services[2 3]. Chronic pain impacts not only individuals' daily activities and overall quality of life, but also social and working contexts[4]. Thus, considerable direct and indirect health-related costs are associated with CP[5] and it represents a major issue for health care services and society at large.

A consensus exists regarding the importance of a holistic perspective integrating social, psychological, and biological factors of CP to accommodate this condition and its implications, and to guide interventions aimed at providing support[6]. Considering the typical complexity of CP, pharmacological treatment alone is usually insufficient in producing sustained relief and recovery of functioning[7]. Instead, management plans should target key behavioural, emotional, cognitive, and social factors in everyday functioning and quality of life[8].

To generate general and lasting benefits across outcome domains, person-centred, behavioural health interventions are critical. The necessity to match the pain treatment with specific needs of each patient has been the focus of discussion for the past decades[9]. Existing evidence supports methods that stem from cognitive behavioural frameworks[10], including the fear-avoidance model of pain and disability[11] and the psychological flexibility model, the model underlying acceptance and commitment therapy (ACT)[12 13]. In this type of treatment, the objective is to optimize effects by individualising treatment through evidence-based therapeutic procedures[14]. In clinical practice, face-to-face therapy dominates in effectively promoting well-being in patients with CP[7 15]. Modes of treatment delivery are evolving, however, as new models of care emerge.

Until now and despite the empirical support, interdisciplinary treatment, including behavioural interventions, are commonly not available or difficult to access for most individuals with CP[16 17]. Digital solutions aiming at promoting health, also known as eHealth, appear promising to bridge this gap as they appear cost-effective, can be tailored to individual needs, applied in everyday life, and used at the patients' convenience[18]. Particularly in light of the COVID-19 pandemic, distance approaches are gaining more attention in the management of CP[19]. However, the development and implementation of evidence-based digital interventions face challenges.

Innovative digital treatments require an accurate scientific evaluation to ensure clinical effectiveness. As it is still seen as the "gold standard", digital interventions for CP are often assessed through research-led randomized controlled trials (RCTs)[18 20 21]. However, a call for real-world and n-of-1 evaluations of efficacy and safety of individual assessment and treatment approaches is also being heard[22]. Compared to RCTs, n-of-1 study designs utilise repeated measurements to provide a more fine-graded, time- and context-sensitive picture of individual trajectories and pattern, thus allowing to evaluate effects at the within-person level[23].

Moreover, it has been shown that eHealth innovations purely originated from an academic context are rarely sustainably implemented into health care practice due to a lack of infrastructure, funding, and time[24]. To avoid research waste when creating new eHealth solutions, a strong user-centred design and focus on implementation is suggested[25 26]. A framework that combines the scientific rigor of traditional research methods with a rapid and iterative digital product development approach is needed. Then, the development of an evidence-based and user-friendly digital behavioural treatment is facilitated that is implementation-ready for applied health care.

The 'mHealth agile development and evaluation lifecycle' (Figure 1) is a framework created to promote the development of evidence-based, effective, and sustainable digital solutions[27]. This framework emphasises practicality, flexibility, rapid evaluation, and the possibility to adjust protocols to meet technological changes and insights that emerge as part of the process. Therefore, Wilson, et al. [27]'s framework will guide the present project. Additionally, the framework commissioned by the Medical Research Council and National Institute for Health Research for developing and evaluating complex interventions will inform the processes[26 28]. By applying these perspectives, the ultimate goal to develop, evaluate, and implement an effective and accessible behavioural treatment will be reached, thus improving health in individuals with CP across Sweden.

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Research objectives

The overall aim of this project is to develop, evaluate, and implement a digital behavioural health treatment to improve well-being in individuals with CP. The treatment will be integrated into a nationally available health care web-platform, which facilitates large scale evaluations, further development, dissemination, and long-term use in clinical practice across Sweden. Within the project, we will (i) develop a prototype of the digital treatment matching the needs of individuals with CP, using focus groups to assess user demands, and discuss possible

treatment structures and content, (ii) pilot the treatment in several iterations to evaluate its feasibility and acceptability, efficacy, and individual change processes by combining intensive (Single case experimental design (SCED)) and extensive methods; (iii) conduct a two-armed RCT enhanced with SCED to assess the clinical effectiveness, cost-effectiveness, and long-term effects compared to treatment as usual (TAU) on a between- and within-person level; and (iv) identify barriers and facilitators, and monitor the implementation process of the treatment, through a business model and stakeholder interviews.

METHODS AND ANALYSIS

Following the mHealth agile lifecycle[27], the DAHLIA (Acronym: Digital behaviourAl HeaLth for chronIc pAin) project consists of an identification phase 0 and four main phases: Development, optimisation, clinical trial evaluation, and post-market surveillance (See overview of the DAHLIA project in Figure 2). Phase 1 includes two studies: focus groups with patients and health care professionals (HCPs) to develop the treatment prototype (Study 1), and stakeholder interviews to prepare for the implementation process by creating a business model and identifying of barriers and facilitators (Study 2). Phase 2 (Optimisation) aims at optimising the treatment and entails 4-6 iterations to test and gradually improve the prototype in a data-driven manner (Study 3). Phase 3 consists of a large-scale clinical trial to evaluate the digital treatment in comparison to TAU in a two-armed RCT enhanced with SCED (Study 4). Finally in phase 4, a post-market surveillance is conducted using interviews with stakeholders from different Swedish regions, also presenting lessons-learned (Study 5). Each phase may inform and alter subsequent phases, in line with the agile approach. Project planning started in January 2020, data collection takes place since end of 2021, and the anticipated completion of the project is 2025. Details of the studies are described in the following paragraphs.

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Project Identification

Involvement of inter-sectorial partners and international collaborators

This project is a collaboration between academia, health care, and industry. The academic partners come from seven universities in four countries (Sweden, Belgium, the Netherlands, and the U.S.). The researchers contribute to the project with their scientific and clinical experience in developing and evaluating digital treatments, implementation sciences, cost-utilisation analysis, CP and related health issues, and the SCED method. The DAHLIA treatment will be designed within the www.1177.se platform in collaboration with health care developers and digital designers in Region Kalmar and supported by the industry partner Inera, who is responsible for the maintenance of the platform. The health care partners currently represent three of the 21 regions in Sweden, and include primary care centres in Region Kalmar, the Pain Clinic at Capio St. Göran Hospital, Region Stockholm, and the Rehabilitation centre in Region Örebro.

Personas as early user research

Personas are typical patient- or user-profiles illustrating the target group of a treatment or product and can be useful in the development of digital interventions to communicate user needs to the development team[29 30]. By giving a narrative and name, personas facilitate a more concrete discussion of patient needs, and to what extent the treatment might match those needs[31]. In the DAHLIA project, three distinct patient personas evolved in an online workshop and were edited over several months until the project partners were developed in a stepwise manner. The personas originated from patient interviews in a previous study[29], and discussed in an online workshop to assess the relevance for the DAHLIA project. The personas were then adjusted based on factors identified in research[32-34], other personas used in digital development projects region Kalmar, and input from the clinical researchers (RW, IF, KB, LMcC, SP). The personas were continuously edited over several months until the project partners agreed on the final versions. The categories for each persona are: (i) *personal information*, including employment, education, family, background and social context, social support, and living area; (ii) *patient pain profile*, including pain problem, consequences, pain behaviour, and attitude to treatment; (iii) *health care and treatment*, including contact with health care, comorbidities, and medicine; and (iv) *personal needs and goals*, specifically related to the treatment. Figure 3 illustrates one of the personas used in the DAHLIA project.

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During the early development of the DAHLIA treatment prototype (version 1.0), and prior to patient involvement, personas were used to ensure that relevant characteristics and contextual factors were considered[35]. The personas were presented at the start of treatment workshops to discuss, for instance, if and how the treatment content and structure fit the personas' characteristics and met their needs. Potential problems for a persona in relation to treatment elements were identified, resulting in further discussions and consensus-based adjustments.

Guiding principles in the development process of the DAHLIA treatment

When developing and evaluating complex interventions, one might either rely on already existing treatments or adapt these to the context, or chose to build a new treatment based on research evidence and theory of the problem[26]. In the present project, the latter was chosen for the following reasons. Firstly, the initiative for this project originated from the Swedish Region Kalmar identifying the need for a digital treatment for chronic pain patients, which resulted in a collaboration with the research team. Furthermore, contextual factors such as organisational

aspects, technical systems, and licencing agreements define the conditions for in this project. Finally, by creating a new treatment together with stakeholders (i.e., managers, regional developers, therapists, patients) and building on an existing digital structure (www.1177.se), the digital treatment can accommodate all identified requirements.

The following process was therefore followed to create the new treatment: Four three-hour online workshops took place between June 2020 and June 2021 to discuss the theoretical framework, conceptual model, and treatment components. Project partners presented their previous work related to behavioural treatment approaches and conferred on the guiding principles for the prototype development. The group reached consensus on using learning theory[36] as the theoretical framework for assessment and treatment. Furthermore, it was agreed that the fear-avoidance model[11] and psychological flexibility model[10 14 37] should be used as conceptual models for the DAHLIA treatment. Conclusively, the primary objective of the treatment is to increase resilience to pain and distress by promoting and training behavioural skills of relevance to the individual's functioning and well-being. Furthermore, a self-guided micro-learning format[38] was chosen, including brief and frequent sessions (micro-sessions), delivered digitally and accessible via a smartphone or desktop computer (www.1177.se; details see 'Stakeholder interviews (Study 2)).

Based on the theoretical framework and conceptual models, values-oriented exposure is considered to be the core procedure. Exposure implies the use of systematic contact with negative experience such as pain and feelings of emotional distress that promotes avoidance, in a way that reduces their adverse influence and produces more flexible, varied, and engaged patterns of behaviour. Essentially, the function of exposure is to reduce negatively reinforced behaviour focused on alleviating unwanted experiences, in favour of positively reinforced behaviour focused on approaching goals in daily life. Exposure is enabled by several behavioural processes, such as identifying life values and noticing own thoughts and emotions, known as defusion (OPEN), flexible attention to the present (AWARE), and the building of extended habits of engagement (ACTIVE)[10].

At the end of Phase 0, the following is envisioned: The DAHLIA treatment will run over six weeks and includes four self-guided micro-sessions per week. Each session will include a set of key elements (see Figure 4). The extent to which each of these elements will be included in the session can vary. It should be noted that due to the agile process, data-driven decisions might result in changes to this suggested structure.

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A chat function will enable patients to connect with their health care professionals (HCPs, see details section 'participants and recruitment') for additional guidance, asynchronous feedback, and further instructions. The role of the HCP is to encourage and motivate patients to remain in the program and intervene in case the individual situation worsens. At the start of the treatment, a specific weekday will be agreed on, during which the HCP replies to the patient's message. Potentially, the reply could also be a chat message, a phone call, or a video call. The contact with the HCP will take place once a week, with a minimum of six individual interactions between the HCP and patient. HCPs will receive training, a manual, and supervision to provide the treatment.

Furthermore, patients will be prompted to fill in a pre-scheduled digital diary twice a day. The digital diary has the purpose to enable self-monitoring for increased self-awareness of own behaviours, emotions, and routines, and thus enhanced orientation towards values and goals[39], and data collection to gain insight into the individual change processes and effects of the treatment in the context of the SCED. The full list of the daily diary items can be found in the 'Individual change processes' section.

After the main six-week intervention period, the treatment also entails booster-sessions delivered through the www.1177.se web-platform after two and four months. The participants get invited via SMS or emails to revisit the web-platform where they can engage in short behavioural exercises. Booster sessions are suggested in other contexts to support long-term behavioural changes[40] and reinforce patients learned coping strategies. Figure 5 summarises the DAHLIA treatment components.

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Participants and recruitment

In the DAHLIA project, participants will be people who either use or deliver the digital treatment, or who facilitate the treatment implementation. Thus, study participants are (i) patients with CP, (ii) HCPs treating patients with CP, (iii) health care managers, (iv) developers of the www.1177.se web platform, (v) other stakeholders identified in the process (e.g., policy makers, representatives from patient organisations). Health care professionals will be licensed psychologists or psychotherapists trained in cognitive behavioural therapy. Health care managers, developers, and other stakeholders need to be directly or indirectly connected with the treatment (e.g., decision-making on an organisational level; technical support etc.), but no other requirements apply.

Patients are eligible for inclusion if they: are older than 18 years of age; report a pain duration of ≥ 3 months; are able to communicate in Swedish; and have access to a computer, smartphone, and internet in their home environment. The exclusion criteria are: injury or illness that require immediate assessment and treatment, or is expected to progress significantly during the next 6 months; unstable medication (based on self-report: changes in medication during the past 3 months or expected within the next 3 months that could influence well-being and functioning substantially, such as opioids, anti-epileptic drugs, antidepressants); previous CBT treatment (including ACT) during the past 6 months; severe psychiatric co-morbidity (for instance, high risk of suicide). For study 1 (focus groups), only the exclusion criteria "severe psychiatric co-morbidity (for instance, high risk of suicide) will be applied as long-term health aspects are not expected to cause practical or ethical issues.

Information regarding the DAHLIA project and specific sub-studies will be provided to the clinics, including detailed instructions for eligibility. Regions recruiting patients are Kalmar, Stockholm, and Örebro. Additional regions have expressed interest in participating and recruitment might be extended. Patients will be approached via their health care centres and once patients have expressed interest in study participation, a formal eligibility check will be conducted. Potential participants will be screened at their respective clinic via a face-to-face or online meeting by their treating care professionals, including psychologist and pain physicians. A short interview will be conducted to confirm eligibility and ensure that none of the exclusion criteria are met. Informed consent is then obtained from all participants prior to enrolment in the study. Sociodemographic and pain-descriptive information will be collected from all participants including age, sex, level of education, occupation, location, level, and duration of pain, pain diagnosis (if applicable), and approaches to relief pain (e.g., medication, heat, physiotherapy).

Phase 1: Development

Focus groups (Study 1)

The aim of this study is to (i) identify the needs of patients and HCPs and (ii) match the treatment content to their needs. At least three focus groups will be conducted in autumn 2021, one with HCPs (i.e., psychologists/ psychotherapists trained in CBT) and two with patients. Per focus group, 6-8 participants will join[41]. An attempt will be made to recruit a heterogeneous group of patients in terms of such characteristics as pain condition, sex, and socio-economic background. The focus groups will be held online and take 90-120 minutes. A semi-structured

guide inspired by Gruters, et al. [42] will be followed. In addition to a general discussion around health and individual needs at the start, the focus group leader (i.e., research assistant and clinical coordinator) will ask participants to reflect on the design, set-up, content, and prospective feasibility of the DAHLIA treatment (details see Appendix 1). The group conversations will be audio- and video-taped. Field notes will provide further insight into relevant cues and observations.

The recordings will be transcribed verbatim and the data analysis will be performed by two independent researchers. The information for the patient groups and HCP group will be analysed separately. A combination of inductive and deductive content analysis will be used. First, the deductive approach will determine the themes emerging from the semi-structured guide: (i) health needs and determinants to live well with CP, and (ii) feedback on the DAHLIA treatment. Then, an indicative analysis will be performed to identify categories within the themes. The transcript will be read carefully and open coding will be used. A consensus meeting with a third researcher will be conducted as a final step. This approach has been described previously and appears valid to answer the research question[42 43]. The results from the focus groups will be integrated into the treatment prototype (version 2.0).

Stakeholder interviews (Study 2)

The aim of this study is to develop a preliminary business model for the digital behavioural treatment and identify barriers and facilitators of the prospective implementation process. An explicit focus on implementation and economic aspects early during treatment development has been recommended[44 45]. Particularly, business modelling in the context of eHealth technologies can help to create a set of success factors that will influence uptake, sustainability, and effectiveness[46]. A business model is part of the implementation strategy and also presented a foundation for conversations with users and stakeholders regarding the value and purpose of an eHealth technology[46]. Moreover, to build the knowledge base across the multiple studies and settings, the consolidated framework for implementation research (CFIR)[47] will be used. The CFIR has five major domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation. It is utilized as part of the analysis, as explained below.

As a first step, a preliminary version of the business model canvas was filled in by the research team (SB, SJ, RW, HC). As suggested by Osterwalder and Pigneur [48] 'a business model describes the rationale of how an organization creates, delivers, and captures value' (p.14) and demonstrates the logic of how a company or organisation intends to generate profit

for a service or product. The nine blocks of the business model cover four areas of a business: customers, offers, infrastructure, and financial viability. Figure 6 presents the template of the business model canvas and short definitions for each segment, including example aspects relevant for the DAHLIA project.

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In the present study, the treatment will be integrated into the national public health care website (www.1177.se), using the digital platform for behavioural health ('Stöd och Behandling'). This digital platform is free from commercial interests, maintained by Inera, which is owned by the county councils and regions. The general aim of this national website is to increase access to healthcare, strengthen the position of the patient, and contribute to improved public health. The website (www.1177.se) contains health care information, inspiration, and e-services. Each of the 21 regions in Sweden is responsible for coordinating activities and services provided on www.1177.se, which are conducted by own staff or contracted providers. Through a national network, providers and regions can cooperate and share licenses for services.

The business model will be discussed and refined as part of the stakeholder interviews. Currently identified stakeholders are software developers, HCPs, and health care managers. A semi-structured guide inspired by a previous study on eHealth implementation[49] will structure the interviews and gather information on gatekeepers, barriers, and facilitators for prospective dissemination and use. Questions are tailored to the different stakeholders and include, for example, '*If/how is the interventions' content updated?*', '*Who is responsible/ involved in the maintenance of the intervention?*', '*What could facilitate/ hinder the implementation process?*', and '*Do you think this intervention has the potential to become successful in your care facility?*'. The full guide can be seen in Appendix 2. As part of the agile process, the guide may be adjusted based on information collected during the interviews and tailored to additional stakeholders including policy makers or representatives from patient organisations.

A minimum of eight interviews will be conducted and snow-ball sampling will identify additional participants that can inform the process. Interviews will be conducted until data saturation is achieved and no new topics seem to emerge. The interviews will be executed online, take 60-90 min, and the conversation will be recorded. The qualitative data will be transcribed. Then, a qualitative thematic analysis will be performed[50] with statements related to potential barriers and facilitators. An inductive approach to group the information will applied in order to best scope the replies and map categories onto the CFIR domains[47] as previously described.

Finally, implementation strategies matching the emerging topics will be formulated[51]. Together with the business model, these two elements represent the implementation plan for the DAHLIA project. Findings from this study may furthermore influence the post- market surveillance (Study 5, see details below).

Phase 2: Optimisation (Study 3)

The aim of the optimisation phase is to pilot the treatment and improve it through an iterative data-driven process using small patient cohorts. The primary objective is to determine the treatment feasibility and acceptability, and the secondary objectives are to examine individual change processes, and efficacy across iterations on a group-level. The general procedures include the eligibility check, and four assessment periods: baseline, main treatment period, post-intervention, and 3- and 6-months follow-ups. Results from each iteration will be integrated into the subsequent iteration, then tested again, until satisfaction is reached and no new major issues seem to emerge. In the optimisation studies, different methodologies will be combined namely momentary data collection using digital diaries, retrospective questionnaires, and semi-structured interviews. The latter will be conducted by a research assistant, while the diaries and questionnaires will be completed online. Figure 7 provides an overview of the procedure in relation to the research objectives.

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In total, 40 to 60 patients and their treating HCPs will be included, with n=10 patient-HCP dyads each iteration. Four iterations have been seen as sufficient in a previous study to optimise a digital treatment[52], therefore, a minimum of four iterations will be conducted in the DAHLIA project. In accordance with the agile approach, additional iterations may be performed if deemed necessary. The rationales for the approaches and methodological details are described below.

Feasibility and acceptability

The mixed-method procedure to evaluate the feasibility and acceptability of the treatment includes self-reports, interviews, and technical data. Short self-reports will be collected after each micro- and booster-session. Specifically, patients will be asked to rate the micro-session on its usefulness, enjoyment, and comprehension ('*I experienced today's session as helpful/ enjoyable/ understandable.*', rated on a 7-point numerical scale from 1=not at all, to 7=very much).

Furthermore, at the end of the main intervention period, interviews will be conducted following a semi-structured guide to assess the participants' general experience and different treatment components, specifically the diary, micro-sessions, and chat function. Questions are first rated on a 7-point numeric scale and participants are then encouraged to elaborate on their response with further details, if possible. Examples of questions are '*Did the intervention hinder your daily occupation?*', '*Were the micro-sessions difficult or unclear?*', '*Did you experience the digital diary as burdensome?*', or '*Would you recommend the treatment to a friend?*' (details see Appendix 3). This guide is based on other feasibility studies[52 53] and tailored to the DAHLIA treatment components. The HCPs will also be interviewed using a guide that follows the same structure (i.e., numeric scale and open elaborations), but the specific questions will be informed by the focus groups (study 1).

Additionally, technical data generated from the www.1177.se website will be collected. These data include time and frequency of log-ins, duration of engagement with the treatment, and use of components. Technical data will be used to describe the overall use and adherence, and allows mediation analyses to determine the influence of engagement rates on treatment outcomes.

Data from the feasibility assessments will be analysed using descriptive statistics and qualitative synthesis to identify trends. The results will be presented reflecting the two core variables from the Technology Acceptance Model (TAM): 'Perceived Usefulness' and 'Perceived Ease of Use'[54]. After each iteration, the insight gathered will be fed back to the developers and integrated to gradually improve the feasibility and acceptability through data-driven adjustments of the treatment. Next to the qualitative self-report, quantitative ratings of the treatment components, and technical usage data, outcome measure to determine the feasibility and acceptability also include flow of participant recruitment and retention (i.e., number of participants that were approached, signed informed consent, and started/ completed the treatment), treatment-fidelity rates (i.e., post-treatment therapist self-report "*Was the treatment delivered as planned?"*), treatment compliance (i.e., indicated through log-in data, self-report from patients and therapists), and (reasons for) dropouts in each iteration.

Individual change processes

The optimisation studies implement a sequential replicated and randomized single case experimental design (SCED) to gain detailed insight into within-person behavioural changes, and to develop and test the DAHLIA intervention, which has been recommended in the context of CP[55]. In SCEDs, each case functions as their own control and changes are evaluated

comparing levels of the outcome variables across different phases (e.g., baseline phase 'A' and treatment phase 'B')[56]. The methodology aims to demonstrate cause-effect relationships between the treatment (independent variable) and the target behaviour (dependent variable)[57].

When planning a SCED study, the Risk of Bias in N-of-1 Trials (RoBiNT) Scale, a critical appraisal tool that evaluates the methodological quality of intervention studies using single-case methodology, can be followed as guidance [57 58]. The design decision made in the present study were based on this appraisal tool to ensure a scientifically robust approach. Table 1 provides details on the design elements.

Table 1. Methodological SCED approach of the DAHLIA study based on the RoBiNT Scale.

Item	RoBiNT Scale	SCED details, per optimisation iteration (*anticipated points)*
INTERNAL VALIDITY SUBSCALE		
1	Design	A **replicated randomised AB-design** with 10 x A-B (total of 20 phases), providing the opportunity to observe the experimental effect 10 times. (*2 points*)
2	Randomisation	The **start of the treatment phase** and therefore length of baseline phase will be determined **randomly** for each participant, with the baseline phase lasting between 5 to 10 days. This means that the treatment phase will start on any day between the 6th and 11th assignment. (*2 points*)
3	Sampling behaviour during all phases	The baseline phase will last at least 5 days, with twice daily sampling, resulting in **10 data points** or more **(phase A)** (assuming 100% compliance to diary). The treatment phase will run over 6 weeks, with twice daily sampling on at least 4 days per week (6 weeks x 4 days x twice daily sampling), resulting in **48 data points** or more **(phase B)** (assuming 100% compliance to diary). Even if the compliance rate should be lower, the amount of data points will lie >5 data points. *(2 points)*
4	Blinding of participants and HCP delivering the treatment	**Blinding** of the participant and practitioner is **not feasible** in the DAHLIA project. The behavioural treatment is delivered through a web-platform independently of the HCP; however, the HCP provides weekly, tailored support in addition to the online treatment. Neither the participant nor the HCP are blinded. (*0 points*).
5	Blinding (masking) of assessors	Patients complete self-report diaries and are **not blinded** to treatment phase, therefore, not independent of the therapy process. *(0 point)*
6	Inter-rater agreement	The measure of the target behaviour is a **subject measure** relying on **self-reports** from the digital diaries. (*0 points*)
7	Treatment adherence	The treatment is delivered through a **web-platform** following a standardized approach. Adherence to treatment (%) is calculated using **digital log-in data**. (*2 points*)
EXTERNAL VALIDITY AND INTERPRETATION SUBSCALE		
8	Baseline characteristics	A short interview by an HCP as part of the eligibility check will be conducted. Furthermore, a **case formulation** including information on age, sex, aetiology of CP, and severity of CP will be presented when presenting the results; this information will be based on a baseline assessment (online self-report). (*2 points*)
9	Setting	Information on the **general location** (Swedish region, hospital/ pain clinic) will be provided; however, the participant will engage with the online treatment in their everyday life, and therefore, it will not be possible to include details about the specific environment. (*1 point*)
10	Dependent variable (target behaviour)	Table 2 provides an overview of all diary items, which are scores on a 7-point Likert-Scale, except from the pain level item (0-100). **Process outcome measures**: 5 items on psychological (in)flexibility (see Table 2), 2 items on pain self-efficacy, 1 item on pain avoidance. **Primary outcome measures**: 1 item on pain level, 1 item on pain interference, 1 item on pain catastrophizing. **Secondary outcome**

		measures: 3 items on sleep, 2 items on affect, 1 item on stress, 1 item on fatigue. (*2 points*)
11	Independent variable (treatment)	A detailed description of the DAHLIA treatment is given above, including the **treatment content**, and **number, duration, and frequency of sessions**. (*2 points*)
12	Raw data record	**Ten cases** will be recorded (4-6 iteration with n=10 participants per iteration). Raw data will be presented with a data point for each diary entry. (*2 points*)
13	Data analysis	Data will be analysed and reported for each participant individually. **Structured visual analysis, effect size measures** and a **randomization test wrapper** for **multilevel models** will be applied. (*2 points*).
14	Replication	**Ten participants** will be included (per optimisation iteration). Across all iterations, data from n=40-60 participants will be available. (*2 points*)
15	Generalization	Patients will be heterogeneous in their characteristics. Furthermore, retrospective self-reports will be completed by each participant **pre-post treatment,** including two **FUs** (details see Table 3)**.** (*1 point*)

Under the condition that all choices can be executed as intended, the internal validity of this SCED study will reach 8/14 points, and the external validity will reach 14/16 points. The total interpretation score will be 22/30 points. This score indicates a moderate methodological rigour [59].

Target behaviours will be assessed via self-reports collected through a digital diary. This diary will be prompted through the SMS function of REDCap, or a smartphone application (e.g., www.mpath.io). Both data collection methods will be piloted with participants to ensure that the diary works reliably. Participants will be prompted to complete the diary twice daily (for details see Table 2). Proposed diary items are based on traditional questionnaires and diary studies[60], and were chosen as they assess relevant aspects in the context of CP. More specifically, sleep items are based on the Insomnia Severity Index[61], mood, stress, and fatigue items are adapted from previous digital diaries studies[60], psychological (in-) flexibility items (experiential avoidance/ acceptance; lack of contact with present moment/ present moment awareness; self as context/ context; (de-)fusion; (lack of contact with) values); inaction/ committed action) are based on Multidimensional psychological flexibility inventory[62], the pain level item is based on a Pain Rating Scale[63], pain catastrophizing item are based on the Pain Catastrophizing Scale[64], the pain avoidance item is based on the Psychological Inflexibility in Pain Scale[65], pain interference categories are based on the Brief Pain Inventory Scale[66], and pain self-efficacy items are is based on the Pain Self-Efficacy Questionnaire[67].

Generally, items should be short and easily to answer quickly[60]. The order of the items will be the same in each prompt to allow participants to get used to the questions, minimise time to complete the diary, and thus limit interference with their daily flow. The reliability, validity, and sensitivity of the items will be explored through pilot studies and as part of the optimisation studies using suggested statistics (e.g., P-technique factor analysis). Idiosyncratic

items might also be discussed with patients, in line with the agile approach, to improve validity and potentially patient engagement and ownership. Based on user-input, scientific evidence, and insight gained, diary items might be optimised and adjusted, and any adjustments made will be reported in prospective publications.

Table 2. Proposed daily diary items.

LUNCH/ EVENING DIARY			
Instructions (Availability to fill out: Lunch diary 12-14h, evening diary 18-20h)		LUNCH: Hello & welcome to your digital diary! Please reflect on last night and this morning, and rate the following statements. Self-reflections can help to understand your daily routines and needs better. Let's get started. EVENING: Welcome back to your daily diary. Please take 2-3 minutes to reflect on this afternoon.	
	Construct	Item	Answering scale
		Last night, …	
1	Sleep[1]	… I had problems falling asleep.	7-point numeric scale
2	Sleep[1]	… I had problems sleeping.	7-point numeric scale
3	Sleep[1]	… I woke up too early.	7-point numeric scale
		During the morning/ During the afternoon…	
4	Positive affect	… I felt happy, energetic, at ease, or enthusiastic.	7-point numeric scale
5	Negative affect	… I felt down, irritated, depressed, or hopeless.	7-point numeric scale
6	Stress	… I felt stressed.	7-point numeric scale
7	Fatigue	… I felt tired.	7-point numeric scale
8	Experiential avoidance/ Acceptance[2]	… I tried to distract myself when I felt unpleasant emotions. … I opened myself to all my feelings, the good and the bad.	7-point numeric scale
9	Lack of contact with present moment/ Present moment awareness[2]	… I did most things on "automatic" with little awareness of what I was doing. … I was attentive and aware of my emotions.	7-point numeric scale
10	Self as content/ Self as context[2]	… I criticized myself for having irrational or inappropriate emotions. … I tried to see the larger picture, even when I was down, depressed, or hopeless.	7-point numeric scale
11	Fusion/ Defusion[2]	… distressing thoughts tended to spin around in my mind like a broken record. … I was able to notice my thoughts and feelings without getting overwhelmed by them.	7-point numeric scale
12	Lack of contact with values/ Values[2]	… I didn't have time to focus on things that are important to me. … I tried to connect with what is truly important to me.	7-point numeric scale

13	Inaction / Committed action[2]	… negative feelings trapped me in inaction. … I didn't quit working towards what is important even if it was though.	7-point numeric scale
14	Pain level	… my overall pain level was:	0 (no pain) to 10 (worst pain imaginable)
15	Pain interference	… my pain interfered with my…	7-point numeric scale o General activities o Mood o Walking abilities o Normal work (including housework) o Relations with others o Enjoyment of life
16	Pain catastrophizing (rumination)	… I kept thinking about how much I hurt.	7-point numeric scale
17	Pain catastrophizing (magnification)	… I felt my pain overwhelmed me.	7-point numeric scale
18	Pain catastrophizing (Helplessness)	… I was afraid that my pain would get worse.	7-point numeric scale
19	Pain avoidance	… I avoided planning activities because of my pain.	7-point numeric scale
20	Pain self-efficacy	… I could do some form of housework/ paid/ unpaid work, despite the pain.	7-point numeric scale
21	Pain self-efficacy	… I could live a normal lifestyle, despite the pain.	7-point numeric scale
22	Open question	I would also like to share this about my morning/ afternoon:	Free text
23	Treatment interaction[3]	Today, I completed a treatment module.	o Yes. o No, because it was a 'module free day'. o No, but I will do it tonight. No, because: *free text*
	Instructions	LUNCH: Thank you & have a nice afternoon! EVENING: Thank you very much for taking the time to fill in your diary. Have a nice evening!	

7-point numerical scale ranges from 1: not at all, to 7: very much; alternatively, based on user input, a visual analogue slider scale from 0: not at all, to 100: very much might be used. Note: [1]Sleep items only as part of the morning questionnaire; [2]Both psychological flexibility and inflexibility items will be tested to determine with are more feasible and suitable to use; [3]Treatment interaction item only as part of the evening questionnaire.

In addition to the information in Table 1, the analysis will be executed as follows. Diary data have a multilevel structure because repeated measurements (level 1) are nested within individuals (level 2). First, structured visual analysis will be conducted for each individual separately following the four steps described in Kratochwill, et al. [56] to examine the within- and between-phase patterns in respect to the effects on level, trend, variability, immediacy, overlap, and consistency. Additionally, effect size measures will be calculated at the individual level using standardized mean difference and Tau-U, and at a group level using the between-case standardised mean difference[68]. Finally, to avoid making distributional and random sampling assumptions, the randomization test wrapper for multilevel models will be used to synthesise the data from the whole group of cases and evaluate treatment effects[69]. Scientific advisors of this project will provide expertise and support in the SCED analyses. Results will be presented following the RoBiNT scale and SCRIBE guideline[70].

Efficacy across iterations

In the optimization studies, efficacy will be determined using both intensive (SCED) as well as extensive methods (retrospective self-reports from baseline, post-intervention and FUs; see Figure 7). The diary and questionnaire data will be aggregated across all iterations, thus include data from 40-60 participants. This approach allows to investigate the generalisability of results of the SCED and evaluate treatment effects in applied research[71]. MultiSCED will be used for the SCED data [72].

The proposed retrospective questionnaires used can be separated into process, primary, and secondary outcome measures (see Table 3). Additionally, negative treatment effects may occur in the context of internet interventions, and therefore, need to be acknowledged and systematically assessed[73]. Negative treatment effects are here assessed post-treatment using the negative effects questionnaire (NEQ), a tool with reliable and valid psychometrics[74].

Descriptive statistics of the retrospective questionnaires will summarize demographics and pre-treatment clinical characteristics of the sample. To evaluate changes in treatment outcomes over time, linear multilevel modelling (MLM) will also be used. MLM accounts for repeated measures within subjects and can handle missing data, which will be addressed per variable. Using a random intercept model, time will be treated as a categorial variable and pre-

treatment values will be specified as the reference point. Therefore, results will be interpreted as a change from pre-treatment to post-treatment and, from pre-treatment to follow-up assessments. Anchor-based methods will be applied to determine clinical significance of changes in outcome measures[75]. Separate linear growth models[76] will be computed for each variable, while controlling for multiple testing. Significance level is set at Alpha *(α)*=0.05.

Table 3. Proposed outcome variables and tools used to assess efficacy using extensive methods.

Focus	Variables	Instrument	Supported psychometrics
Process outcome measures	Open/ Acceptance	Chronic Pain Acceptance Questionnaire (CPAQ)	Internal consistency and criterion validity (Swedish version) [77]
	Aware	5 items on,'acting with awareness' from the Five Facets Mindfulness Questionnaire (FFMQ)	Internal consistency, reliability, and construct validity (Swedish version) [78]
	Engaged/ committed actions	(i) Valuing questionnaire; (ii) Committed action questionnaire	(i) Internal consistency and construct validity (Swedish version) [79]; (ii) Proven validity and reliability (Swedish version) [80]
	Psychological flexibility	Swedish translation of the Multidimensional psychological flexibility inventory (MPFI)	Convergent and discriminant validities (English version) [62]
	Self-efficacy	General self-efficacy scale (S-GSE)	Reliable with high internal consistency (Swedish version) [81]
	Pain self-efficacy	Pain self-efficacy questionnaires (PSEQ-2)	Evidence for reliability and validity (English version) [67], translated into Swedish [82]
	Avoidance	Avoidance subscale of Psychological Inflexibility in Pain Scale (PIPS)	Internal validity and construct validity (Swedish version) [65]
Primary outcome measure	Catastrophizing	3-Item Daily Pain Catastrophizing Scale (PCS)	Recommended instrument to understand mechanims[64]
	(Dis)ability/ pain screening	Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ)	Clinically reliable and valid (Swedish version) [83]
	Work ability	Work ability index (WAI)	Validated (Swedish version) [84]
	Functioning	Brief pain inventory (BPI-SF)	Reliable and valid in multiple languages (including Swedish version) [66]
Secondary outcome measure	Well-being/ depression	Patient Health Questionnaire (PHQ-9)	Satisfactory content validity and sufficient reliability (Swedish version) [85]
	Perceived stress	Perceived Stress Scale (PSS)	Internal reliability and construct validity (Swedish version) [86]
	Sleep problems	Insomnia Severity Index (ISI)	Satisfactory factor structure, internal reliability, and concurrent validity (Swedish version) [61]

	Health-related quality of life	EQ-5D	Standardised measure of health-related quality of life develop by the EuroQol Group[87]

Phase 3: Clinical evaluation (Study 4)

Randomized controlled trial enhanced by SCED

To determine the clinical effectiveness of the DAHLIA treatment, a RCT enhanced with SCED will be conducted. While RCTs provide estimates of between-subject treatment responses, differences in average scores between groups, they are unable to indicate specific within-subject responses. Simons, et al. [88] apply a similar design and argue that SCED is a valuable addition to a traditional RCT design. One reason for this combined approach is that RCTs provide information on the population level, whereas SCEDs focus on the individual level. Furthermore, heterogeneity of treatment effects might remain undetected in a traditional RCT design[89]. Additionally, the need for large cohorts of patients for adequate sub-group analysis[90], and a lack of feasibility to reach certain patient groups[91] limits the insights from a traditional RCT. Applying SCED and multilevel modelling, even group results from small and distinct cohorts can be performed on a meta-analysis level[88].

Outcome measures will be the same as in the optimisation studies, including the diary items for the SCED (see Table 2), and retrospective questionnaires (see details Table 3; including NEQ post-treatment[74]). A priori computations based on a power of .95, four questionnaire assessment points and a medium effect size shows that 360 participants (180 in each arm) are sufficient to generate stable findings in the analyses of treatment effects. With an estimated attrition rate of 18%, this implies that 295 participants will provide post-treatment data, which is considered adequate also for moderator/ predictor and cost-effectiveness evaluations. However, outcome measures and calculated sample size will be updated and might be modified based on iterations in the prior phase.

Treatment arm randomization is conducted by a research assistant following the decision on study inclusion by the HCP and after the baseline assessment (sociodemographic information, questionnaires, A-phase of SCED) is completed. Participants are randomized to the treatment arm or treatment as usual (TAU) using a block randomization strategy to ascertain equal distributions across the arms. Randomization is conducted by a local project manager who is not involved in the screening or intervention. Next, participants undergo treatment; then all participants complete the post-intervention assessment (questionnaires and 5-day digital diary). Booster-sessions will be sent to the participants in the intervention group at 2- and 4-

months. Finally, at the 3- and 6-month follow-ups (FUs), all participants complete the questionnaires and 5-day digital diary period. In case participants decide to discontinue the study at any point in time, they might choose to provide a reason.

To examine changes in process, primary and secondary outcome measures (Table 3), linear mixed models will be conducted comparing the DAHLIA treatment to TAU. Analysis will be performed using group as a fixed between-person factor (two levels: DAHLIA treatment and TAU), and time as a fixed within-person variable (four levels: baseline, post-treatment, 3-month FU, 6-month FU). The linear mixed model will estimate fixed effects (regression slopes) for change in the intervals during (baseline to post-treatment assessment), and after (post-treatment to 3- and 6-month FU) the treatment period. The intervals will be entered as a categorical dummy variable (three levels). Potential confounders will be added to the model as covariates (i.e., age, gender, pain diagnosis, pain duration). Data will be analysed with the support of a statistician and using the latest version of SPSS. Mean change will be reported and test of significance will be two-sided with a set alpha level of 0.05.

Health economic evaluation

A short-term health economic evaluation will compare the DAHLIA treatment and the TAU at the primary endpoint (post-treatment). Additionally, an equivalent long-term evaluation will be performed at the end of the FU period using cumulative data collected up to that assessment point. Costs in both trial arms will be estimated from a societal perspective for each participant in the trial based on resource items and associated relevant unit costs. The use of societal resources comprises information on the use of resources related to healthcare contacts and medication (medical records and register data), and productivity losses related to absence from work (the LISA database). Costs to deliver the digital intervention will be estimated based on, for instance, HCPs' time spent on treatment. Total costs will be aggregated by trial arm.

The self-report tool EQ5D[87] will be completed by the participants at pre-, post-treatment and FUs and used to measure changes in health-related quality of life (HRQoL), to calculate quality adjusted life years (QALYs). Total QALY gains for participants over the trial will be estimated using the area under the curve method[92]. Cost data and QALYs will be analysed using generalized linear models to account for non-normal distributions[93]. Data will be analysed controlling for the influence of covariates, and by adjusting for baseline data. Cost-utility analysis (CUA) will be conducted with QALYs gained as primary outcome, comparing incremental costs with incremental changes in QALYs for digital treatment and TAU. Results will be presented as an incremental cost-effectiveness ratio (ICER), representing the ratio

between the difference in costs and the difference in QALY gained between the digital treatment and TAU. Incremental cost-effectiveness ratio will be expressed as cost per additional QALY, which is the most common approach in health economics[94]. Uncertainty around the cost and outcome data will be explored and presented on cost-effectiveness plans, representing the distribution of the cost and outcome differences between both conditions. The probability of digital treatment being cost-effective compared to TAU will be presented across a range of price values a decision-maker would be willing to pay, represented by a cost-effectiveness acceptability curve[95].

Phase 4: Post-market surveillance (Study 5)

Similar to the development phase (Study 2), interviews with stakeholders will be conducted, recorded, and transcribed. The stakeholders participating in study 2 will be approached, along with additional key stakeholders identified during the implementation process. Appendix 4 provides the full overview of the interview questions. Questions reflect on the process so far (e.g., '*What kind and how many resources were needed to bring this intervention into practice?*'), on the current status (e.g., '*What issues are you currently facing?'*), and prospective adjustments (e.g., *'What will the prospective maintenance and upkeep look like?'*). These questions are preliminary and may be adjusted based on findings of Phase 1-3. Even though the www.1177.se website is free for the end users (i.e., patients and HCPs), special attention may also be paid to financing, as a lack thereof can be a barrier for long-term implementation of eHealth interventions[96].

The qualitative data will be analysed following the same process as that used in Phase 1. Specifically, an inductive analysis to identify and summarise themes will be performed, and information will be mapped onto the domains of the CFIR[47]. The implementation strategy and plan will be reviewed, and lessons-learned will be presented to inform prospective implementation studies.

Patient and public involvement

This is a study protocol and due to ethical and practical reasons, no patients were directly involved in the project yet. However, the Personas originated from interviews with patients, as described above, and patients and other stakeholders will be involved in all planned phases of the DAHLIA project. Dissemination to patients and the public is described in more detail the section 'Ethics and Dissemination'.

DISCUSSION

Chronic pain is a huge public health problem, in suffering, disability, and costs for individuals and society. Widely accessible and sustainable behavioural treatment options could help to address this problem. An agile and user-centred development integrating a data-driven decision-making process and scientific evaluation of effects is essential to produce an evidence-based intervention of this type for individuals with CP. To our knowledge, this is the first project utilizing the mHealth agile development framework[27] to systematically build a digital behavioural treatment within a nationally used health care hub. The purpose of this project is to improve the standard of care for individuals with CP by applying the innovative development framework, thus providing an accessible, user-friendly, and empirically supported behavioural treatment to maintain or improve resilience, functioning, and well-being in this population.

Strengths include (i) the execution of the project by a multi-disciplinary, inter-sectorial, and international research team, (ii) the overall agile, iterative, and data-driven process, and (iii) the involvement of patients and different stakeholders early and throughout the development. Furthermore, (iv) the richness of methodologies using mixed methods, combining a traditional clinical trial evaluation on the population level (RCT), fine-graded data collection (SCED) on the level of the individual, and (v) an explicit focus on cost-effectiveness and determinants of implementation will be highlighted. The project is (vi) based on innovative strategies in the field of eHealth and digital treatments, and (vii) key gatekeepers such as regional leaders support the initiative. The DAHLIA approach is also in line with the widely used MRC/NIHR framework by considering contextual and economical aspects, building on theory, involving stakeholders, and refining the intervention[26 45].

Due to the ambitious and multifaceted nature of the project, several inherent challenges and risks should also be acknowledged. In case a sub-study should be delayed, e.g., due to recruitment difficulties or technical development issues, this delay could affect the whole project. Subsequently, adjustments following the agile approach could be discussed to balance the practical feasibility of executing the study and limiting the impact on its robustness.

Furthermore, the multidisciplinary, inter-sectorial approach is certainly a strength of the DAHLIA project, however, it might also have inherent challenges. For example, interests of stakeholders might differ, which needs to be considered and addressed. Here, communication is key, but compromises might be needed to ascertain satisfactory benefits for all parties involved.

Regarding the DAHLIA treatment itself, a high level of patient engagement (e.g., four micro-session per week combined with frequent diary assessments) will be required. These demands might be perceived as burdensome by some individual. However, contact with HCPs will support participants' motivation and engagement. Furthermore, the focus groups and optimisation studies will provide insight into the perceived intensity, thus feasibility of the intervention set-up, and the agile process allows to adjust it accordingly. Specially, tailoring of the length of the micro-sessions and frequency of diary prompts will be explored.

Furthermore, the DAHLIA treatment may not be suitable for all people with CP and the question of "what fits for whom" will be continuously discussed. The website (www.1177.se) is a national health care hub in Sweden, but research shows that older adults, people with cognitive problems, or disabilities are less likely to use technologies[97], which could result in a bias in recruitment and usability. To improve inclusivity, the possibility to provide additional training for certain populations, such as older adults[98], will be explored. An additional issue is that the project is currently executed in Swedish, which excludes people with limited proficiency in Swedish. Therefore, translation into other languages and further cultural adaptations will be considered.

The DALHIA treatment may have the potential to become a widely implemented first line of treatment. However, some CP groups will likely benefit from an alternative treatment format (e.g., face-to-face), or complementary interventions. Thus, additional studies may explore if and how physiotherapists, general practitioners, or occupational therapists can deliver the DAHLIA treatment.

Finally, the treatment could prospectively be scaled and adjusted for other groups of patients with CP, e.g., children and adolescents, people with disabilities, and/or other medical conditions such as individuals with severe mental or physical co-morbidities. In addition, support offered as part of the DAHLIA treatment can be extended to significant others and family members of people living with CP. Thus, by using an agile development approach, the DAHLIA project might grow to support the heterogeneous group of individuals with CP and their complex health needs.

Ethics and Dissemination

The study received approval from Swedish ethical review authorities (Dnr 2021-02437). All participants will receive a detailed patient information sheet, have one week time to consider participation, and sign informed consent prior to participation. Each study participant will receive a unique study code to ensure anonymity and confidentiality. Data will be stored in accordance with Swedish regulations on secure servers at Karolinska Institutet.

The project is announced on the Karolinska Institutet website (Rikard Wicksell's research group), and on social media, primarily twitter. The general outline of the project has been presented at online conferences. Next to the study protocol paper, the intention is to publish a number of peer-reviewed manuscripts, in which any protocol modifications will also be communicated. The results will be presented at (inter-)national conferences and networking events. Popular science articles, podcasts, radio interviews, and animated videos are additionally planned to disseminate the results to the wider public.

Author's contribution

SB, SJ, KB, LMcC, IFl, SP, and RW were involved in the conception and design of this project. RW acquired and received the funding. HC provided specific input on the topic of implementation, IFe contributed with her expertise on health economy, and LS, PO, and JV added valuable knowledge on the single-case experimental design aspects of the project. SB drafted the manuscript, and all authors revised the manuscript and checked the intellectual content. All authors gave final approval and agree to be accountable for all aspects of the work.

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Completing interests

None declared.

Access to data and protocol details

Only the research team will have access to the raw data and participant code. Anonymised data will be made available as part of publications, whenever possible. Researchers from other universities may request to receive access to other information (e.g., informed consent sheets, data management plan).

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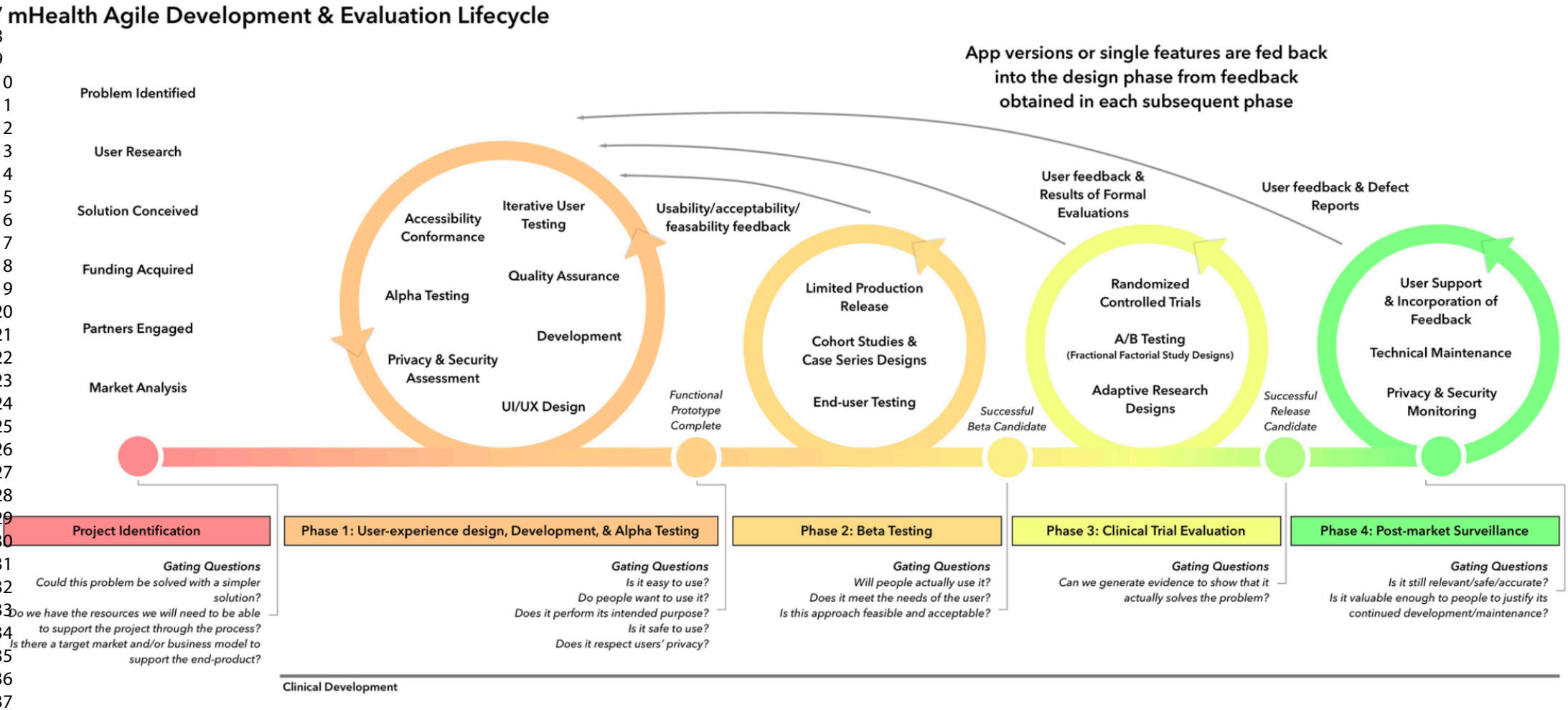
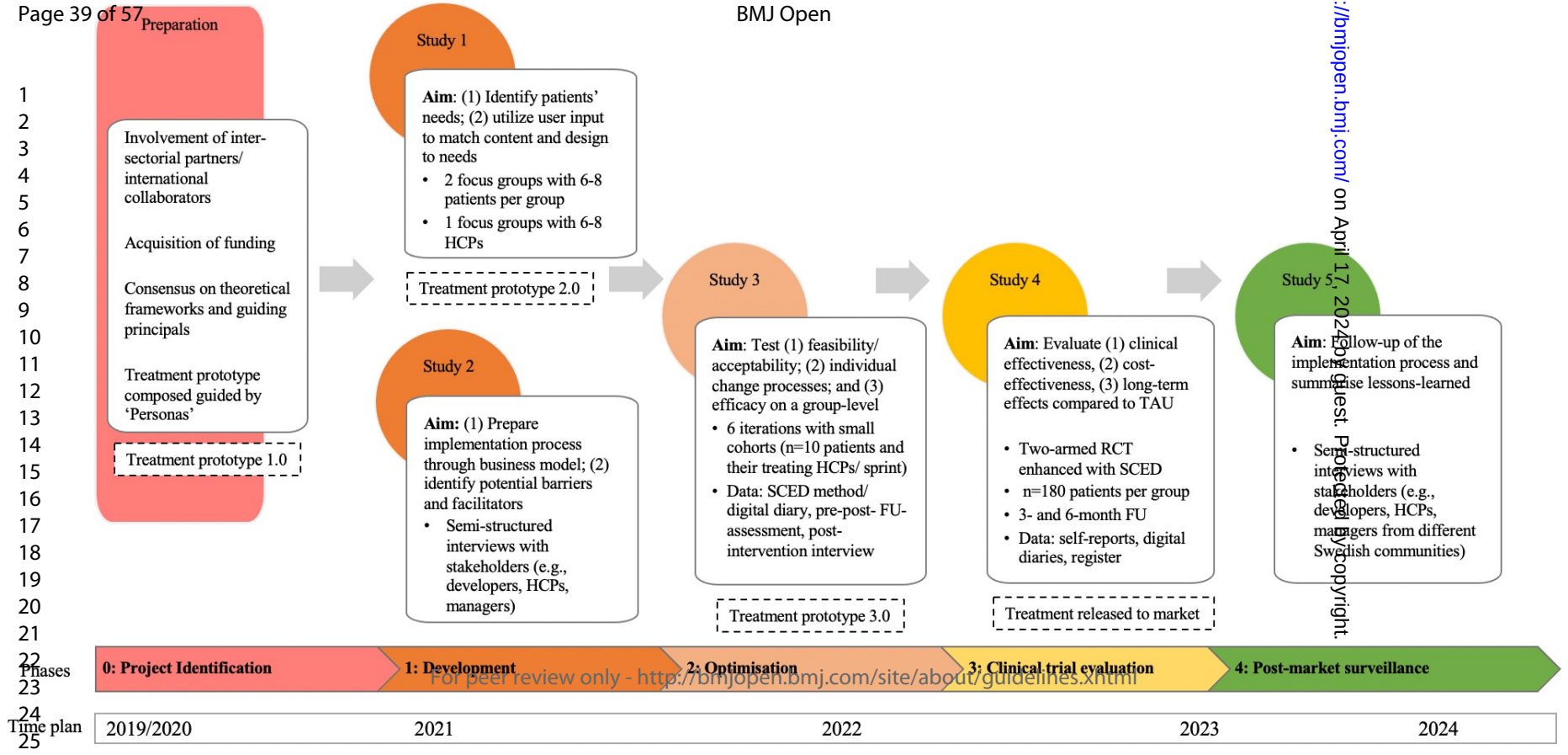
Figure legend

- Figure 1. mHealth Agile Development & Evaluation Lifecycle (Wilson et al., 2018).
- Figure 2. DAHLIA project overview including highlights of each study and time plan. HCP= health care professional; SCED= single case experimental design; TAU= treatment as usual; RCT= randomised controlled trial; FU= follow-up.
- Figure 3. Example of a DAHLIA Persona with chronic pain.
- Figure 4. DAHLIA treatment micro-session elements. HCP= health care professional. Note: The name "DAHLIA treatment" is mainly for academic settings; in the www.1177.se web-platform, a more intuitive treatment name will be chosen.
- Figure 5. The DAHLIA treatment components.
- Figure 6. Template of business model canvas (based on Osterwald & Pigneur, 2010). Grey boxes: Example aspects of the DAHLIA business model; the final model will be a result of the stakeholder interviews.
- Figure 7. General overview of the optimisation studies and specific procedure in each iteration. SCED= Single-case experimental design. FU= Follow-up. HCP= Health care professional.





AIDA
18 yrs. old

Employment:
N/A, high school student.

Education:
Primary school
Upper secondary school (ongoing).

Family:
Mother and father with foreign background, four younger siblings.

Background and social context:
Born in Pakistan, moved to Sweden when she was four years old. Leads an active life with hobbies and after-school activities. Frequently works out at the gym, pushing herself.
Aida has many friends and it is important for her to be popular. She is ambitious in school with high demands from her home-environment. She often feels stressed and does not think she is performing as expected. Aida carries a lot of responsibility at home. She has a high level of technological literacy and uses her smartphone for everything.

Social support (related to pain): Despite her family and many friends, Aida feels lonely with her pain. She feels that no one understands or takes it seriously. Her parents are constantly nagging, stressing that the health services should be able to help. Aida finds it strange that she is in so much pain even though she works out a lot and does everything she is "supposed to". Despite her efforts, there are days when she is paralyzed by pain and the feeling of being under pressure.

City/ countryside: Apartment in large city.

PATIENT PAIN PROFILE

Pain problems:
- No clinical diagnosis.
- Recurrent headaches.
- Tensions in shoulders and neck.
- Stomach ache.

Consequences:
- Difficult to concentrate when in pain.
- Although Aida really wants to go to school, she is increasingly staying at home as she cannot manage.
- "Yoyo behaviour" – some days she keeps active and works out, while other days she is completely exhausted.

Pain behaviour:
- Wants a "quick fix" and prefers to continue pushing rather than taking a step back and think.
- Exercises to get in better shape to handle the pain.
- Keeps on going to alleviate anxiety despite feeling the need to rest.

Attitude to treatment:
- Wants to be a "good patient" and do everything she is told (and then some).
- Happy to visit doctors but does not see herself as someone who needs mental health support or treatment.

HEALTH CARE & TREATMENT

Contact with health care:
- Undertaken eye test and has gone through various investigations for the recurrent headaches.
- Visited dentist focusing on temporomandibular joints (jaw region).
- Sought care due to various somatic disorders (head, neck, stomach).

Comorbidities:
- Stress
- Anxiety
- Sleeping difficulties

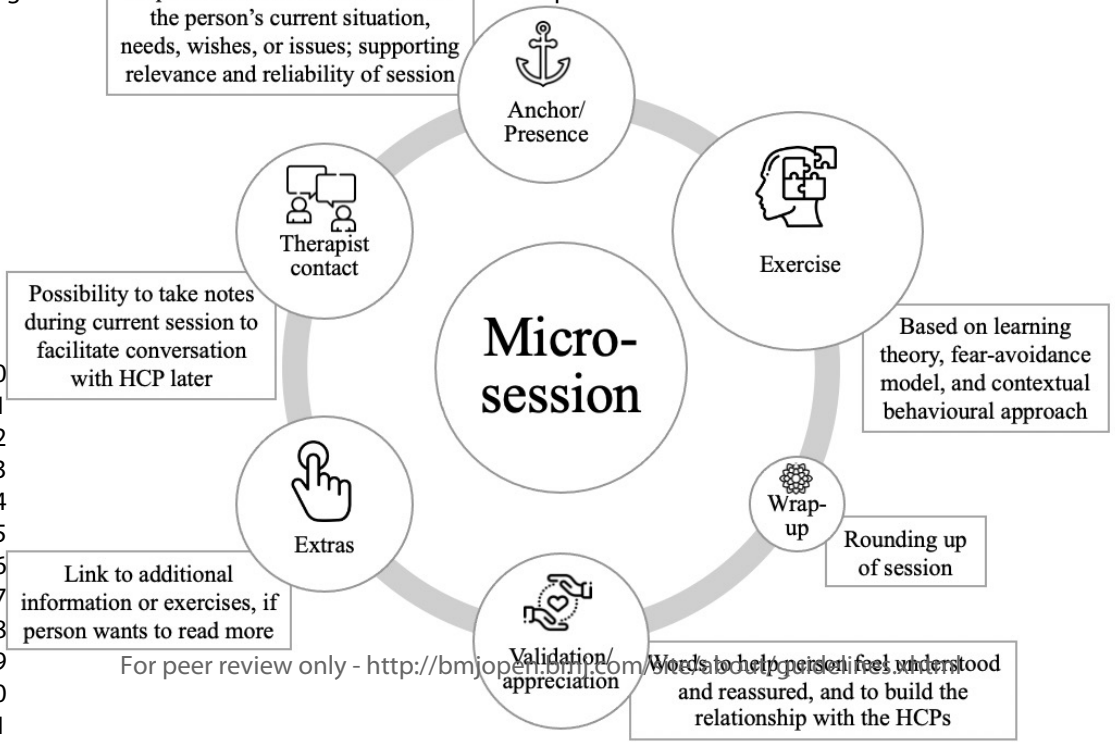
Medicine:
- Pain killers

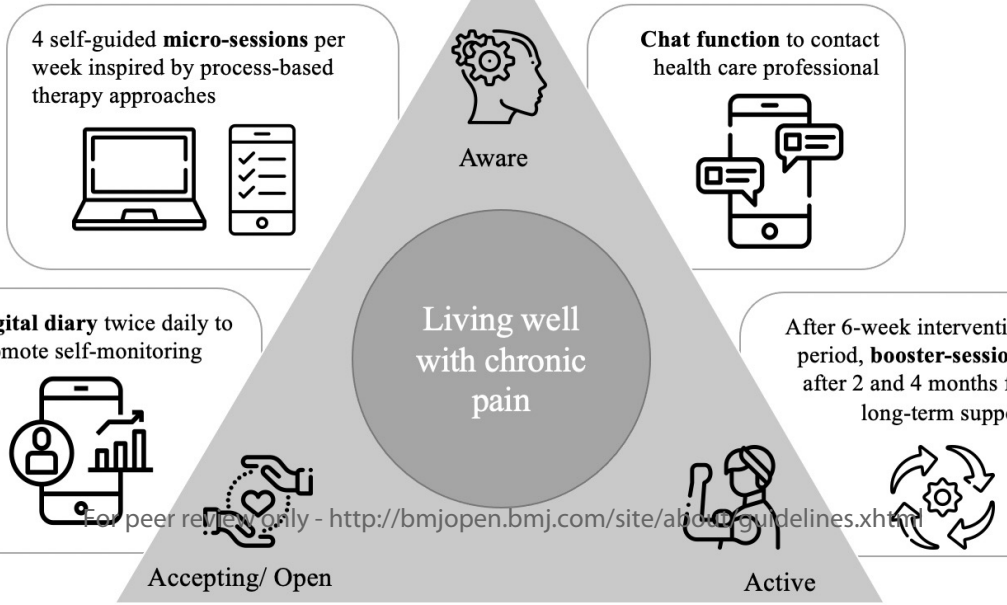
PERSONAL NEEDS & GOALS

Treatment needs:
- Wants to be independent and take an active part in her treatment. Needs to feel that she can influence her situation.
- Wants to follow/have an overview of own progress.

Goals:
- To live an active and productive life without pain.
- To learn how to maintain a balanced lifestyle without guilt when resting.

Figure 3. Example of a DAHLIA Persona with chronic pain.





Key Partners

(8) Describes the network of suppliers and partners that make the business model work, e.g.:

- Optimization and economy of scale
- Reduction of risks and uncertainty
- Acquisition of particular resources and activities

➢ *Soft ware partners*
➢ *Health care*

Key Activities

(7) Describes the most important things a company must do to make its business model work, e.g.:

- Production
- Problem solving
- Platform/ Network

➢ *Developing content*
➢ *IT support and development*

Key Resources

(6) Describes the most important assets required to make a business model work, e.g.:

- Physical
- Intellectual
- Human
- Financial

➢ *IT upkeep*

Value Propositions

(2) Describes the bundle of products and services that create value for a specific customer segment, e.g.:

- Newness
- Performance
- Customisation
- "Getting the job done" Design
- Brand/Status
- Price
- Cost reduction
- Risk reduction
- Accessibility
- Convenience/Usability

➢ *Usable, effective, evidence-based treatment*
➢ *Accessible and free for patients*

Customer Relationships

(4) Describes the types of relationships a company establishes with specific customer segments, e.g.:

- Personal assistance
- Self-service
- Automated services
- Communities
- Co-creation

➢ *Personal assistance*
➢ *Co-creation*

Channels

(3) Describes how a company communicates with and reaches its customer segments to deliver a value proposition (direct/indirect), e.g.:

- Sales Force
- Web sale
- Own stores
- Partner stores
- Wholesaler

➢ *Information on 1177*

Customer Segments

(1) Defines the different groups of people or organizations an enterprise aims to reach and serve. e.g.:

- Mass market
- Niche market
- Segmented
- Diversified
- Multi-sided platforms (multi-sided markets)

➢ *Patients with chronic pain*
➢ *Health care organisations*

Cost Structure

(9) Describes all costs incurred to operate a business model, e.g.:

- Cost-driven
- Value-driven
- Fixed costs
- Variable costs
- Economies of scale
- Economies of scope

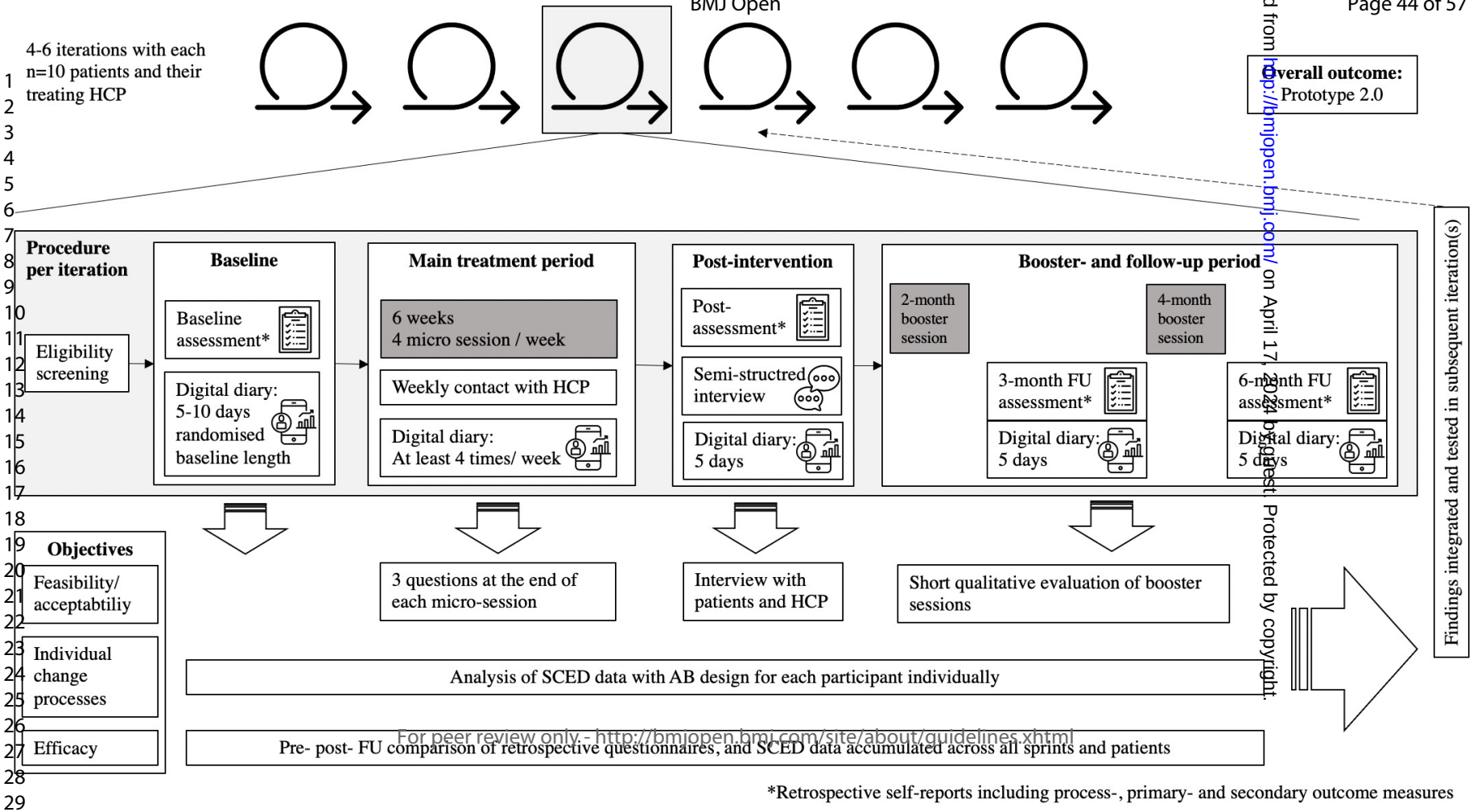
➢ *Platform and content development/ upkeep*

Revenue Streams

(5) Represents the cash a company generates from each customer segment (costs must be subtracted from revenues to create earnings), e.g.:

- Asset sale
- Usage fee
- Subscription fees
- Lending/ renting/ leasing
- Licensing
- Brokerage fees
- Advertising

➢ *Free for patients*
➢ *Licensing for regions*



*Retrospective self-reports including process-, primary- and secondary outcome measures

Appendix 1:

Semi-structured focus group guide
6-8 participants per focus group

FOR PATIENTS (*2 focus groups; heterogenic in terms of age, gender, pain condition, pain history, etc.*):

1. General introduction, informed consent, collect sociodemographic details (10min.)
2. Short introduction round (10min.)

3. Core question 1: **Living with chronic pain** (30min.)
   It would be amazing to have a magic pill to just take all the pain away, so you could live without it. But unfortunately, we don't have that magic pill. Instead, we want to help you and other people with chronic pain to find a way to live well with the pain. (*Presentation on definition of health (Huber et al., 2011): ability to adapt and self-manage physical, mental and social aspects of health, and examples*).
   a. Based on this definition of health, can you describe your own health needs? Which (aspects of your) needs are currently unmet?
   b. In which moments of your life do you feel happiest/ most engaged/ most satisfied?
   c. What helps you to engage in these 'happy moments'?
   d. What are barriers to engage in these 'happy moments'?
   e. What would you need to engage in these moments more often?

BREAK 10 Min.

4. Core question 2: **The DAHLIA treatment**
   Presentation of the proposed treatment, aim, design, theoretical background, and examples of exercises (10min); following a discussion (30min)
   a. What do you think of this treatment? What do you like, what do you dislike? (Please reflect on (1) design, (2) set-up, (3) content, (4) other (e.g., terminology: treatment, intervention, program; patient vs. person))
   b. How feasible would it be to do this treatment?
   c. Do you think this treatment meets you needs?
   d. Is there anything else you would like to add?

FOR HEALTH CARE PROFESSIONALS (*1 focus group, psychologists/ psychotherapists trained in cognitive-behavioural therapy; heterogenic in terms of age, gender, cultural background)*:

1. General introduction, informed consent, collect sociodemographic details (10min.)
2. Short introduction round (10min.)

3. Core question 1: **Supporting people with chronic pain** (30min)
   People with chronic pain have complex needs and treatment has to meet these needs. We are interested in your experiences in what works well to improve

the overall health and well-being of patients with chronic pain. (*Presentation on definition of health (Huber et al., 2011): ability to adapt and self-manage physical, mental and social aspects of health, and examples*).

a. Which (aspects of) your patient's health needs are unmet? What is needed to support chronic pain patients in the best way?
b. What barriers and facilitators to deliver support to chronic pain patients do you face? Please reflect on elements related to the patient, treatment options, and the health care in general.

BREAK 10 Min.

4. Core question 2: **The DAHLIA treatment**

Presentation of the proposed treatment, aim, design, theoretical background, and examples of exercises (10min); following a discussion (30min)

a. What do you think of this treatment? What do you like, what do you not like? (Please reflect on (1) design, (2) set-up, (3) content, (4) other (e.g., terminology: treatment, intervention, program; patient vs. person))
b. How feasible would it be for you to deliver this treatment?
c. Does the treatment meet the needs of the patients with chronic pain?
d. Is there anything else you would like to add?

Appendix 2. Baseline interviews with stakeholders

Various stakeholders will be approached, including developers, health care professionals, and managers. Through snow-ball sampling, other potential stakeholders will be identified and approached (e.g., individuals from policy making or municipality representatives).

Stakeholder: developers

I. General

Theme: Experience and development of digital interventions within the 1177 web-platform

1. What is your job description and what are your responsibilities?
2. How is the 1177 web-platform structured, in the region of Kalmar and Sweden?
3. How many digital interventions are available within 1177 in your region?
4. Who developed these interventions; who integrated them in the platform?
5. How are these interventions financed?
6. Who is responsible/ involved in the maintenance of the interventions?
7. If/ how is the interventions' content updated?
8. If/ how are the interventions used and promoted in health care?
9. If/how is user satisfaction with interventions evaluated?
10. If/how do collaborations with other regions look like?

II. Specifics (focus about DAHLIA project)

1. How would you describe the anticipated implementation process of this intervention?
2. What is needed to support the implementation process?
3. What could facilitate the implementation process?
4. What could hinder the implementation process?
5. What are benefits for you/ the 1177 web-platform when developing this intervention?
6. Are you enthusiastic about this intervention, if so, why?
7. Do you think this intervention has the potential to be successful in your region, and Sweden?
8. Where would you like to see this intervention in 5 years?

Stakeholder: health care professionals

I. General

Theme: Experience and use of digital interventions with patients

1. What is your job description and what are your responsibilities?
2. What is your experience in delivering interventions via the 1177 web-platform?
3. If/when there is a new intervention available in the 1177 web-platform, how do you usually hear about it?
4. What makes it attractive to deliver such an intervention?
5. What resources are needed for you to deliver these interventions (e.g., time, knowledge, managerial support)?
6. What hinders you to deliver these interventions?

II. Specifics (short introduction of DAHLIA project and details of digital behavioral health treatment for people with chronic pain)

1. Do you think there is a need for this intervention? Please elaborate.
2. What benefits for yourself/your work do you anticipate through this intervention?
3. What benefits for your patients do you anticipate?
4. What disadvantages or problems do you anticipate when delivering this intervention?

5. What disadvantages or problems for your patients when receiving the intervention do you anticipate?
6. What would hinder you to deliver this intervention?
7. What would facilitate you to deliver this intervention?
8. Are you enthusiastic about this intervention, if so, why?
9. Do you think this intervention has the potential to be successful in your care facility?
10. Where would you like to see this intervention in 5 years?

Stakeholder: health care managers

Theme: Experience and promotion of digital interventions in care facility

1. What is your job description and what are your responsibilities?
2. How many digital interventions are currently offered by the 1177 web-platform (and used) in your care facility?
3. What is needed to implement an intervention from the 1177 web-platform in your care facility?
4. How do digital interventions get financed in your care facility?
5. What is your involvement in digital interventions in your care facility? How do you support the use of digital interventions?
6. What hinders the implementation of these interventions, in your eyes?
7. If/ how does your care facility collaborate with other regions regarding digital interventions from the 1177 web-platform?

II. Specifics (short introduction of DAHLIA project and details of digital behavioral health treatment for people with chronic pain)

1. Do you think there is a need for this intervention? Please elaborate.
2. What kind of benefits do you anticipate for employees through this intervention?
3. What kind of benefits do you anticipate for patients through this intervention?
4. What kind of disadvantages or problems for employees do you anticipate through this intervention?
5. What kind of disadvantages or problems for patients do you anticipate through this intervention?
6. Are you enthusiastic about this intervention, and if so, why?
7. How will you promote this intervention in your care facility?
8. Do you think this intervention has the potential to be successful in your care facility?
9. Where would you like to see this intervention in 5 years?

Final question for all participants:

The main points I take away from this interview are [summary]. I appreciate the time you took for this interview. Who else should we talk about regarding the implementation of this intervention? Is there anything else you think would be helpful for me to know?

Appendix 3. Feasibility/ acceptability; questionnaire.

Table 1. Semi-structured interview guide to evaluate the general feasibility and acceptability of the treatment.

Topics	**Questions**	**Answering scores**	**Open question**
You recently completed the 6-week treatment. For us, it is very important to hear how you experienced it so that we can improve the content, design, and other aspects further. Thank you for taking the time to provide us with your input. First, we would like to ask you to reflect on and rate the **past weeks and treatment** in general.			
General	Were the past 6 weeks usual weeks for you?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Did special events occur?		
	Were you able to read the text in the treatment well?		
	Was the text understandable?		
	Did the intervention hinder your daily occupations?		
	Did technical issues occur?		
	Would you recommend this treatment to a friend?		
Secondly, we would like to ask you to reflect on and rate the four short **sessions** that were offered each week.			
Micro-sessions	Did you like doing the sessions?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Were the sessions difficult or unclear?		
	Did you experience the sessions as helpful?		
	Have the sessions influenced your behavior?		
	Have the sessions influenced your emotions?		
	Have the sessions influenced your thoughts?		
	Did you experience the sessions as time consuming?		
	Did you experience the sessions as boring?		
Third, we would like to ask you to reflect and rate the **messenger function** with which you could communicate with your health care professional.			
Messenger function/ health care professional	Was the messenger function overall helpful?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Did you experience the weekly messages sent by your health care professional as motivating?		
	Did you feel supported by your health care professional?		
Fourth, we would like to ask you to reflect on and rate the **daily diary**.			
Digital diary	Did you experience the daily diaries as burdensome?	7-points Likert-scale: from 1='not at all' to 7= 'very much'	Please elaborate if possible
	Was it enjoyable to complete the digital diary?		
	Did you become more aware of your thoughts using the digital diary?		
	Did you become more aware of your behavior using the digital diary?		
	Did you become more aware of your emotions using the digital diary?		
Is there anything else you would like to add?			Free text

Appendix 4: Follow-up interviews with stakeholders

The stakeholders from the baseline assessment will be approached again. Furthermore, through snow-ball sampling, potential new stakeholders will be identified and also approached.

Stakeholder: developers

Process so far:

1. When reflecting on the overall development, evaluation, and implementation process, what went well?
2. When reflecting on the overall development, evaluation, and implementation process, what did not go well?
3. What factors supported the process of bringing this intervention into practice?
4. What factors hindered the process of bringing this intervention into practice?
5. What kind and how much resources were needed?
6. Did the process go as anticipated? If not, what was surprising?
7. How satisfied are you with the process so far?
8. What was most challenging during the implementation process?

Current use:

1. What are you currently doing to keep the intervention implemented?
2. Do you have sufficient resources? Please elaborate.
3. What issues are you currently facing? What solutions for these issues do you have?

Prospective adjustments:

1. What will the prospective maintenance and upkeep look like?
2. Who is responsible for that?
3. If there should be a change in employment, who ensures that the intervention remains updated?

Stakeholder: health care professionals

Process so far:

1. How often did you deliver the digital intervention?
2. What kind of benefits for yourself, your work, and/or your patients did you experience?
3. What kind of disadvantages for yourself, your work, and/or your patients did you experience?
4. What kind of support for delivering the intervention (e.g., training, technical guidance when issues arose) did you receive?
5. What hindered you in delivering the intervention?
6. What facilitated you to deliver the intervention?

Current use:

1. How satisfied are you with the intervention overall?
2. Which elements of the intervention need improvement?

Prospective adjustments:

1. Do you plan on delivering the intervention in the future? If not, please elaborate.
2. Would you recommend the intervention to a colleague?
3. What kind of problems do you anticipate in the future; and do you have potential solutions for them?

Stakeholder: health care managers

Process so far:

1. How would you describe your involvement in implementing the intervention?
2. How many resources were needed for the implementation?
3. Did the implementation process go as expected? If not, what was surprising?
4. How did you support your employees to deliver the intervention?

Current use:

1. How satisfied are you currently with the intervention (e.g., reflecting on use, content, promotion, required resources, (technical) issues)?
2. What aspects of the current implementation/ practical use need improvements?

Prospective adjustments:

1. Do you plan to offer the intervention in your region in the future? Please elaborate.
2. Would you recommend this intervention to another region/ other health care organizations? Please elaborate.
3. What kind of problems do you anticipate in the future?

Final question for all participants:

The main points I take away from this interview are [summary]. I appreciate the time you took for this interview. Who else should we talk about regarding the implementation of this intervention? Is there anything else you think would be helpful for me to know?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	28
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,28
Roles and	#5b	Name and contact information for the trial sponsor	1

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	6-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8, Fig. 2
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11,12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	11

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11, Fig 4, Fig 5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12, 14,15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Fig 7, Tab 2, Tab 3, and related sections
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, Fig 7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12, 13, 14, 21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11,12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for	21, Tabl. 1

		stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21, Fig 7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14, 21
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a (Tab 1)
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Described for each sub-study
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in	26, 28

		the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Tab 1, 19-21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-14, 21, 22,
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19, 20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	28
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21 (NEQ)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3, 27
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	27

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11-12, 27
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	27, 28
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	28
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	27
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	28
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	28
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a