BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016394
Article Type:	Protocol
Date Submitted by the Author:	13-Feb-2017
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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rheumatology, Research methods, Mental health
Keywords:	Rehabilitation medicine < INTERNAL MEDICINE, MENTAL HEALTH, PAIN MANAGEMENT, QUALITATIVE RESEARCH, Information technology < BIOTECHNOLOGY & BIOINFORMATICS

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Study Protocol

Serious gaming during multidisciplinary rehabilitation for patients with complex chronic pain and fatigue complaints: study protocol for a controlled trial and process evaluation

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Version 1.0 (10/02/2017)
Number of words: 3986

ABSTRACT

Introduction:

Many individuals suffer from chronic pain or functional somatic syndromes and face boundaries for diminishing functional limitations by means of bio-psychosocial interventions. Serious gaming could complement current interventions through enjoyment and independent accessibility. A study protocol is presented for studying whether, how, for which patients, and under what circumstances serious gaming improves patient health outcomes during regular multidisciplinary rehabilitation.

Methods and analysis:

A mixed-methods design is described that prioritizes a 2-armed naturalistic quasi-experiment. An experimental group is composed of patients who follow serious gaming during an outpatient multidisciplinary programme at two sites of a Dutch rehabilitation centre. Control group patients follow the same programme without serious gaming in two similar sites. Multivariate mixed modelling analysis is planned for assessing how much variance in 220 complete records of routinely monitored pain intensity, pain coping and cognition, fatigue, and psychopathology outcomes is attributable to serious gaming. Embedded qualitative methods include unobtrusive collection and analyses of stakeholder focus group interviews, participant feedback, and semi-structured patient interviews. Process analyses are carried out by a systematic approach of mixing qualitative and quantitative methods at various stages of the research.

Discussion:

Study validity might be limited by a lack of randomized participant sampling and treatment allocation. However, realist evaluation principles and mixed-methods used may enhance future assessment of serious gaming effects across patients and health care settings.

Ethics and dissemination:

The Ethics Committee of the Tilburg School of Social and Behavioural Sciences approved the research after reviewing the protocol for the protection of patients' interests in conformity to the letter and rationale of the applicable laws and research practice (EC 2016.25t).

Trial registration:

A protocol for the naturalistic quasi-experimental outcome evaluation was entered in the Dutch trial register (NTR6020).

ARTICLE SUMMARY

Article focus

- Describe a protocol for a naturalistic quasi-experiment with embedded mixed-methods for evaluating if, when, and how serious gaming improves health outcomes during multidisciplinary rehabilitation in a regular health care setting.
- Pain intensity, pain coping and cognition, fatigue, and psychopathology are primary patient outcomes.

Key messages

- Serious gaming may be complementary in enhancing the accessibility and/or effectiveness of bio-psychosocial interventions.
- Health outcomes of a serious game intended for behavioural change (LAKA) are evaluated for the first time in patients with chronic pain or functional somatic syndromes.

- Complication of intervention effects can be addressed by means of realist evaluation principles and mixed-methods.

Strengths and limitations of this study

- The novelty of the intervention and study methods is a strength.
- Using a pragmatic approach to study serious gaming when deployed in a regular health care setting enables to understand under what conditions serious gaming will (not) work.
- Study limitations come with the naturalistic design, due to pragmatic reasons, that prevents random treatment assignment and stringent diagnostic methods.

INTRODUCTION

Background and rationale

Video games are vividly debated to their behavioural and clinical outcomes, which may be negative or positive depending on game content and player attributes.[1 2] Serious (health) games primarily target promotion of health benefits.[3] A new serious game, called LAKA, aims to facilitate patient learning about living with complex chronic somatic complaints.[4] Based on the results of a feasibility study, LAKA is deployed in a regular health care setting, as an additional component of outpatient multidisciplinary rehabilitation. The current protocol presents an innovative mixed-methods study for gaining insight into the effectiveness of serious gaming as a complementary modality during regular multidisciplinary rehabilitation.

Using a variety of definitions and measures of pain and disability, the worldwide prevalence estimates for chronic pain range between 7% and 64%.[5-9] Individuals are in chronic pain (CP) when complaints persist beyond the usual 3 to 6 months of organic recovery.[10] Functional somatic syndromes (FSS) are diagnosed in individuals that seek medical help for functional disturbance and chronic somatic symptoms without a satisfactory explanation by organ pathology or disease.[11] CP and FSS may have a biological explanation in central nervous system sensitization.[12 13] Predisposition to these disorders is probably determined by a combination of genetic factors and personality characteristics.[14 15] Symptom patterns are often precipitated by trauma or social factors.[16-18] Maladaptive thoughts, feelings, and behaviour are assumed to maintain the symptoms.[17 19-21] Regarding treatment, support has been found for a stepped care approach with active bio-psychosocial treatment when unimodal treatments are insufficient.[17] Unfortunately, only small long-term improvements have been found in low back pain patients with severe and long-lasting pain and disability.[17 22] Recent research addresses 'matching' and 'blending' therapeutic strategies and delivery modes. As such treatment access, reach, adherence and effectiveness could be enhanced.[23 24]

Serious gaming could be of aid here. Previously investigated strategies are exergaming to improve motivation for physical activity,[25] 'brain training games' against dullness in the remediation of cognitive functions,[26] 'virtual reality' for safety in graded activity or exposure,[27] and 'health behaviour gaming' for fun while addressing behavioural antecedents.[3] In the fields of rehabilitation and pain management, virtual environments have shown promise in reducing acute pain by distraction, or in activity management to restore physical functioning.[28 29] Outcome improvement after computer-based treatment in CP or FSS patients may be mediated by changes in beliefs (about illness, control, fear avoidance), coping (catastrophizing, psychological inflexibility), or mood.[30 31] It is plausible that features of a health behaviour game such as interactivity, storytelling, simulation, sound effects and visuals can be leveraged for behavioural change.[3 32] If game tasks correspond with an intended piece of knowledge and/or skill, learning may benefit from immersion, and intrinsic motivation.[32-34] Studying how such gaming mechanisms affect treatment may help to understand variation in outcomes and aid in design improvement.

However, within the outcome evaluation of multidisciplinary interventions several complicating factors arise. These consist of the multidimensionality[35] and dependency on implementation in actual health care settings.[36] In other words, characteristics at the levels of organization, care providers, patients and interventions all affect outcome levels.[37 38] Therefore, ideally, multiple sources of information are used to evaluate to what extent, for whom, when and under what circumstances an

innovation of multidisciplinary treatment improves outcomes in patients with CP or FSS.[39] [40] For example, some intervention studies show different outcomes of a computer delivered therapy when applied in different countries.[41] Likewise, serious gaming outcomes may vary according to whether, when, and how 'debriefing' is delivered to exploit game-play experiences for learning outcomes. [42] Debriefing can be offered via software or professional support via chat, e-mail, or face-to-face in groups or individually. Indeed, more adequately powered clinical trials are needed.[2] [3] [43] Moreover, pragmatic trials and realist evaluation principles are needed to determine how serious gaming relates to patient outcomes depending on how it is deployed in actual health care settings.

Study aims

Here we describe the protocol for outcome and process evaluations of complementary serious gaming during regular multidisciplinary rehabilitation for patients with CP or FSS, which holds three study aims.

The first aim is to investigate the effectiveness of serious gaming as a treatment complement. We question to what extent multidisciplinary rehabilitation with an additional serious gaming component is more effective than multidisciplinary rehabilitation without serious gaming for symptom reduction and clinically relevant improvement. Primary outcomes are pain intensity, pain coping and cognition, fatigue complaints, anxiety and depression. Secondary outcomes are patients' impression of overall improvement, general subjective health, and satisfaction with functioning and treatment.

Secondly, we aim to understand which organization, provider, patient, and/or innovation level factors influence the outcomes of serious gaming for patients. Innovation level factors concern serious gaming features. Patient level facilitators or barriers could be demographic, health status and (co-) intervention history factors. Serious gaming outcomes could also depend on complex provider behaviour by attitude, skill, and/or time constraints. Finally, outcomes of serious gaming could be influenced by its organization in a clinical setting. Therefore, we pose the question: what are the barriers and facilitators of outcome improvement through serious gaming according to patients, providers, and other stakeholders? Furthermore, we question how variation in serious gaming outcomes can be decomposed with plausible patient level differences and/or delivery conditions within the treatment setting (i.e. size of a debriefing group).

The third aim concerns *how* serious gaming contributes to patient outcomes. For this, we explore various serious gaming mechanisms, being the subjective experiences and objective performances in context that may affect health outcomes. In addition, plausible linear effects between mechanisms and patient outcome variables are investigated. Achievement of all three research aims will inform the further development of a valid and practical programme theory of serious gaming outcomes in regular health care for patients with CP or FSS.
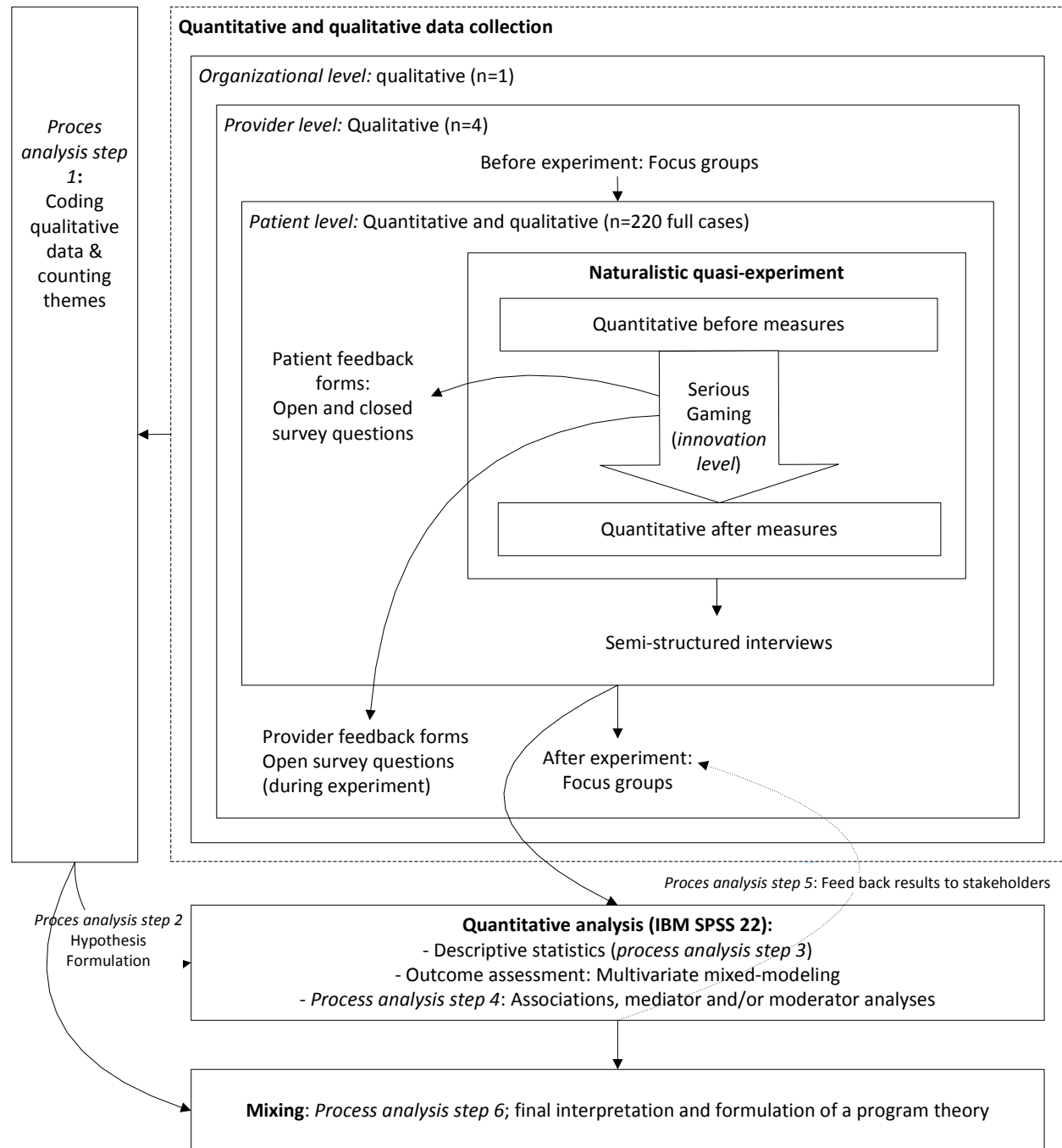
METHODS AND ANALYSIS

Study design and procedure

An embedded experimental mixed-methods design is created by an integrated multidisciplinary research team (MV, HV, MJ, AZ, AM) to address all three research aims in a single study (see figure 1). For studying the first research aim, which is to estimate patient level outcome improvement due to serious gaming during regular outpatient rehabilitation, a two-armed naturalistic quasi-experiment is prioritized (displayed at the centre of figure 1). A serious gaming intervention is deployed, for usage by

all patients, at two sites of a Dutch outpatient rehabilitation clinic. Therefore, an intervention group is constituted of patients who receive the multidisciplinary rehabilitation programme with an additional serious gaming intervention. The control group consists of patients who simultaneously follow the same programme in two similar sites of the same clinic without serious gaming. Codified quantitative data from patient records will be retrieved and analysed to examine between group outcome differences. The protocol for the naturalistic quasi-experiment was entered in the Dutch trial register (NTR6020).

Figure 1: Overview of the Mixed-Methods design

Embedding qualitative methods before, concurrently to, and after the quasi-experiment suits our second and third study aims. This mixed-method design is ideal for examining intervention processes, understanding mechanisms related to variables, and supporting programme theory development.[44] Herein, no intermediate qualitative results are communicated with providers and implementers during the experiment. Data collection started in April 2016 and is planned to end in March 2017, quantitative outcome data will be retrieved when concurrently collected qualitative data are analysed (February 2017).

Recruitment

Sites and professionals

Two intervention sites where serious gaming is deployed participate in the study. For the recruitment of control subjects, two other sites (out of 18 sites as part of the same treatment centre) are selected based on similarity with regard to patient characteristics, facilities, protocols, history, personnel, location in or near a city in the southern Netherlands, and the absence of disruptive events planned during the intervention period. The treatment centre provides rehabilitation care covered by health insurance in association with a university medical centre. Professional study participants are local stakeholders of serious gaming, including experts, implementers, and providers.

Patients

Patient candidates received an indication of eligibility for outpatient multidisciplinary rehabilitation from a rehabilitation physician, and completed half of their rehabilitation programme at a participating site. Physician indications of eligibility are followed, which are based on the results of diagnostic surveys, physical and psychological investigations, and clinical interviewing via teleconference. Accordingly, patient participant inclusion criteria are: being between 18 and 67 years of age, reporting the presence of pain for more than 6 months, or fatigue complaints or a musculoskeletal disease for more than 3 months, having no (more) indication for another (cost-) effective medical treatment, and have concomitant psychosocial problems. Patients are excluded from participation if: psychiatric symptoms are not adequately controlled, there is significant risk of psychological decompensation through a rehabilitation treatment, language or communication problems make it impossible to follow rehabilitation, and/or demonstrable inability to change behaviour (due to personality disorders, third party liabilities, or otherwise). An information letter, consent form, and verbal explanation are provided by local care providers. The recruitment process is monitored to ensure that all candidates are invited.

Interventions

Multidisciplinary rehabilitation programme

The outpatient multidisciplinary rehabilitation programme includes common bio-psychosocial approaches, and incorporates a focus on well-being and participation.[45] The standardized 16-week programme consists of on average 95 hours of individual or group sessions that are organized in modules and assigned in accordance with individual care needs. Each patient is treated by a team of two physiotherapists and two registered master's degree psychologists. Psychotherapeutic techniques include Cognitive Behavioural Therapy and psychodynamic approaches. For all patients, treatment contains rationales, goal setting and feedback, social support, exposure treatment, behavioural

repetition and substitution, skills training (in relaxation, social skills, and meditation), and identity development techniques. Allocation of cognitive restructuring, eye movement desensitization (EMDR), and an intensive 2-day well-being course depend on screening results for psychopathological symptoms[46] and fear avoidance beliefs,[47] post-traumatic stress, and psychological well-being.

Serious gaming

Theory and change techniques of the serious game LAKA

Developer assumptions for the game LAKA have been documented throughout development and related to conceptual frameworks (see appendix).[48] Serious gaming is proposed to promote practice for well-being improvement, and for identifying and diminishing distortions and biases of self. This may be helpful for patients with CP or FSS in reducing the burden of their symptoms.[49] Based on a review of information about the design rationale, functionality, validity proof (before outcome evaluation), and data protection measures of LAKA, an independent jury awarded 3 out of 5 attainable stars for quality (see appendix).[50]

The serious game LAKA promotes practice through an Avatar model. Before the game starts, participants are invited to identify with an Avatar of their chosen gender and name (table 1). The storyline introduces an Avatar who recently experienced physical and social deterioration, senses an urgency to change, and engages in a trip around the world to learn about 'the art of living'. Player tasks are: to explore and select virtual action plans for 'encounters' with non-playing characters, to evaluate their 'satisfaction' about chosen actions, and to perform skills training in focused attention and open monitoring meditation exercises.[51] Encounter scenarios model uncertain events resulting in varying Avatar states depending on action plans chosen by players. Encounters are increasingly influenced by distant cultural meanings to challenge anticipation of the course of events (i.e. depending on the scenario, agreeable responding can result in a pleasant interaction or involvement in a scam). Players receive global feedback on the extent to which chosen actions correspond with a reference model for values (see appendix). Self-reflective elements are interspersed with short casual action and puzzle games, images, and information associated with the location of the Avatar. These features are included to vary game play, and can be skipped.

Table 1: Features, dose, and tasks

Features	Dose (in game frequency)	Tasks
Introduction	1	- Choose Avatar gender and name - Receive instruction: to identify with the personal Avatar - Introduction to Avatar storyline - Receive task instructions from LAKA (non-playing character with a mentoring role)
Encounters (See screenshot in the appendix)	16	- Select action plans for the Avatar in encounters with non-playing characters (each instance offers 5 optional action plans, which are modelled after a reference set of values: generosity, moral discipline, patience, enthusiastic perseverance).
Mood scenarios	8	- Select action plans for the Avatar when subjected to an adverse event. - Given the adverse scenario: think of what your own affective state would be in this situation, and bear in mind the depicted emotional state of the Avatar.
Reflections	4	- Assess satisfaction about selected Avatar actions on a scale of 0-10.

		-	Receive feedback from LAKA on chosen action plans.
		-	Receive feedback about the correspondence between satisfaction rating and LAKA assessment.
Attention training:	3	-	Guided (focused attention and open monitoring) meditation exercises for mental stability.
Tours:	16	-	Skip or listen to 'tour-guide' voiceovers informing about pictures of the location visited by the Avatar.
Loading screens	-	-	See where travel destinations are located on a geographical map.
Mini-games:	8	-	Action games: Steering a vehicle (by using tilt mechanism of tablet pc, or keyboard arrow controls) to arrive at the next encounter (reference: 'rocket bird').
		-	Puzzle: Fix a road by connecting parts of the road to arrive at the next encounter (reference: 'plumber games').
Festive closing	1	-	Replay of 'extreme' responses throughout the game.

Mode of delivery

In accordance with patient suggestions for optimal reach, the rehabilitation clinic delivers professional assistance and the occasion for playing the serious game LAKA on site, besides downloading and playing on a home computer[4]. Suitable rooms with Wi-Fi connection, tablet computers with LAKA installed, and headphones are provided. Four 1-hour sessions of serious gaming are planned for 1 to 6 patients simultaneously during weeks 9-12 of their rehabilitation programme. The sessions are scheduled in connection with other therapy sessions to ease coordination with daily activities. In the first session, patients are briefly introduced to the serious game LAKA and instructed to complete the game independently during the second and third sessions. In the fourth session, patients participate in a debriefing. Experienced therapists (1 physiotherapist, and 3 psychologists) provide the introduction and debriefing sessions.

Programme theory

The framework of context, mechanism, outcome (CMO) configurations is used to structure ongoing development of a programme theory for serious gaming as a complement during multidisciplinary rehabilitation.[52] To illustrate, a patient with an active coping style self-exposed for a short amount of time to unsupported serious gaming during multidisciplinary rehabilitation (context), experienced enjoyment and discrepancy regarding valued self-identities (mechanism), and expected this to contribute to health improvement (outcome)[4]. Timely building blocks for CMO configurations for serious gaming are deduced from the literature. Outcomes are interpreted using models of self and well-being (appendix), and relevant outcome domains for patients with CP or FSS.[35 53 54] Two comprehensive implementation models are used for the classification of context factors.[55 56] Finally, mechanisms of serious gaming are discerned as gaming behaviours (frequency, length, and performance of game play), and user experiences of gaming, simulation, and information systems. More specifically, subjective mechanisms may involve sense of presence,[57] technology acceptance,[58] positive and negative affect,[59] game-based learning,[60] and perceived 'learning transfer' to daily life.[42]

Measures

Quantitative data

Patient web-survey self-assessments for routine outcome monitoring will be used, which are taken at the indication of eligibility (at baseline), after 8 weeks of treatment (intermediate), and again after 16

weeks of treatment (post). Surveying procedures include the facilitation of patients without convenient computer access and promotion of follow-up completion.[4 61] Primary outcome measures are selected from those available in patient records based on whether instruments are deemed valid and relevant (see table 2).[35] These endpoints include a numerical rating scale for current pain intensity,[62] the pain coping and cognitions list (PCCL),[63] fatigue as assessed by the Checklist Individual Strength (CIS),[54] and psychopathological symptoms as measured by the Symptom Checklist (SCL-90).[46] Secondary measures focus on other relevant outcomes such as patients' global impression of improvement after treatment.[35] Another widely used single item Likert-scale rating is used for measuring general health (poor to excellent).[64] Finally, numerical rating scale items are available to assess patients' satisfaction about treatment and functioning (see table 2).

Table 2: Quantitative outcome measures

Variables	Measures	Time of measurement
Primary outcomes		
Current pain intensity	1 item Numerical Rating Scale (NRS) 0-10	Baseline, intermediate, post treatment
Pain coping and cognition	Pain Coping and Cognitions List (PCCL)	"
Fatigue	Checklist Individual Strength (CIS)	"
Psychopathological symptoms	Symptom Check List (SCL-90)	"
Secondary outcomes		
Clinically relevant improvement	Patient Global Impression of Change (PGIC)	Intermediate, post treatment
General subjective health	"What do you think of your current health in general?"	"
Perceived functioning	"Please indicate how satisfied you are generally taken with your current level of functioning"	"
Treatment satisfaction	Three Likert scale items, i.e. "Would you recommend this treatment centre to other rehabilitation patients?"	Post treatment

Case-mix variables will be retrieved from patient records. Patient variables are based on screening records and involve demographic, health status, and treatment history information (see table 3).

Table 3: Patient characteristics

Variables	Measures
Age	Years of age
Gender	% Female
Socio-economic status	Highest education level, source of income
Coping style	Utrecht Coping List (UCL)[65]
Environment	Presence of problems with regard to social life, financial situation, trauma, work situation.
Symptoms	Duration (months), course, and location of somatic (pain) complaints
Physical status	Body Mass Index, blood pressure, musculoskeletal conditions
Other treatment	Presence of and changes in medication usage. Frequency of health care visits. Previous visits to medical specialists, physiotherapists, and/or psychologist.
Treatment (modules) received	Automatic logs (session presence)

Intervention mechanisms may cover subjective experiences and objective behaviours of serious gaming (see table 4). Automatic registrations in patient files enable objective assessment of serious gaming frequency, duration, progress, and performance. Moreover, a short survey was composed in

collaboration with the rehabilitation centre to measure subjective experiences shortly after serious gaming. This survey contains items on perceptions of using a serious game (regarding usefulness, ease of use, trust, enjoyment, goal clarity, challenge, and learning[4 58 60]), the 10-item short form of the positive and negative affect scale,[66] the involvement and realism scales from the Igroup Presence Questionnaire,[57] and (0-10) numerical rating scale item on perceived learning transfer. A reminder was sent to intervention group participants if the survey was not completed within a week after their last gaming session. Finally, a questionnaire on patient values may be used to explore relationships between mechanisms and outcomes of serious gaming.

Table 4: Quantitative indicators for mechanisms

Variables	Measures	Respondents	Time of measurement
Reach, dose, gaming performance	Data logs: frequency, timing, length, progress, and scores of play	Intervention group	During SG (automatic)
Acceptability and playability	Selection of UTAUT 2 items (perceived usefulness, ease of use, trust, enjoyment) Selection of EGameFlow items (clear goals, challenge, perceived learning)	Intervention group	Post Serious Gaming
Positive and negative affect	PANAS-SF	Intervention group	Post Serious Gaming
Presence (general, involvement, and realism)	IGroup Sense of Presence Questionnaire item for general sense of presence, and subscales for involvement and realism.	Intervention group	Post Serious Gaming
Learning transfer	Numerical rating scale (0-10): "Use the following slider to indicate to what extent you expect that the LAKA sessions contribute to your own treatment"	Intervention group	Post Serious Gaming
Values (expressed in thoughts and behaviour)	Values questionnaire*: 5-point Likert scales, i.e. "If I find it necessary, I'll intervene to help or to protect others".	Intervention and control groups	Baseline, intermediate, post treatment

*Psychometric properties are still under investigation. Empirical support for good scale internal consistency, and strong associations with psychological well-being in rehabilitating patients were documented in a report for the Dutch Committee on Test Affairs (COTAN).

Qualitative data

Protocols for focus group and semi-structured patient interviews are informed by the CMO building blocks and principles for interviewing in realist evaluation.[67] Accordingly, the role of the interviewer ranges from open and explorative towards more educational and evaluative when CMO configurations become better delineated. Providers are expected to be especially knowledgeable about context and mechanisms of serious gaming, while patients may say the most about context and outcomes. Purposive sampling of participants is used until reaching a point of data saturation. All interviews are tape-recorded and verbatim transcribed. Transcripts and a summary of findings are sent to participants by e-mail to enable them to check if their views are accurately reflected.

Provider (focus group) interviewing

Four focus group interviews are held, two before and two after the naturalistic experiment, to involve stakeholders in the ongoing development of serious gaming and programme theory. Participant selection and topics are based on actual data needs. Heterogeneous groups of care providers, implementers, and experts (in ICT, well-being, and serious gaming) are invited for the first and last

discussion meetings. The first interview focused on the research goals for an open discussion. The last group interview will focus on programme theory for member checking and refinement. Homogenous groups of provider participants may be invited for the second and third focus groups for more in-depth information. Provider participants are asked to share positive and/or negative feedback about serious gaming via a secured web-form. This includes information on the occurrence and management of adverse events and/or unintended effects during serious gaming.

Patient interviewing

Two open interview questions about gaming experience and perceived learning transfer are added to the post-gaming survey for intervention group participants. Patient participants with high and low scores on a 1-item numerical rating scale (0-10) for perceived learning transfer are invited for a semi-structured interview after their rehabilitation treatment. These interviewees are asked to describe their health outcomes during rehabilitation, and to list the three most important reasons why serious gaming did, or did not, contribute positively or negatively to this process. A point of saturation is reached if the three factors (context and/or mechanisms) mentioned are all richly described. Control group interviewees are matched to some of the intervention group interviewees to compare rehabilitation outcome changes for similar cases with versus without serious gaming.

Analysis

Statistical outcome evaluation

Quantitative data will be imported in SPSS 22, described after statistical inferences, and analysed on intention-to-treat basis. All case-mix variables are described for individual study participants, as well as the differences between intervention group and control group participants. Multivariate mixed-linear modelling techniques will be used to evaluate the extent to which serious gaming predicts variance in patient outcome levels between the intermediate and final outcome assessments of the rehabilitation programme. Effective sample size and intra-class coefficients will be calculated to determine dependency on hierarchical patterns in outcome variation by care provider levels. An optimal prediction model will be specified, correcting for potential unbalances between the study groups (at baseline and/or intermediate), and/or important higher-level random effects.

Process analyses

A programme theory will be created after a sequence of analysis steps. In each step, analyses will be performed completely by MV and in part by MJ or AZ (independent coding of interviews, and re-running syntax), and discussions will be held involving a third author (HV) to resolve differences and find agreement about the results. First, concurrently collected qualitative data analyses will be performed to identify plausible CMO configurations from the perspectives stakeholders. All qualitative data will be coded in vivo and higher order coded using CMO building blocks to determine configurations. Secondly, a selection of key CMO configurations will be made based on counts of the number of participants supporting them in their open text responses to the post-gaming survey. Hypotheses will contain specific expectations of (linear) relationships implied by the CMOs. If needed, additional provider or site level data (i.e. debriefing session group sizes) will be retrieved from clinical administration records. Third, quantitative data will be screened by testing internal consistency in SPSS or data triangulation

with qualitative data if possible. Fourth, hypotheses will be tested with available and valid quantitative data. Fifth, data from the last focus group will be coded. Sixth, quantitative and qualitative findings will be mixed for an overall interpretation and drawing final conclusions.

Power calculation

From practical, theoretical and statistical perspectives, a powerful primary outcome assessment was anticipated by focusing on recruiting a sufficient number of individual patients from the four participating treatment facilities. The rehabilitation centre (n=1), intervention sites (n=2), as well as the number of time-points (3), are practically fixed. Analysis of unpublished pilot data suggested that variation in baseline to post treatment outcome changes between treatment locations might be negligible relative to individual variation within sites (intra-class correlations > .05).

Using G*Power, a required sample size of 212 participants was calculated for determining a small effect by means of a MANOVA test of global effects. A small to medium effect size was expected based on a meta-analysis about the effect of Serious Games for Health on cognition, motivation, and psychological outcomes[3]. Therefore, the following parameters were inserted: for power (1-Beta), 0.8; effect-size (f^e(V)), .0625; type-II error probability (alpha) = .05; number of dependent variables, 5; and number of groups, 2. Anticipating some level dependence and/or randomly missing data (pain coping and cognition measures are not filled out by patients reporting 0 pain intensity at baseline), 250 patient participants will be recruited. Assuming 20% treatment and study attrition rates and an average weekly inflow of 9 patients starting with their treatment within each of the four facilities, outcome data are available 6 months after recruiting the first patient.

ETHICS AND DISSEMINATION

Ethical approval for the mixed-methods protocol was obtained from the psychological ethics committee of Tilburg School of Social and Behavioural Sciences (EC-2016.25t). In the absence of a legal obligation for medical ethics review, independent judgement was provided on the protection of patient rights by conformity to the letter and rationale of the applicable laws and research practice. Patient participants are consented before participation, that is before receiving the additional (5-10 minute) survey (intervention group), being invited for a semi-structured interview, or retrieving their codified data. Participants were protected against harm by regular clinical safety measures throughout. Professional participants are also consented before participation in qualitative data collections. Under supervision of MJ, MV is responsible for safe storage and the accessibility of (codified) research data to all authors. Qualitative and quantitative results will be presented and discussed together in one or more research article(s), and at one or more international scientific conferences. A summary of study results will be provided to the study participants.

DISCUSSION

The novelty of the serious gaming intervention and study methods are strengths of the proposed evaluation, but imply limitations as well. LAKA is the first serious game that promotes practice for self-process enhancement under highly prevalent adverse conditions such as CP or FSS. CMO configurations may be identified that are transferable to other populations and settings where similar approaches to behavioural change are beneficial[68]. However, internal and external validity are threatened due to

divergence from the golden standard procedures of a (cluster) randomized controlled (multi-centre) trial. Instead, pragmatic considerations for the deployment of serious gaming during rehabilitation in two sites of a single Dutch centre led treatment allocation and recruitment methods. Different comparisons with serious gaming (i.e. usual care, waiting list, or text based computer-based intervention), more elaborate psychiatric assessment, and/or long-term follow up measurement are precluded. The realist evaluation principles and mixed-methods used in this study are increasingly accepted in scientific communities as means to compensate for practical study limitations and to build programme theories that enhance future predictions of intervention effects across patients and health care settings.[69] [70]

Legitimate application of mixed-methods is promoted by the protocol in various ways. First, participant recruitment and selection methods for quantitative and qualitative examinations allow a strong representation of patients receiving bio-psychosocial treatment in a regular outpatient setting. This differs from studies in which the eligibility of applicants for computer-based intervention depends on motivation and/or ability to use a computer or internet facilities.[71] [72] Secondly, perspectives of insiders (patients, health care providers and developers) and outsiders (independent experts and members of the research team) will be utilized. Third, relevant theoretical constructs are specified before quantitative and qualitative data collections to prevent process analysis results being strongly affected by the sequencing of qualitative and quantitative methods. Fourth, predefined steps structure data convergence and switches in epistemological paradigms when qualitative methods are used to propose quantitative results (in advance) and to explain them (afterwards).

Dr. Vugts reports employment by Ciran, and is provided time and occasion to conduct independent doctoral research by way of agreement at Tranzo, Scientific Centre for Care and Welfare, Tilburg University. The terms of this arrangement have been reviewed and approved by Tranzo in accordance with its policy on objectivity in research.

Dr. Joosen has nothing to disclose.

Dr. Zedlitz has nothing to disclose.

Dr. Vrijhoef reports personal fees from Ciran, outside the submitted work.

Dr. Mert has nothing to disclose.

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SUPPLEMENTARY FILE

Content:

1. Developer assumptions
2. Screenshot example
3. Information about the design rationale, functionality, validity proof (before outcome evaluation), and data protection

1. Developer assumptions

Developer assumptions	Related theory
The rehabilitation program is based on a (four dimensional) bio-psycho-social-spiritual treatment model in which Eastern and Western (medical) interventions are integrated. Interventions are aimed at improving 'mobility of mind', which is defined as: flexibility in accommodating 2 dynamic processes: 1) participation in private, social, and work roles, and 2) the ability to participate. Ability to participate depends on four aspects: symptoms (signals due to organ system injury or disturbance in shaping and controlling one's life or 'existence'), autonomy, perspective ('to see one's opportunities for finding meaning in life through inspiration'), and values. A reference for values is given by generosity, moral discipline, patience, enthusiastic perseverance, and mental stability. LAKA was designed to offer covert learning and skills training for enhancing a sense of self characterized by autonomy, values, and perspective.	This learning content may converge with and diverge from related concepts known in published scientific literature, including: - Categories of the International Classification of Functioning: specific (higher) mental functions, and activities and participation domains 6-9.[1] - Coping flexibility under conditions of CP or FSS.[2] - Eudaemonist process of psychological well-being.[3] - Autonomously motivated pro-social behaviour.[4 5] - (Neuro)psychological processes associated with similar practices (focused attention, open monitoring, and ethical enhancement) in general: self-awareness, self-regulation, and self- transcendence.[6]
Improvement in mobility of mind is associated with better health outcomes after rehabilitation in patients with complex pain or fatigue (1st and 2nd).	Learning content may converge with and diverge from similar plausible targets in non-pharmacological treatment for patients with CP or FSS: Internal control beliefs (+), avoidance (-), self-acceptance (+), mindfulness (+), values-based action (+), rumination (-), catastrophizing (-), negative (-) and positive (+) mood[2 7]
(Video) game mechanics can be leveraged to enhance learning by through player's self-awareness and intrinsic motivation. The game is of a relatively short duration, but aims to promote continued practice by any means outside the game.	Plausible ways in which video game mechanics may affect the self in players. - Self-efficacy theory: vicarious learning in health behaviour games.[8] - Self-determination theory: gaming elicits representations of valued self-identities in players (through autonomy, competence, and relatedness).[9] - Meta-cognitive processing is a likely consequence of, and characterizes interaction in the context of video game-play.[10]

2. *Screenshot (London Hyde Park)*

Sorry about that. Doesn't do that normally.

Hond Eigenaar

3. *Information about the design rationale, functionality, validity proof (before outcome evaluation), and data protection*

Category	Item	Question	Answer
Game description			
Meta-data	Operating system	Operating systems of the game	Android, iOS, Windows, OS X
	Version	Version	Beta+
	Web-link	Web-link	Yes*[1]
	Project type	Commercial, non-commercial, other	Non-commercial
	Access	Public / restricted / other	Restricted
	Adjunct devices	Is an adjunct device needed?	No adjunct device needed
Development	Funding	How was development funded? Eg, funding agencies, investors	Investors (Ciran)*[2]
Sponsoring / Advertising	Advertisement policy	Is the game free of commercial pop-ups?	Yes
		If not, what is advertised?	NA
	Sources of income	Are there sources of income within the game?	No
	Sources of income outside game	What are the sources of income of the owner/distributor?	The owner and distributor (Ciran) is a foundation providing outpatient rehabilitation care covered by health insurance.
Potential conflicts of interest	Affiliations	What affiliations do the publishers have that could influence content or user group?	Publishers are affiliated with the owner/distributor
	Conflicts of interest	What interests do the publishers have that could influence the game's content or user group?	Content and user groups are based on the objective of Ciran to improve outpatient rehabilitation for patients with complex chronic pain and/or fatigue. The primary (tentative) purpose of game design is the improvement of (independent) engagement with learning content during a rehabilitation program.
	Disclosure	Are conflicts of interest disclosed?	Yes
Rationale			
Purpose	Goal or purpose	What is (are) the purpose(s) of the game?	To facilitate learning and promote practice for 'mobility of mind' (see developer assumptions) to support recovery in patients with complex chronic pain and/or fatigue.
	Disclosure	Is (are) the purpose(s) disclosed to users?	Yes
Medical device	Medical device	Is the serious game a medical device, or not?	Not
	Class	If yes, which class?	NA
	Approval by legal bodies	If yes, does it comply with the necessary requirements (FDA-approval, CE-mark?).	NA
User group	Specific user groups	For each user group: disease/condition	Patients with chronic pain and fatigue, and problems in multiple (other) domains of functioning.

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	Description	Please specify gender, age (range), and other relevant descriptive items.	See inclusion and exclusion criteria as listed in the main body of the article.
	Limits	Are there age limits, or other limits?	According to PEGI classification, the content of the game was found suitable for people who are at least 12 years of age, because it contains some events of mild swearing.
	Disclosure	Is the intended user group disclosed?	Yes
Setting	Patient care	Is the game used in patient care?	Yes
	Training courses	Is the game used in training courses or -curricula?	No
	SCORM compliancy	If used in training courses or curricula, is the serious game SCORM-compliant?	NA
Functionality			
Purposes / didactic features	For every purpose of the game:		
	Learning or behavioural goals	What content will the player learn?	Learning content is based on a reference set of values that manifest in (pro-social) thought and behaviour. These values correspond with the 'perfections' of Mahayana Buddhism. Learning this content is, for research purposes, interpreted as a process of psychological well-being through self-awareness, self-regulation, and self-transcendence (see developer assumptions).
	Relation learning and game play	How does the learning content relate to the game play?	Players are supported in imagining how valued states (or 'selves') are attainable when going on a trip around the world (as a metaphor for private, social, or work participation). Before the game starts, players are explicitly instructed to identify with an Avatar (of their chosen gender and name). It is stated that Avatar choices reflect you as a player. In an introductory cut-scene, this Avatar meets a non-playing character (NPC), named LAKA. The personal Avatar is introduced as someone who experienced deterioration in physical and social domains of functioning, and is determined to improve his/her life. Then, LAKA challenges the Avatar 'to cope well with others' on a trip to 4 destinations (London, Turkey, Asia, and Africa). Meanwhile, most of the mechanics of LAKA enable (virtual) exploration and affirmation of values by selecting action plans for the personal Avatar. At each travel destination, the Avatar faces 4 encounters with NPC's under various circumstances. These encounters are designed as complex interactions between Avatar actions and unpredictable responses of the NPC/environment (rendering variety in cultural settings). For each Avatar action, players select an action plan out of 5 programmed options for physical acting, saying, and/or avoiding. The action plans are modelled by their level of correspondence with values for a given situation. After visiting a destination (after 4 encounters), LAKA appears and asks the Avatar to provide a self-rating of his/her performance, provides feedback on chosen action plans (by giving a certain number of puzzle pieces), and feeds back how well Avatar

			self-ratings and LAKA ratings correspond (by providing additional puzzle pieces). Finally, LAKA delivers focused attention and open monitoring exercises (explaining and illustrating how to practice meditation, prompting practice, providing a means for stress management). Learning elements are interspersed with short (casual) action and puzzle games, images, and information associated with the location of the Avatar. These features promote enjoyment by varying game play and rewarding curiosity, and can be skipped if preferred.
	Instruction	What intervention leads to the learning transition (eg, tutorial, instructions (in-game))	Besides prompting identification with the Avatar, and adding feedback by LAKA as a form of in-game debriefing, face-to-face debriefings by care providers are offered to improve the transition from game play to learning for daily life improvements.
	Assessment (progress) in game	Through which parameters is progress in the game measured?	Number of encounters completed (progress does not depend on player learning level), but feedback is provided on actions chosen by players.
	Assessment parameters	Which parameters are to designers' opinion indicative for measuring learning effects?	Primary health outcomes (i.e. pain, fatigue) may be an indirect result of learning. Parameters that may indicate a learning effect more directly may be plausible mediators of outcome improvement after behavioural interventions in CP or FSS patients (see developer assumptions). Parameters of game play may also directly reflect learning effects: 1) LAKA assessments may reflect whether a patient thinks and acts in accordance with values, 2) the level of correspondence between self-assessment and LAKA assessment may contain information about the extent to which the player understands what sort of thinking and behaviour relates to psychological well-being.
Content Management	Content Management system	Is the Content Management System restricted to specified persons or institutions?	Yes
	User uploaded content	If no, are users allowed to upload their own content?	NA
	Content monitoring	How is uploaded content checked?	NA
	Restrictions and limits of the serious game	Please describe restrictions and limits of the serious game. What content on the learning goals is not covered?	The game itself does not contain detailed explicit knowledge on relationships between learning content and health outcomes. Complementary delivery modes of rehabilitation (i.e. handbooks, group therapy sessions) serve this purpose. An argument for withholding highly explicit feedback is that the adequacy of action plans (coping) is context dependent. The game enables safe exploration of options for (non-automatic) responding to contextual clues. Consequently, the game triggers reflection by leaving some ambiguity about what might be the 'right' sort of behaviour. This ambiguity might diminish levels of acceptance/playability (perceptions on feedback or challenge) in some players. Professional support may partially compensate this issue when embedding the game within regular treatment. The game was found to be engaging enough to play ones or twice (2-5 hours), which is

			not expected to be enough for moderate or strong average effects on player behaviour and health outcomes.
Potentially undesirable effects	Potentially undesirable effects	What potential undesirable effects could the game have?	No undesirable effects were expected and none were observed in qualitative analysis during a feasibility study*[3].
	Disclosure	Are such potential undesirable effects disclosed to the user?	NA
	Measures taken	What measures are taken to prevent potential undesirable effects?	Based on the result of feasibility study, we expect no undesirable effects. During the present evaluations, undesirable effects will be investigated again.
Validity			
Design process	Medical expert complicity	Were medical experts (content experts) involved in the design process from the start?	Lama's from the Tibetan Institute Yeunten Ling, a psychometric expert; A.H. Akkerman, and Ciran; A.H.M.M. van Bergen, and J.J. Jochijms created the 'mobility of mind' questionnaire that operationalizes the content on which LAKA is based. They were also involved in the formulation of program requirements, or provided feedback on prototypes of LAKA.
	User group complicity	Were representatives from the user group involved in the design process from the start?	No
	Educationalist complicity	Were educationalists involved in the design process from the start?	Educationalists have been affiliated with Tilburg University: Prof. Jac L.A. Geurts (gaming expert) had been guiding the process of demand specifications for LAKA. M.A.P. Vugts MSc has been involved as a researcher from the start.
User testing	User testing	Did user testing take place? What were the results, and how were these incorporated in the design?	User testing was performed in feasibility piloting*[3]. The game is free of technical issues. Some comments on playability have not been addressed, because their impacts on outcomes are ambiguous. The only change to the version used in the feasibility study is that mini-games can be skipped after one failed attempt (instead of 3) to increase tailoring to user preferences.
Stability	Platform stability	Does the game produce the same results on different platforms?	Yes
Validity (effectiveness)	Face validity	Do educators and trainees view it as a valid way of instruction?	Yes. Educators agree that learning content is integrated in a valid way (according to the creators of the Mobility of Mind model (see 'content validity'), and agree that its content corresponds with processes of mental well-being as described by the S-ART model (MV, AZ). A group of self-selected patient users recognize that learning content correspond to what is learned by other means (from psychotherapists) during the rehabilitation program*[3]

	Content validity	How is its content validated to be complete, correct, and nothing but the intended medical construct?	A structured self-report questionnaire to assess thought and behaviour in correspondence with values as defined in the teaching model of the 6 perfections was created by Ciran in collaboration with the Yeunten Ling institute (Belgium). A validation report on this test was assessed by an independent Dutch commission for test affairs (COTAN). It was found that questionnaire scores have good reliability, and are strongly correlated with psychological well-being (as expected). Game scenarios were constructed by a professional writer who was familiar with the model and made explicit references to questionnaire items within screen plays for content validity checks. The quality of scenario's and operationalization was monitored under supervision of a creator of the test.
	Construct validity	Is the game able to measure differences in skills it intends to measure?	Research in progress
	Concurrent validity	How does learning outcome compare to other methods assessing the same medical construct?	Concurrent validity was studied using unreported data that were collected in the pilot phase (n=67 patients). A preliminary measure of game score was calculated as the average of all chosen action plans (the quality of each action plan is scaled ordinal; 0, 1, 2, 3, or 4). Performance was assessed by summing the scores for 5 scales corresponding with the behavioural domains of the values questionnaire (generosity, moral discipline, patience, enthusiastic perseverance, and mental stability). Pearson correlations between game scores and the behavioural domain of the values questionnaire were found to be significant, and of a small to moderate size. Self-assessed values measured at baseline (measured within a month before playing the game) correlated .29 with game scores. Values measured post-intervention (1-2 months after playing the game) correlated .39 with game scores. This agreement is encouraging given the differences in how to construct indicators were measured.
	Predictive validity	Does playing the game predict skills improvement in real life?	Research in progress
<u>Data protection</u>			
Data protection and privacy	Data processing	How is data collected in the serious game?	The game can only be accessed by clients of Ciran by logging in with their treatment ID number and self-chosen password. Log-data are encrypted, send over the internet, and stored by Ciran to save proceedings and enable feedback of game scores. No patient-specific data are stored on devices.
	Patient privacy	Are patient-specific data stored in the game?	Data are recorded by Ciran includes IP addresses, name given to the Avatar (no name, or alias is possible), which could be used to identify users.

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		If yes, are patient informed consent criteria met according to relevant national standards?	Yes. All clients at Ciran are informed before the start of their treatment about the use of a digital tracking system for creating and maintaining a patient record, and about their rights for managing their personal records. Therefore, game data concern progress of the treatment and can only be used for scientific research under strict conditions. Therefore, a research protocol describing the codified processing of log-data (thus not including potentially patient specific IP addresses and Avatar names) for the evaluation of LAKA was approved by the ethical committee of Tilburg School of Social and Behavioural Sciences. Medical ethics review is not required for the research.
	Data ownership	Who owns and stores the data resulting from play?	Ciran
	Data storage period	During what period are data stored?	In accordance with the legal storage of medical records (15 years)
	Data removal	Can the user delete data temporarily and/or permanently?	Yes
	Data storage security	Is the data storage secured in conformity with laws of the countries stated above?	Yes
	Data transmission security	Is the data transmission secured in conformity with laws of the countries stated above?	Yes
	Disclosure	Are all items on "data protection" disclosed to the user?	Yes. All items are disclosed to patients before starting their treatment. Specific information on the storage of game data for progress tracking and feedback have not been highlighted in the consent procedure.

[1] Prototype trailer (English): http://www.ciran.nl/laka/lakaEnglish.php; Trailer of the experimental version of the game (Dutch): http://www.ciran.nl/laka/lakaNed.php

[2] https://www.ciran.nl/

[3] Vugts MA, Joosen MC, van Bergen AH, et al. Feasibility of Applied Gaming During Interdisciplinary Rehabilitation for Patients With Complex Chronic Pain and Fatigue Complaints: A Mixed-Methods Study. JMIR serious games 2016;**4**(1).

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Serious gaming during multidisciplinary rehabilitation for patients with complex chronic pain or fatigue complaints: study protocol for a controlled trial and process evaluation

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6   3   **Serious gaming during multidisciplinary rehabilitation for patients with complex chronic pain or**
7   4   **fatigue complaints: study protocol for a controlled trial and process evaluation**
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ABSTRACT

Introduction:

Many individuals suffer from chronic pain or functional somatic syndromes and face boundaries for diminishing functional limitations by means of bio-psychosocial interventions. Serious gaming could complement multidisciplinary interventions through enjoyment and independent accessibility. A study protocol is presented for studying whether, how, for which patients, and under what circumstances, serious gaming improves patient health outcomes during regular multidisciplinary rehabilitation.

Methods and analysis:

A mixed-methods design is described that prioritizes a 2-armed naturalistic quasi-experiment. An experimental group is composed of patients who follow serious gaming during an outpatient multidisciplinary programme at two sites of a Dutch rehabilitation centre. Control group patients follow the same programme without serious gaming in two similar sites. Multivariate mixed modelling analysis is planned for assessing how much variance in 250 patient records of routinely monitored pain intensity, pain coping and cognition, fatigue, and psychopathology outcomes is attributable to serious gaming. Embedded qualitative methods include unobtrusive collection and analyses of stakeholder focus group interviews, participant feedback, and semi-structured patient interviews. Process analyses are carried out by a systematic approach of mixing qualitative and quantitative methods at various stages of the research.

Ethics and dissemination:

The Ethics Committee of the Tilburg School of Social and Behavioural Sciences approved the research after reviewing the protocol for the protection of patients' interests in conformity to the letter and rationale of the applicable laws and research practice (EC 2016.25t). Findings will be presented in research articles and international scientific conferences.

Trial registration:

A protocol for the naturalistic quasi-experimental outcome evaluation was entered in the Dutch trial register (NTR6020).

ARTICLE SUMMARY

Strengths and limitations of this study

- The novelty of the intervention and study methods is a strength.
- Using a pragmatic approach to study serious gaming when deployed in a regular health care setting enables to understand under what conditions serious gaming will (not) work.
- Study limitations come with the naturalistic design, due to pragmatic reasons, that prevents random treatment assignment and stringent diagnostic methods.

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1 **INTRODUCTION**

2 **Background and rationale**

3 Video games are vividly debated to their behavioural and clinical outcomes, which may be negative or

4 positive depending on game content and player attributes.[1] [2] Serious (health) games primarily target

5 promotion of health benefits.[3] A new serious game, called LAKA, aims to facilitate patient learning about

6 living with complex chronic somatic complaints.[4] Based on the results of a feasibility study, LAKA is

7 deployed in a regular health care setting, as an additional component of outpatient multidisciplinary

8 rehabilitation. The current protocol presents an innovative mixed-methods study for gaining insight into

9 the effectiveness of serious gaming as a complementary modality during regular multidisciplinary

10 rehabilitation.

11 Using a variety of definitions and measures of pain and disability, the worldwide prevalence

12 estimates for chronic pain range between 7% and 64%.[5-9] Individuals are in chronic pain (CP) when

13 complaints persist beyond the usual 3 to 6 months of organic recovery.[10] Functional somatic syndromes

14 (FSS) are diagnosed in individuals that seek medical help for functional disturbance and chronic somatic

15 symptoms without a satisfactory explanation by organ pathology or disease.[11] CP and FSS may have a

16 biological explanation in central nervous system sensitization.[12] [13] Predisposition to these disorders is

17 probably determined by a combination of genetic factors and personality characteristics.[14] [15] Symptom

18 patterns are often precipitated by trauma or social factors.[16-18] Maladaptive thoughts, feelings, and

19 behaviour are assumed to maintain the symptoms.[17] [19-21] Regarding treatment, support has been found

20 for a stepped care approach with active bio-psychosocial treatment when mono-disciplinary treatments

21 are insufficient.[17] Randomized controlled trials that compared symptoms and functioning after

22 multidisciplinary rehabilitation versus alternative treatments in patients with CP or chronic fatigue

23 syndrome generally reported up to medium-sized differences.[22-25] Nonetheless, recent research

24 addresses improvement of bio-psychosocial intervention models,[26] [27] 'matching' and 'blending'

25 therapeutic strategies and delivery modes,[28] [29] and promotion of patient engagement.[30] As such, access,

26 reach, adherence and effectiveness of bio-psychosocial interventions may be enhanced.

27 Serious gaming could be of aid here. Previously investigated strategies are 'exergaming' to

28 improve motivation for physical activity,[31] 'brain training games' against dullness in the remediation of

29 cognitive functions,[32] 'virtual reality' for safety in graded activity or exposure,[33] and 'health behaviour

30 gaming' for fun while addressing behavioural antecedents.[3] In the fields of rehabilitation and pain

31 management, virtual environments have shown promise in reducing acute pain by distraction, or in

32 activity management to restore physical functioning.[34] [35] Despite of promising results for various mono-

33 disciplinary applications of gaming and simulation, no evident application seems to exist for supporting

34 biopsychosocial adjustment processes in patients with CP or FSS.[2] [3] [32-37] Outcome improvement after

35 treatment in CP or FSS patients may be mediated by changes in aspects of self (beliefs about illness and

36 fear avoidance, catastrophizing, and psychological flexibility), coping behaviour, and affect.[38] [39] Features

37 that distinguish serious games from traditional modes include covert learning techniques, interactivity,

38 storytelling, sound effects, visuals, and 'debriefings'. They could offer relative benefits for behavioural

39 change processes through distinctive attentional (presence), affective (enjoyment), and meta-cognitive

40 processes.[40-43] Further research into gaming mechanisms is needed,[42] and may also inform about how

41 biopsychosocial intervention mechanisms could be strengthened'.

3

1   However, within the outcome evaluation of multidisciplinary interventions several complicating

2   factors arise. These consist of outcome multidimensionality and dependency on implementation in

3   actual health care settings.[44] [45] In other words, characteristics at the levels of organization, care

4   providers, patients and interventions all affect outcome levels.[46] [47] Therefore, ideally, multiple sources of

5   information are used to evaluate to what extent, for whom, when and under what circumstances an

6   innovation of multidisciplinary treatment improves outcomes in patients with CP or FSS.[48] [49] For

7   example, some intervention studies show different outcomes of a computer delivered therapy when

8   applied in different countries.[50] This is also an important issue for the outcomes of serious gaming,

9   which are clearly sensitive to context factors. [51] [52] Therefore, 'debriefings' are suggested as a method for

10   discussing and exploiting game-play experiences and strengthening learning outcomes.[53] Previous

11   studies leave uncertainties about how to effectively organize instructional support, i.e. via software or

12   delivered by (trained) health care staff, via internet or face-to-face, in groups or individually. There is

13   strong consensus that adequately powered clinical trials are needed to determine the effectiveness of

14   serious gaming.[2] [3] [37] Moreover, pragmatic trials and realist evaluation principles are needed to

15   determine how serious gaming relates to patient outcomes depending on how it is deployed in actual

16   health care settings.

17

18   **Study aims**

19   Here we describe the protocol for outcome and process evaluations of complementary serious gaming

20   during regular multidisciplinary rehabilitation for patients with CP or FSS, which holds three study aims.

21   The first aim is to investigate the effectiveness of serious gaming as a treatment complement. We

22   question to what extent multidisciplinary rehabilitation with an additional serious gaming component is

23   more effective than multidisciplinary rehabilitation without serious gaming for symptom reduction and

24   clinically relevant improvement. Primarily, interdependent outcome domains of pain, fatigue, and

25   emotional functioning (pain intensity, pain coping and cognition, fatigue complaints, and psychological

26   distress) are studied, because they are considered to be relevant and plausible for the intervention and

27   population.[27] [45] Secondary outcomes are patients' impression of overall improvement, general subjective

28   health, and satisfaction with functioning and treatment.

29   Secondly, we aim to understand which innovation, patient, provider, and organization level

30   factors influence the outcomes of serious gaming for patients. Innovation level factors could be design

31   quality and compatibility with user routines. Patient level facilitators or barriers could be demographic,

32   health status and intervention history factors. Serious gaming outcomes could also depend on complex

33   provider behaviour by attitude, skill, and/or time constraints. Finally, outcomes of serious gaming could

34   be influenced by its organization in a clinical setting. Therefore, we pose the question: what are the

35   barriers and facilitators of outcome improvement through serious gaming according to patients,

36   providers, and other stakeholders? Furthermore, we question how variation in serious gaming outcomes

37   can be decomposed with plausible patient level differences and/or delivery conditions within the

38   treatment setting (i.e. size of a debriefing group).

39   The third aim concerns *how* serious gaming contributes to patient outcomes. For this, we

40   explore various serious gaming mechanisms, being the subjective experiences and objective

41   performances in context that may affect health outcomes. In addition, plausible linear effects between

4

mechanisms and patient outcome variables are investigated. Achievement of all three research aims will inform the further development of a valid and practical programme theory of serious gaming outcomes in regular health care for patients with CP or FSS.

METHODS AND ANALYSIS

Study design and procedure

An embedded experimental mixed-methods design is created by an integrated multidisciplinary research team (MV, HV, MJ, AZ, AM) to address all three research aims in a single study (see figure 1). For studying the first research aim, which is to estimate patient level outcome improvement due to serious gaming during regular outpatient rehabilitation, a two-armed naturalistic quasi-experiment is prioritized (displayed at the centre of figure 1). A serious gaming intervention is deployed, for usage by all patients, at two sites of a Dutch outpatient rehabilitation clinic. Therefore, an intervention group is constituted of patients who receive the multidisciplinary rehabilitation programme with an additional serious gaming intervention. The control group consists of patients who simultaneously follow the same programme in two similar sites of the same clinic without serious gaming. Codified quantitative data from patient records will be retrieved and analysed to examine between group outcome differences. The protocol for the naturalistic quasi-experiment was entered in the Dutch trial register (NTR6020).

Figure 1: Overview of the Mixed-Methods design

Embedding qualitative methods before, concurrently to, and after the quasi-experiment suits our second and third study aims. This mixed-method design is ideal for examining intervention processes, understanding mechanisms related to variables, and supporting programme theory development.[54] Herein, no intermediate qualitative results are communicated with providers and implementers during the experiment. Data collection started in April 2016 and is planned to end in March 2017, quantitative outcome data will be retrieved when concurrently collected qualitative data are analysed (February 2017).

Recruitment

Sites and professionals

Two intervention sites where serious gaming is deployed participate in the study. For the recruitment of control subjects, two other sites (out of 18 sites as part of the same treatment centre) are selected based on similarity with regard to patient characteristics, facilities, protocols, history, personnel, location in or near a city in the southern Netherlands, and no other research projects planned during the intervention period. The treatment centre provides rehabilitation care covered by health insurance in association with a university medical centre. Professional study participants are local stakeholders of serious gaming, including experts, implementers, and providers.

5

1   Patients

2   Patient candidates received an indication of eligibility for outpatient multidisciplinary rehabilitation from

3   a rehabilitation physician, and completed half of their rehabilitation programme at a participating site.

4   Physician indications of eligibility are followed, which are based on the results of diagnostic surveys,

5   physical and psychological investigations, and clinical interviewing via teleconference. Accordingly,

6   patient participant inclusion criteria are: being between 18 and 67 years of age, reporting the presence

7   of pain for more than 6 months, or fatigue complaints or a musculoskeletal disease for more than 3

8   months, having no (more) indication for another (cost-) effective medical treatment, and have

9   concomitant psychosocial problems. Patients are excluded from participation if: psychiatric symptoms

10   are not adequately controlled, there is significant risk of psychological decompensation through a

11   rehabilitation treatment, language or communication problems make it impossible to follow

12   rehabilitation, and/or demonstrable inability to change behaviour (due to personality disorders, third

13   party liabilities, or otherwise). An information letter, consent form, and verbal explanation are provided

14   by local care providers. The recruitment process is monitored to ensure that all candidates are invited.

15

16   **Interventions**

17   Multidisciplinary rehabilitation programme

18   The outpatient multidisciplinary rehabilitation programme includes common bio-psychosocial

19   approaches, and incorporates a focus on well-being and participation.[26] The standardized 16-week

20   programme consists of on average 95 hours of individual or group sessions that are organized in

21   modules and centrally assigned to individual patients based on diagnostic findings. Each patient is

22   treated by a team of two physiotherapists and two registered master's degree psychologists.

23   Psychotherapeutic techniques include Cognitive Behavioural Therapy and psychodynamic approaches.

24   For all patients, treatment contains rationales, goal setting and feedback, social support, exposure

25   treatment, behavioural repetition and substitution, skills training (in relaxation, social skills, and

26   meditation), and identity development techniques. Allocation of physical therapy, cognitive

27   restructuring, eye movement desensitization, and an intensive 2-day well-being course depend on

28   diagnostic findings for physical status, psychopathological symptoms[55] and fear avoidance beliefs,[56]

29   post-traumatic stress, and psychological well-being.

30

31   Serious gaming

32   *Theory and change techniques of the serious game LAKA*

33   Developer assumptions for the game LAKA have been documented throughout development and

34   related to conceptual frameworks (see appendix).[57] Serious gaming is proposed to promote practice for

35   well-being improvement, and for identifying and diminishing distortions and biases of self. This may be

36   helpful for patients with CP or FSS in reducing the burden of their symptoms.[58] Based on a review of

37   information about the design rationale, functionality, validity proof (before outcome evaluation), and

38   data protection measures of LAKA, an independent jury awarded 3 out of 5 attainable stars for quality

39   (see appendix).[59]

40   The serious game LAKA promotes practice through an Avatar model. Before the game starts,

41   participants are invited to identify with an Avatar of their chosen gender and name (table 1). The

6

1 storyline introduces an Avatar who recently experienced physical and social deterioration, senses an

2 urgency to change, and engages in a trip around the world to learn about 'the art of living'. Player tasks

3 are: to explore and select virtual action plans for 'encounters' with non-playing characters, to evaluate

4 their 'satisfaction' about chosen actions, and to perform skills training in focused attention and open

5 monitoring meditation exercises.[60] Encounter scenarios model uncertain events resulting in varying

6 Avatar states depending on action plans chosen by players. Encounters are increasingly influenced by

7 distant cultural meanings to challenge anticipation of the course of events (i.e. depending on the

8 scenario, agreeable responding can result in a pleasant interaction or involvement in a scam). Players

9 receive global feedback on the extent to which chosen actions correspond with a reference model for

10 values (see appendix). Self-reflective elements are interspersed with short casual action and puzzle

11 games, images, and information associated with the location of the Avatar. These features are included

12 to vary game play, and can be skipped.

13

14 *Table 1: Features, dose, and tasks*

Features	Dose (in game frequency)	Tasks
Introduction	1	- Choose Avatar gender and name - Receive instruction: to identify with the personal Avatar - Introduction to Avatar storyline - Receive task instructions from LAKA (non-playing character with a mentoring role)
Encounters (See appendix for screenshot and user interface)	16	- Select action plans for the Avatar in encounters with non-playing characters (each instance offers 5 optional action plans, which are modelled after a reference set of values: generosity, moral discipline, patience, enthusiastic perseverance).
Mood scenarios	8	- Select action plans for the Avatar when subjected to an adverse event. - Given the adverse scenario: think of what your own affective state would be in this situation, and bear in mind the depicted emotional state of the Avatar.
Reflections	4	- Assess satisfaction about selected Avatar actions on a scale of 0-10. - Receive feedback from LAKA on chosen action plans. - Receive feedback about the correspondence between satisfaction rating and LAKA assessment.
Attention training:	3	- Guided (focused attention and open monitoring) meditation exercises for mental stability.
Tours:	16	- Skip or listen to 'tour-guide' voiceovers informing about pictures of the location visited by the Avatar.
Loading screens	-	- See where travel destinations are located on a geographical map.
Mini-games:	8	- Action games: Steering a vehicle (by using tilt mechanism of tablet pc, or keyboard arrow controls) to arrive at the next encounter (reference: 'rocket bird'). - Puzzle: Fix a road by connecting parts of the road to arrive at the next encounter (reference: 'plumber games').
Festive closing	1	- Replay of 'extreme' responses throughout the game.

15

16 *Mode of delivery*

17 In accordance with patient suggestions for optimal reach, the rehabilitation clinic delivers professional

18 assistance and the occasion for playing the serious game LAKA on site, besides downloading and playing

19 on a home computer[4]. Suitable rooms with Wi-Fi connection, tablet computers with LAKA installed, and

7

1 headphones are provided. Four 1-hour sessions of serious gaming are planned for 1 to 6 patients

2 simultaneously during weeks 9-12 of their rehabilitation programme. The sessions are scheduled in

3 connection with other therapy sessions to ease coordination with daily activities. Staff members are

4 available for consultation on accessing serious gaming (i.e. for technical issues and adaptation to special

5 needs). Experienced therapists (1 physiotherapist, and 3 psychologists) facilitate the first session

6 (introduce LAKA and instruct to complete the game independently during session 2 and 3) and the

7 fourth session (debriefing). The goal of the debriefings was to discuss experiences of game play,

8 technology acceptance and learning, and facilitate learning transfer to daily life. For external validity, no

9 specific roles were assigned to other local stakeholders for the delivery of serious gaming (i.e. to observe

10 'natural' problem solving by implementers).

11

12 Programme theory

13 The framework of context, mechanism, outcome (CMO) configurations is used to structure ongoing

14 development of a programme theory for serious gaming as a complement during multidisciplinary

15 rehabilitation.[61] To illustrate, a patient with an active coping style self-exposed for a short amount of

16 time to unsupported serious gaming during multidisciplinary rehabilitation (context), experienced

17 enjoyment and discrepancy regarding valued self-identities (mechanism), and expected this to

18 contribute to health improvement (outcome)[4]. Timely building blocks for CMO configurations for serious

19 gaming are deduced from the literature. Besides by symptom categorization, serious gaming outcomes

20 were interpreted by frameworks of rehabilitation mechanisms as self-improvements (see appendix).[27 45]

21 [57 58 62 63] Two comprehensive implementation models are used for the classification of context factors,

22 such as planning and compatibility relative to other treatment components.[64 65] Finally, mechanisms of

23 serious gaming are discerned as gaming behaviours (frequency, length, and performance of game play),

24 and user experiences of gaming, simulation, and information systems. More specifically, subjective

25 mechanisms may involve sense of presence,[66] technology acceptance,[67] positive and negative affect,[68]

26 game-based learning,[69] and perceived 'learning transfer' to daily life.[53]

27

28 **Measures**

29 Quantitative data

30 Outcome and case-mix variables are retrieved from routinely administered clinical patient records after

31 all participants have completed their rehabilitation programme. All patient variables are collected by the

32 clinic through a standardized and secured web-surveying procedure, including facilitation of patients

33 without convenient computer access and promotion of follow-up completion.[4 70] Outcomes are

34 monitored at the indication of eligibility (at baseline), after 8 weeks of treatment (intermediate), and

35 again after 16 weeks of treatment (post). Relevant and valid measures were available for assessing the

36 primary outcomes (see table 2)'. These endpoints include a numerical rating scale for current pain

37 intensity,[71] the pain coping and cognitions list (PCCL),[72] fatigue as assessed by the Checklist Individual

38 Strength (CIS),[63] and psychopathological symptoms as measured by the Symptom Checklist (SCL-90).[55]

39 Secondary measures focus on clinical relevance, such as patients' global impression of improvement

40 after treatment.[45] Another widely used single item Likert-scale rating is used for measuring general

8

1   health (poor to excellent).[73] Finally, numerical rating scale items are available to assess patients'

2   satisfaction about treatment and functioning (see table 2).

3

4   *Table 2: Quantitative outcome measures*

Variables	Measures	Time of measurement
Primary outcomes		
Current pain intensity	1 item Numerical Rating Scale (NRS) 0-10	Baseline, intermediate, post treatment
Pain coping and cognition	Pain Coping and Cognitions List (PCCL)	"
Fatigue	Checklist Individual Strength (CIS)	"
Psychopathological symptoms	Symptom Check List (SCL-90)	"
Secondary outcomes		
Clinically relevant improvement	Patient Global Impression of Change (PGIC)	Intermediate, post treatment
General subjective health	"What do you think of your current health in general?"	"
Perceived functioning	"Please indicate how satisfied you are generally taken with your current level of functioning"	"
Treatment satisfaction	Three Likert scale items, i.e. "Would you recommend this treatment centre to other rehabilitation patients?"	Post treatment

5

6   Patient variables are demographic, health status, and treatment history information (see table 3).

7

8   *Table 3: Patient characteristics*

Variables	Variables (measurement)
Age	Years of age (calculated from registered date of birth)
Gender	% Female
Socio-economic status	Highest education level, source of income (categorical rating items)
Coping style	Utrecht Coping List (UCL)[74] (validated questionnaire)
Environment	Presence of problems with regard to social life, financial situation, trauma, work situation (categorical rating items)
Symptoms	Duration (months; calculated from the date of onset), course (categorical rating item), and pain location (standard physical examination report)
Physical status	Body Mass Index, blood pressure, musculoskeletal conditions (standard physical examination report)
Other treatment	(Changes of) presence of medication usage, frequency of health care visits, previous visits to health providers (medical specialists, physiotherapists, and/or psychologist) (categorical rating items).
Treatment (modules) received	Automatic logs of session presence (determined from absence registrations by health care providers)

9

10   Intervention mechanisms may cover subjective experiences and objective behaviours of serious gaming

11   (see table 4). Automatic registrations in patient files enable objective assessment of serious gaming

12   frequency, duration, progress, and performance. Moreover, a short survey was composed in

13   collaboration with the rehabilitation centre to measure subjective experiences shortly after serious

14   gaming. This survey contains items on perceptions of using a serious game (regarding usefulness, ease of

15   use, trust, enjoyment, goal clarity, challenge, and learning[4 67 69]), the 10-item short form of the positive

16   and negative affect scale,[75] the involvement and realism scales from the Igroup Presence

17   Questionnaire,[66] and (0-10) numerical rating scale item on perceived learning transfer. A reminder was

9

1 sent to intervention group participants if the survey was not completed within a week after their last

2 gaming session. Finally, a questionnaire on patient values may be used to explore relationships between

3 mechanisms and outcomes of serious gaming.

4

5 *Table 4: Quantitative indicators for mechanisms*

Variables	Measures	Respondents	Time of measurement
Reach, dose, gaming performance	Data logs: frequency, timing, length, progress, and scores of play	Intervention group	During serious gaming (automatic)
Acceptability and playability	Selection of UTAUT2*1 items (perceived usefulness, ease of use, trust, enjoyment) Selection of EGameFlow items (clear goals, challenge, perceived learning)	Intervention group	Post serious gaming
Positive and negative affect	PANAS-SF*2	Intervention group	Post serious gaming
Presence (general, involvement, and realism)	IGroup Sense of Presence Questionnaire item for general sense of presence, and subscales for involvement and realism.	Intervention group	Post serious gaming
Learning transfer	Numerical rating scale (0-10): "Use the following slider to indicate to what extent you expect that the LAKA sessions contribute to your daily life"	Intervention group	Post serious gaming
Values (expressed in thoughts and behaviour)	Values questionnaire*3: 5-point Likert scales, i.e. "If I find it necessary, I'll intervene to help or to protect others".	Intervention and control groups	Baseline, intermediate, post treatment

6 *1 Unified theory of acceptance and use of technology

7 *2 Positive and negative affect scale – short form

8 *3 Psychometric properties are still under investigation. Empirical support for good scale internal consistency, and strong

9 associations with psychological well-being in rehabilitating patients were documented in a report for the Dutch Committee on

10 Test Affairs (COTAN).

11

12 Qualitative data

13 Protocols for focus group and semi-structured patient interviews are informed by the CMO building

14 blocks and principles for interviewing in realist evaluation.[76] Accordingly, the interviewer starts with an

15 open and explorative style, but may sometimes take an explanatory role to raise discussion about

16 programme theory elements when CMO configurations become better delineated. Providers are

17 expected to be especially knowledgeable about context and mechanisms of serious gaming, while

18 patients may say the most about context and outcomes. Purposive sampling of participants is used until

19 reaching a point of data saturation. All interviews are tape-recorded and verbatim transcribed.

20 Transcripts and a summary of findings are sent to participants by e-mail to enable them to check if their

21 views are accurately reflected.

22

23 *Stakeholder (focus group) interviewing*

24 Four focus group interviews are held, two before and two after the naturalistic experiment, to involve

25 stakeholders in the ongoing development of serious gaming and programme theory. Participant

26 selection and topics are based on actual data needs. Heterogeneous groups of care providers,

27 implementers, and experts (in ICT, well-being, and serious gaming) are invited for the first and last

28 discussion meetings. The first interview focused on the research goals for an open discussion. The last

29 group interview will focus on programme theory for member checking and refinement. Homogenous

10

1 groups of provider participants may be invited for the second and third focus groups for more in-depth
2 information. Provider participants are asked to share positive and/or negative feedback about serious
3 gaming via a secured web-form. This includes information on the occurrence and management of
4 adverse events and/or unintended effects during serious gaming.
5

6 *Patient interviewing*
7 Two open interview questions about gaming experience and perceived learning transfer are added to
8 the post-gaming survey for intervention group participants. Patient participants with high and low
9 scores on a 1-item numerical rating scale (0-10) for perceived learning transfer are invited for a semi-
10 structured interview after their rehabilitation treatment. These interviewees are asked to describe their
11 health outcomes during rehabilitation, and to list the three most important reasons why serious gaming
12 did, or did not, contribute positively or negatively to this process. A point of saturation is reached if the
13 three factors (context and/or mechanisms) mentioned are all richly described. Control group
14 interviewees are matched to some of the intervention group interviewees to compare rehabilitation
15 outcome changes for similar cases with versus without serious gaming.
16

17 **Analysis**
18 Statistical outcome evaluation
19 Quantitative data will be imported in SPSS 22, described after statistical inferences, and analysed on
20 intention-to-treat basis. All case-mix variables are described for individual study participants, as well as
21 the differences between intervention group and control group participants. Multivariate mixed-linear
22 modelling techniques will be used to evaluate the extent to which serious gaming predicts variance in
23 patient outcome levels between the intermediate and final outcome assessments of the rehabilitation
24 programme. Effective sample size and intra-class coefficients will be calculated to determine
25 dependency on hierarchical patterns in outcome variation by care provider levels. An optimal prediction
26 model will be specified, correcting for potential unbalances between the study groups (at baseline
27 and/or intermediate), and/or important higher-level random effects.
28

29 Process analyses
30 A programme theory will be created after a sequence of analysis steps. In each step, analyses will be
31 performed completely by MV and in part by MJ or AZ (independent coding of interviews, and re-running
32 syntax), and discussions will be held involving a third author (HV) to resolve differences and find
33 agreement about the results. First, concurrently collected qualitative data analyses will be performed to
34 identify plausible CMO configurations from the perspectives stakeholders. All qualitative data will be
35 coded in vivo and higher order coded using CMO building blocks to determine configurations. Secondly,
36 a selection of key CMO configurations will be made based on counts of the number of participants
37 supporting them in their open text responses to the post-gaming survey. Hypotheses will contain
38 specific expectations of (linear) relationships implied by the CMOs. If needed, additional provider or site
39 level data (i.e. debriefing session group sizes) will be retrieved from clinical administration records.
40 Third, quantitative data will be screened by testing internal consistency in SPSS or data triangulation
41 with qualitative data if possible. Fourth, hypotheses will be tested with available and valid quantitative

11

1   data. Fifth, data from the last focus group will be coded. Sixth, quantitative and qualitative findings will

2   be mixed for an overall interpretation and drawing final conclusions.

3

4   **Power calculation**

5   From practical, theoretical and statistical perspectives, a powerful primary outcome assessment was

6   anticipated by focusing on recruiting a sufficient number of individual patients from the four

7   participating treatment facilities. The rehabilitation centre (n=1), intervention sites (n=2), as well as the

8   number of time-points (3), are practically fixed. Analysis of unpublished pilot data suggested that

9   variation in baseline to post treatment outcome changes between treatment locations might be

10   negligible relative to individual variation within sites (intra-class correlations < .05).

11   G*Power was used for sample-size calculations[77]. A required sample size of 212 participants was

12   calculated for determining a small to medium effect by means of a MANOVA test of global effects. Effect

13   size estimation was based on meta-analysis results for the effects of serious games on cognition,

14   motivation, and psychological outcomes[3]. The following parameters were inserted: for power (1-Beta) =

15   0.8; effect-size f^2 (V) = .0625; type-II error probability (alpha) = .05; number of dependent variables = 5;

16   and number of groups = 2. By the same standards, it was checked if the determined sample size would

17   also be sufficient for independent univariate tests of variance on each of the primary outcomes.

18   Anticipating some level dependence and/or randomly missing data (pain coping and cognition

19   measures are not filled out by patients reporting 0 pain intensity at baseline), 250 patient participants

20   will be recruited. Assuming 20% treatment and study attrition rates and an average weekly inflow of 9

21   patients starting with their treatment within each of the four facilities, outcome data are available 6

22   months after recruiting the first patient.

23

24   **ETHICS AND DISSEMINATION**

25   Ethical approval for the mixed-methods protocol was obtained from the psychological ethics committee

26   of Tilburg School of Social and Behavioural Sciences (EC-2016.25t). In the absence of a legal obligation

27   for medical ethics review, independent judgement was provided on the protection of patient rights by

28   conformity to the letter and rationale of the applicable laws and research practice. Patient participants

29   are consented before participation, that is before receiving the additional (5-10 minute) survey

30   (intervention group), being invited for a semi-structured interview, or retrieving their codified data.

31   Participants were protected against harm by regular clinical safety measures throughout. Professional

32   participants are also consented before participation in qualitative data collections. Under supervision of

33   MJ, MV is responsible for safe storage and the accessibility of (codified) research data to all authors.

34   Qualitative and quantitative results will be presented and discussed together in one or more research

35   article(s), and at one or more international scientific conferences. A summary of study results will be

36   provided to the study participants.

37

38   **DISCUSSION**

39   The novelty of the serious gaming intervention and study methods are strengths of the proposed

40   evaluation, but imply limitations as well. LAKA is the first serious game that promotes practice for self-

41   process enhancement under highly prevalent adverse conditions such as CP or FSS. CMO configurations

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1 may be identified that are transferable to other populations and settings where similar approaches to

2 behavioural change are beneficial[78]. However, internal and external validity are threatened due to

3 divergence from the golden standard procedures of a (cluster) randomized controlled (multi-centre)

4 trial. Instead, pragmatic considerations for the deployment of serious gaming during rehabilitation in

5 two sites of a single Dutch centre led treatment allocation, recruitment, and data collection methods.

6 Different comparisons with serious gaming (i.e. usual care, waiting list, or text based computer-based

7 intervention), more elaborate diagnostic assessment, and outcome measurements including role

8 participation and long-term follow-up are precluded. Still, conditional optimization of quasi-

9 experimental methods is a legitimate strategy for obtaining evidence on the effectiveness of an

10 intervention.[79]Apparent confounding factors (i.e. differences in usual treatment received) should be

11 controlled for by appropriate methods. By the emergence of practical limitations, study strengths shift

12 towards dealing with questions of process. The realist evaluation principles and mixed-methods used in

13 this study are increasingly accepted in scientific communities as means to compensate for practical

14 limitations and to build programme theories that enhance future predictions of intervention effects

15 across patients and health care settings.

16   Legitimate application of mixed-methods is promoted by the protocol in various ways. First,

17 participant recruitment and selection methods for quantitative and qualitative examinations allow a

18 strong representation of patients receiving bio-psychosocial treatment in a regular outpatient setting.

19 This differs from studies in which the eligibility of applicants for computer-based intervention depends

20 on motivation and/or ability to use a computer or internet facilities.[80 81] Secondly, perspectives of

21 insiders (patients, health care providers and developers) and outsiders (independent experts and

22 members of the research team) will be utilized. Third, relevant theoretical constructs are specified

23 before quantitative and qualitative data collections to prevent process analysis results being strongly

24 affected by the sequencing of qualitative and quantitative methods. Fourth, predefined steps structure

25 data convergence and switches in epistemological paradigms when qualitative methods are used to

26 propose quantitative results (in advance) and to explain them (afterwards).

27

33 **AUTHORS' CONTRIBUTIONS**

34 MV, HV, AM, and MJ conceived the protocol. MV drafted the work, which was critically revisited by HV,

35 AZ, AM and MJ for important intellectual content. All authors have given their final approval of the

36 version to be published and agree to be accountable for all aspects of the work.

37

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medical centre (The Netherlands). Qualitative data collection, data management, data analyses, interpretation of results, writing of the report, and publication decisions are authorized by university staff members.

COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form and declare:

Dr. Vugts reports employment by Ciran, and is provided time and occasion to conduct independent doctoral research by way of agreement at Tranzo, Scientific Centre for Care and Welfare, Tilburg University. The terms of this arrangement have been reviewed and approved by Tranzo in accordance with its policy on objectivity in research.

Dr. Joosen has nothing to disclose.

Dr. Zedlitz has nothing to disclose.

Dr. Vrijhoef reports personal fees from Ciran, outside the submitted work.

Dr. Mert has nothing to disclose.

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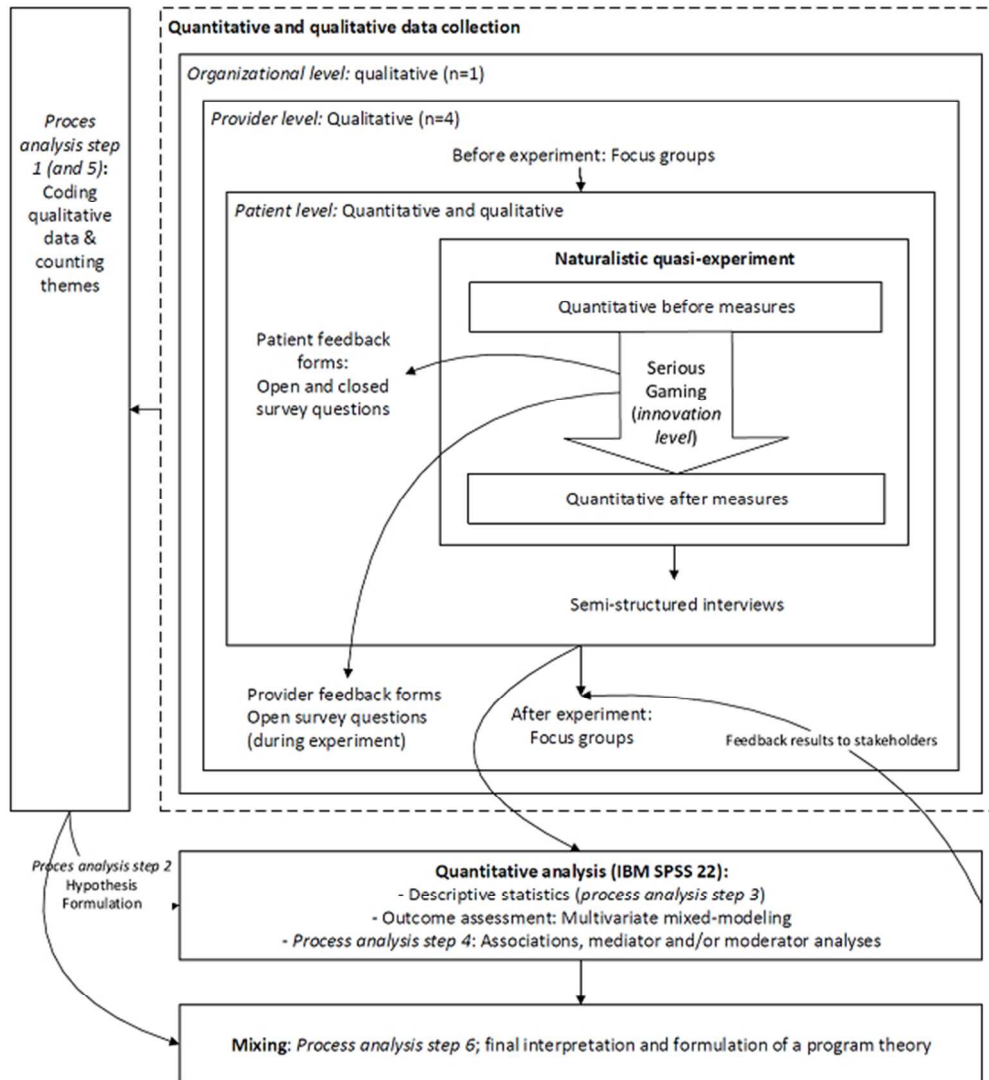53
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Figure 1: Overview of the Mixed-Methods design

173x188mm (96 x 96 DPI)
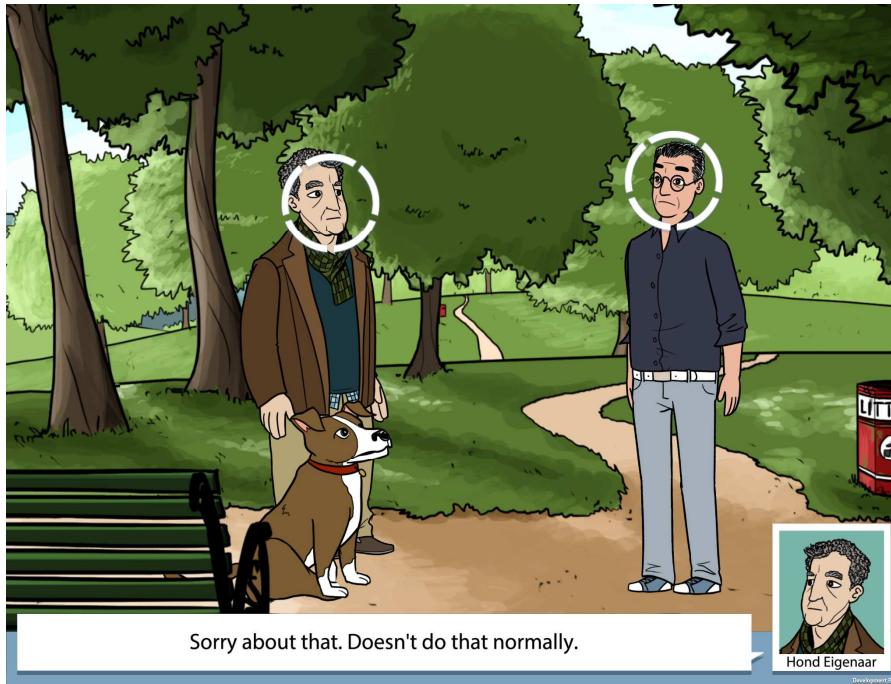
SUPPLEMENTARY FILE

Content:

1. Developer assumptions
2. User interface and screenshot examples
3. Information about the design rationale, functionality, validity proof (before outcome evaluation), and data protection

1. *Developer assumptions*

Developer assumptions	Related theory (interpretation)
The rehabilitation program is based on a (four dimensional) bio-psycho-social-spiritual treatment model in which Eastern and Western (medical) interventions are integrated. Interventions are aimed at improving 'mobility of mind', which is defined as: flexibility in accommodating 2 dynamic processes: 1) participation in private, social, and work roles, and 2) the ability to participate. Ability to participate depends on four interdependent aspects: symptoms (signals due to organ system injury or disturbance in shaping and controlling one's life or 'existence'), autonomy, perspective ('to see one's opportunities for finding meaning in life through inspiration'), and values. A reference for values is given by generosity, moral discipline, patience, enthusiastic perseverance, and mental stability. LAKA was designed to offer covert learning and skills training for enhancing a sense of self characterized by autonomy, values, and perspective.	This learning content may converge with and diverge from related concepts known in published scientific literature, including: - Categories of the International Classification of Functioning: specific (higher) mental functions, and activities and participation domains 6-9.[1] - Coping flexibility under conditions of CP or FSS.[2] - Eudaemonist process of psychological well-being.[3] - Autonomously motivated pro-social behaviour.[4 5] - (Neuro) psychological processes associated with similar practices (focused attention, open monitoring, and ethical enhancement) in general: self-awareness, self-regulation, and self- transcendence.
Improvement in mobility of mind is associated with better health outcomes after rehabilitation in patients with complex pain or fatigue (1st and 2nd).	Learning content may converge with and diverge from similar plausible targets in non-pharmacological treatment for patients with CP or FSS: Internal control beliefs (+), avoidance (-), self-acceptance (+), mindfulness (+), values-based action (+), rumination (-), catastrophizing (-), negative (-) and positive mood and social interaction (+)[2 6]
(Video) game mechanics can be leveraged to enhance learning through player's self-awareness and intrinsic motivation. The game is of a relatively short duration, but promotes continued practice by any means outside the game. 'Serious gaming sessions are planned after educational components (stress management and well-being, cognitive restructuring, and meditation) to enable complementary learning engagement and transfer'	Plausible ways in which video game mechanics may affect the self in players (on different levels): - Self-efficacy theory: vicarious learning in health behaviour games.[7] - Self-determination theory: gaming elicits representations of valued self-identities (through autonomy, competence, and relatedness).[8] - Meta-cognitive processing is a likely consequence of, and characterizes interaction in the context of video game-play.[9] - Distinctive features of serious gaming strengthen (moderate) effects of behavioural change content on outcomes[7]

1

2. User interface and screenshot examples

User interface (accessibility): The human-computer interface is designed for being easy to use (i.e. there is no time pressure). It is controllable by individuals with low computer skill. It involves making decisions by taping on the screen (pre-selecting and confirmation). One of the casual mini-games involves usage of the tilting mechanism of the tablet pc, for steering an object. Progress is never dependent on gaming skills.

2

3. Information about the design rationale, functionality, validity proof (before outcome evaluation), and data protection

Category	Item	Question	Answer
<u>Game description</u>			
Meta-data	Operating system	Operating systems of the game	Android, iOS, Windows, OS X
	Version	Version	Beta+
	Web-link	Web-link	Yes*[1]
	Project type	Commercial, non-commercial, other	Non-commercial
	Access	Public / restricted / other	Restricted
	Adjunct devices	Is an adjunct device needed?	No adjunct device needed
Development	Funding	How was development funded? Eg, funding agencies, investors	Investors (Ciran)*[2]
Sponsoring / Advertising	Advertisement policy	Is the game free of commercial pop-ups?	Yes
		If not, what is advertised?	NA
	Sources of income	Are there sources of income within the game?	No
	Sources of income outside game	What are the sources of income of the owner/distributor?	The owner and distributor (Ciran) is a foundation providing outpatient rehabilitation care covered by health insurance.
Potential conflicts of interest	Affiliations	What affiliations do the publishers have that could influence content or user group?	Publishers are affiliated with the owner/distributor
	Conflicts of interest	What interests do the publishers have that could influence the game's content or user group?	Content and user groups are based on the objective of Ciran to improve outpatient rehabilitation for patients with complex chronic pain and/or fatigue. The primary (tentative) purpose of game design is the improvement of (independent) engagement with learning content during a rehabilitation program.
	Disclosure	Are conflicts of interest disclosed?	Yes
<u>Rationale</u>			
Purpose	Goal or purpose	What is (are) the purpose(s) of the game?	To facilitate learning and promote practice for 'mobility of mind' (see developer assumptions) to support recovery in patients with complex chronic pain and/or fatigue.
	Disclosure	Is (are) the purpose(s) disclosed to users?	Yes
Medical device	Medical device	Is the serious game a medical device, or not?	Not
	Class	If yes, which class?	NA
	Approval by legal bodies	If yes, does it comply with the necessary requirements (FDA-approval, CE-mark?).	NA
User group	Specific user groups	For each user group: disease/condition	Patients with chronic pain and fatigue, and problems in multiple (other) domains of functioning.

	Description	Please specify gender, age (range), and other relevant descriptive items.	See inclusion and exclusion criteria as listed in the main body of the article.
	Limits	Are there age limits, or other limits?	According to PEGI classification, the content of the game was found suitable for people who are at least 12 years of age, because it contains some events of mild swearing.
	Disclosure	Is the intended user group disclosed?	Yes
Setting	Patient care	Is the game used in patient care?	Yes
	Training courses	Is the game used in training courses or -curricula?	No
	SCORM compliancy	If used in training courses or curricula, is the serious game SCORM-compliant?	NA
Functionality			
Purposes / didactic features	For every purpose of the game:		
	Learning or behavioural goals	What content will the player learn?	Learning content is based on a reference set of values that manifest in (pro-social) thought and behaviour. These values correspond with the 'perfections' of Mahayana Buddhism. Learning this content is, for research purposes, interpreted as a process of psychological well-being through self-awareness, self-regulation, and self-transcendence (see developer assumptions).
	Relation learning and game play	How does the learning content relate to the game play?	Players are supported in imagining how valued states (or 'selves') are attainable when going on a trip around the world (as a metaphor for private, social, or work participation). Before the game starts, players are explicitly instructed to identify with an Avatar (of their chosen gender and name). It is stated that Avatar choices reflect you as a player. In an introductory cut-scene, this Avatar meets a non-playing character (NPC), named LAKA. The personal Avatar is introduced as someone who experienced deterioration in physical and social domains of functioning, and is determined to improve his/her life. Then, LAKA challenges the Avatar 'to cope well with others' on a trip to 4 destinations (London, Turkey, Asia, and Africa). Meanwhile, most of the mechanics of LAKA enable (virtual) exploration and affirmation of values by selecting action plans for the personal Avatar. At each travel destination, the Avatar faces 4 encounters with NPC's under various circumstances. These encounters are designed as complex interactions between Avatar actions and unpredictable responses of the NPC/environment (rendering variety in cultural settings). For each Avatar action, players select an action plan out of 5 programmed options for physical acting, saying, and/or avoiding. The action plans are modelled by their level of correspondence with values for a given situation. After visiting a destination (after 4 encounters), LAKA appears and asks the Avatar to provide a self-rating of his/her performance, provides feedback on chosen action plans (by giving a certain number of puzzle pieces), and feeds back how well Avatar

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			self-ratings and LAKA ratings correspond (by providing additional puzzle pieces). Finally, LAKA delivers focused attention and open monitoring exercises (explaining and illustrating how to practice meditation, prompting practice, providing a means for stress management). Learning elements are interspersed with short (casual) action and puzzle games, images, and information associated with the location of the Avatar. These features promote enjoyment by varying game play and rewarding curiosity, and can be skipped if preferred.
	Instruction	What intervention leads to the learning transition (eg, tutorial, instructions (in-game))	Besides prompting identification with the Avatar, and adding feedback by LAKA as a form of in-game debriefing, face-to-face debriefings by care providers are offered to improve the transition from game play to learning for daily life improvements.
	Assessment (progress) in game	Through which parameters is progress in the game measured?	Number of encounters completed (progress does not depend on player learning level), but feedback is provided on actions chosen by players.
	Assessment parameters	Which parameters are to designers' opinion indicative for measuring learning effects?	Primary health outcomes (i.e. pain, fatigue) may be an indirect result of learning. Parameters that may indicate a learning effect more directly may be plausible mediators of outcome improvement after behavioural interventions in CP or FSS patients (see developer assumptions). Parameters of game play may also directly reflect learning effects: 1) LAKA assessments may reflect whether a patient thinks and acts in accordance with values, 2) the level of correspondence between self-assessment and LAKA assessment may contain information about the extent to which the player understands what sort of thinking and behaviour relates to psychological well-being.
Content Management	Content Management system	Is the Content Management System restricted to specified persons or institutions?	Yes
	User uploaded content	If no, are users allowed to upload their own content?	NA
	Content monitoring	How is uploaded content checked?	NA
	Restrictions and limits of the serious game	Please describe restrictions and limits of the serious game. What content on the learning goals is not covered?	The game itself does not contain detailed explicit knowledge on relationships between learning content and health outcomes. Complementary delivery modes of rehabilitation (i.e. handbooks, group therapy sessions) serve this purpose. An argument for withholding highly explicit feedback is that the adequacy of action plans (coping) is context dependent. The game enables safe exploration of options for (non-automatic) responding to contextual clues. Consequently, the game triggers reflection by leaving some ambiguity about what might be the 'right' sort of behaviour. This ambiguity might diminish levels of acceptance/playability (perceptions on feedback or challenge) in some players. Professional support may partially compensate this issue when embedding the game within regular treatment. The game was found to be engaging enough to play ones or twice (2-5 hours), which is

			not expected to be enough for moderate or strong average effects on player behaviour and health outcomes.
Potentially undesirable effects	Potentially undesirable effects	What potential undesirable effects could the game have?	No undesirable effects were expected and none were observed in qualitative analysis during a feasibility study*[3].
	Disclosure	Are such potential undesirable effects disclosed to the user?	NA
	Measures taken	What measures are taken to prevent potential undesirable effects?	Based on the result of feasibility study, we expect no undesirable effects. During the present evaluations, undesirable effects will be investigated again.
Validity			
Design process	Medical expert complicity	Were medical experts (content experts) involved in the design process from the start?	Lama's from the Tibetan Institute Yeunten Ling, a psychometric expert; A.H. Akkerman, and Ciran; A.H.M.M. van Bergen, and J.J. Jochijms created the 'mobility of mind' questionnaire that operationalizes the content on which LAKA is based. They were also involved in the formulation of program requirements, or provided feedback on prototypes of LAKA.
	User group complicity	Were representatives from the user group involved in the design process from the start?	No
	Educationalist complicity	Were educationalists involved in the design process from the start?	Educationalists have been affiliated with Tilburg University: Prof. Jac L.A. Geurts (gaming expert) had been guiding the process of demand specifications for LAKA. M.A.P. Vugts MSc has been involved as a researcher from the start.
User testing	User testing	Did user testing take place? What were the results, and how were these incorporated in the design?	User testing was performed in feasibility piloting*[3]. The game is free of technical issues. Some comments on playability have not been addressed, because their impacts on outcomes are ambiguous. The only change to the version used in the feasibility study is that mini-games can be skipped after one failed attempt (instead of 3) to increase tailoring to user preferences.
Stability	Platform stability	Does the game produce the same results on different platforms?	Yes
Validity (effectiveness)	Face validity	Do educators and trainees view it as a valid way of instruction?	Yes. Educators agree that learning content is integrated in a valid way (according to the creators of the Mobility of Mind model (see 'content validity'), and agree that its content corresponds with processes of mental well-being as described by the S-ART model (MV, AZ). A group of self-selected patient users recognize that learning content correspond to what is learned by other means (from psychotherapists) during the rehabilitation program*[3]

	Content validity	How is its content validated to be complete, correct, and nothing but the intended medical construct?	A structured self-report questionnaire to assess thought and behaviour in correspondence with values as defined in the teaching model of the 6 perfections was created by Ciran in collaboration with the Yeunten Ling institute (Belgium). A validation report on this test was assessed by an independent Dutch commission for test affairs (COTAN). It was found that questionnaire scores have good reliability, and are strongly correlated with psychological well-being (as expected). Game scenarios were constructed by a professional writer who was familiar with the model and made explicit references to questionnaire items within screen plays for content validity checks. The quality of scenario's and operationalization was monitored under supervision of a creator of the test.
	Construct validity	Is the game able to measure differences in skills it intends to measure?	Research in progress
	Concurrent validity	How does learning outcome compare to other methods assessing the same medical construct?	Concurrent validity was studied using unreported data that were collected in the pilot phase (n=67 patients). A preliminary measure of game score was calculated as the average of all chosen action plans (the quality of each action plan is scaled ordinal; 0, 1, 2, 3, or 4). Performance was assessed by summing the scores for 5 scales corresponding with the behavioural domains of the values questionnaire (generosity, moral discipline, patience, enthusiastic perseverance, and mental stability). Pearson correlations between game scores and the behavioural domain of the values questionnaire were found to be significant, and of a small to moderate size. Self-assessed values measured at baseline (measured within a month before playing the game) correlated .29 with game scores. Values measured post-intervention (1-2 months after playing the game) correlated .39 with game scores. This agreement is encouraging given the differences in how to construct indicators were measured.
	Predictive validity	Does playing the game predict skills improvement in real life?	Research in progress
Data protection			
Data protection and privacy	Data processing	How is data collected in the serious game?	The game can only be accessed by clients of Ciran by logging in with their treatment ID number and self-chosen password. Log-data are encrypted, send over the internet, and stored by Ciran to save proceedings and enable feedback of game scores. No patient-specific data are stored on devices.
	Patient privacy	Are patient-specific data stored in the game?	Data are recorded by Ciran includes IP addresses, name given to the Avatar (no name, or alias is possible), which could be used to identify users.

		If yes, are patient informed consent criteria met according to relevant national standards?	Yes. All clients at Ciran are informed before the start of their treatment about the use of a digital tracking system for creating and maintaining a patient record, and about their rights for managing their personal records. Therefore, game data concern progress of the treatment and can only be used for scientific research under strict conditions. Therefore, a research protocol describing the codified processing of log-data (thus not including potentially patient specific IP addresses and Avatar names) for the evaluation of LAKA was approved by the ethical committee of Tilburg School of Social and Behavioural Sciences. Medical ethics review is not required for the research.
	Data ownership	Who owns and stores the data resulting from play?	Ciran
	Data storage period	During what period are data stored?	In accordance with the legal storage of medical records (15 years)
	Data removal	Can the user delete data temporarily and/or permanently?	Yes
	Data storage security	Is the data storage secured in conformity with laws of the countries stated above?	Yes
	Data transmission security	Is the data transmission secured in conformity with laws of the countries stated above?	Yes
	Disclosure	Are all items on "data protection" disclosed to the user?	Yes. All items are disclosed to patients before starting their treatment. Specific information on the storage of game data for progress tracking and feedback have not been highlighted in the consent procedure.

*¹ Prototype trailer (English): http://www.ciran.nl/laka/lakaEnglish.php; Trailer of the experimental version of the game (Dutch): http://www.ciran.nl/laka/lakaNed.php

*² https://www.ciran.nl/

*³ Vugts MA, Joosen MC, van Bergen AH, et al. Feasibility of Applied Gaming During Interdisciplinary Rehabilitation for Patients With Complex Chronic Pain and Fatigue Complaints: A Mixed-Methods Study. JMIR serious games 2016;**4**(1).

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