Aalto University & University of Helsinki

Clinical Investigation Plan

Name of the research:

The effects of videogames on depression symptoms and brain dynamics

CIP identifier:	**MelioraRCT**
CIP version:	2.3
CIP date:	26th February 2024
NCT number:	NCT05426265

The structure and section numbering of this document follows the regulation (EU) 2017/745 on medical devices.

As required by the ClinicalTrials.Gov, all original Finnish text in this document has been translated in English.

Revision history

Version Number	Version Date	Summary of Revisions Made:
1.0	14th Jan 2022	Version approved by the HUS ethical committee. Case number: HUS/3043/2021
2.0	14th Feb 2022	Amendment submitted to the HUS ethical committee. ● CIP restructured to be compliant with REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. ● Restructured the CIP headings to clarify the content. ● Renamed the appendix for clarity. ● The questionnaires are updated as follows: Restructured questionnaires: demography and care status. Removed: BDI, OASIS, BAI, MSI-BDP, SHAPS. Added: QIDS-SR16, GAD7, RRS, PVSS, ASSIST-LITE, BEAQ, SDS, WHO-5, GAS, and IEQ. ● Added treatment-as-usual (TAU) group as a third study arm. ● Clarified the distinction between MEL-T01 and MEL-S01. ● Added a qualitative, experiential interview to complement the quantitative data collection. ● The targeted number of subjects decreased from $N = 1000$ to $N = 800$ according to the new power calculation. ● Added an interim analysis. ● Added information that the pseudonymized data will be shared with study partners (Wellcome Leap) in the USA. This is noted in “Participant Information and Consent Form”, “Confidentiality Obligation and Right of Use” and “Privacy Notice and Impact Assessment” (Appendices 2, 3, and 4). ● Clarified the legal notes about data usage in participant’s information and consent appendices. ● Added a clinical interview (MINI) to confirm the subject’s MDD diagnosis. ● In addition to recruiting subjects from HUS and VSSHP, online channels will also be used. ● Removed brain imaging (MEG, MRI) from the main study and added it as a formal academic sub-study with TMS and EEG (using an identical protocol to one earlier approved by HUS ethical committee at Case Number: HUS-1198-2016-9) as an additional research instrument. Healthy subjects are only included in the sub-study. In the brain-imaging sub-study, the subjects are offered a possibility but no obligation to participate in a TMS study.
2.1	23th Mar 2022	● Highlighted the changes made between versions 1.0 and 2.0 ● CIP 3.15.1. added clarification of compensation and changed contacting channel from phone to email ● Clarified the clinical interview phone call process in Appendix 5 and Appendix S4 ● Added sub-study Appendix S8 - HUS-1198-2016 ● Added sub-study Appendix S9 - TMS laboratory safety screening ● Added sub-study Appendix S10 - TMS safety recommendations

		● Added a statement about the ethical practices to Appendix 11 and Appendix S5. ● Changed CSC, principal and coordinating investigator contact details in Appendix 1, 2, 3, S1, S2, S3
2.2.	25th Apr 2022	● Monika Meimer added as coordinating investigator at HUS, Leena Kähäri added as coordinating investigator at VSSHP.
2.3.	26th February 2024	● Clarified the section 3.7.2. to more clearly take into account the intervention use time. ● Clarified the section 3.7.3. regarding hypothesis testing. ● Added two new members to the research group, Vilma-Reetta Bergman and Paula Partanen.

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3.1 General

3.1.1 Single identification number of the clinical investigation

CIP identifier, CIP version, and CIP date visible on the cover page.

3.1.2 Identification of the sponsor

Name:	Aalto University
Address:	P.O. Box 11000 (Otakaari 1B)
Contact details:	Switchboard: +358 9 47001

Sponsor's contact person or legal representative

Name:	Prof. J. Matias Palva
Address:	Department of Neuroscience and Biomedical Engineering, Aalto University, Rakentajanaukio 2, 02150 Espoo, Finland
Contact details	Email: matias.palva@aalto.fi; Tel.: +358 40 1547779

3.1.3 Principal investigator at each site and the coordinating investigator

PI at HUS BioMag:	Hanna Renvall
Address:	BioMag laboratory, HUS Medical Imaging Centre Helsinki University Hospital, PL 340 00029-HUS
Emergency Contact Details	+358 50 501 0326

PI at HUS Psychiatry:	Erkki Isometsä
Address:	Department of Psychiatry University of Helsinki P.O. Box 63 Biomedicum Helsinki 00014-University of Helsinki
Emergency Contact Details:	+358 9 4716 3728

Coordinating investigator at HUS psychiatry:	Monika Meimer
Address:	Department of Psychiatry University of Helsinki P.O. Box 63 Biomedicum Helsinki 00014-University of Helsinki
Emergency Contact Details:	+358 50 593 6454
PI at VSSHP:	Monika Meimer
Address:	Department of Psychiatry Turku University Hospital Administration of Tyks Psychiatry PL 52, 20521 Turku
Emergency Contact Details:	+358 50 593 6454
Coordinating investigator at VSSHP:	Leena Kähäri
Address:	Department of Psychiatry Turku University Hospital Administration of Tyks Psychiatry PL 52, 20521 Turku
Emergency Contact Details:	+358 50 339 0218
PI at Aalto University:	Matias Palva
Address:	The Department of Neuroscience and Biomedical Engineering Rakentajanaukio 2, 02150 Espoo Aalto University
Emergency Contact Details	+358 40 154 7779

Sub-study PI at Aalto University (TMS):

	Risto Ilmoniemi
Address:	The Department of Neuroscience and Biomedical Engineering Rakentajanaukio 2, 02150 Espoo Aalto University
Emergency Contact Details	+358 50 5562 964

Sub-study PI at University of Helsinki (MEG, MRI):

	Satu Palva
Address	Neuroscience Centre, University of Helsinki PL 21, Haartmaninkatu 3B University of Helsinki
Emergency Contact Details	+358 50 4484742

Coordinating Investigator:	Matias Palva
Address:	The Department of Neuroscience and Biomedical Engineering Rakentajanaukio 2, 02150 Espoo Aalto University
Emergency Contact Details	+358 40 154 7779

For information regarding other researchers and their roles, responsibilities, and qualifications, please see Appendix 10 (Appendix 10 - Researchers and Support Staff).

3.1.4 Financing of the clinical investigation

The research is funded by the following:

- **Business Finland Research2Business** funding for project "Aalto R2B Meliora" granted to Aalto University (1/2021-12/2022); 943.000 €; principal investigator J.M. Palva.
    - This funding covered the development of investigational and comparator digital therapeutics devices, their backend infrastructure, and data management. The funding also covers the launching of the intervention trial with symptom questionnaires as primary and secondary endpoints.
- Technology Industries of Finland Centennial Foundation and Jane and Aatos Erkko Foundation **Future Makers funding program** for project "Using New Game Technology for Digital Therapies in the Treatment of Brain Disorders and the Maintenance of Brain Health" granted to Aalto University (1/2021-12/2023); 500.000 €; principal investigator J. M. Palva.
    - This funding was used to develop the methodological basis for dynamic individualization of the investigational device and comparator to enable their use in the personalised medicine framework.
- **Wellcome Leap Multi-Channel Psych** research funding for the project "Plasticity Stimulation in the treatment of anhedonia" granted to University of Helsinki and Aalto University (12/2021-12/2024); 2.550.000 €; principal investigator S. Palva, co-principal investigators R. Ilmoniemi, E. Castrén and J.M. Palva.
    - This funding covers behavioural phenotyping, the brain imaging and stimulation sub-study (MEG, EEG, MRI, TMS) and personalised brain modelling. This project is part of a $55M Wellcome Leap project that aims to uncover mechanistic biomarkers for anhedonic depression, and is well positioned to yield significant breakthroughs in understanding major depressive disorder and its treatment.

The research does not cause expenses to The Hospital District of Southwest Finland (VSSHP) or The Hospital District of Helsinki and Uusimaa (HUS).

Description of the agreement between the sponsor and the site. This study is based on a collaboration agreement between sponsor (coordinating investigator) and sites. Research permits from HUS and VSSHP for the present project account for agreement between the sponsor and these research sites.

3.1.5 Abbreviations

AE	Adverse event
ASSIST-LITE	Alcohol, smoking and substance involvement screening test lite
BEAQ	Brief experiential avoidance questionnaire
CSC	Clinical subject coordinator
DTx	Digital therapeutics
EMI	Electro-magnetic interference
GAD-7	General anxiety disorder questionnaire
MEL-T01	Active investigational device in this study
MEL-S01	Active comparator device in this study
GAS	7 item game addiction scale
GCP	Good Clinical Practice
GPP	Good Programming Practices
HUS	Helsinki and Uusimaa hospital district
IEC	Institutional ethics committee
IEQ	Immersive experiences questionnaire
IRB	Institutional review board
LPFC	Lateral prefrontal cortex
MDD	Major depressive disorder
MINI	International neuropsychiatric interview
PCL-5	PTSD checklist for DSM-5
PGSI	Problem gambling severity index
PHQ-9	Patient health questionnaire
PVSS	Positive valence systems scale
QIDS-SR16	Quick inventory of depressive symptomatology
RCT	Randomised controlled trial
RRS	The ruminative response scale

SAE	Serious adverse event
SDS	Sheehan disability scale
TAU	Treatment as usual
VMPFC	Ventro-medial prefrontal cortex
VSSHP	The Hospital District of Southwest Finland
WHO-5	The World Health Organisation -five well-being index

3.1.6 Synopsis of the clinical investigation

Name of sponsor/company: Aalto University
Study identification code: MelioraRCT
Title of the study: The effects of videogames on depression symptoms and brain dynamics
Study period: Planned first subject visit: 1.3.2022. Planned study completion: 31.12.2023.
Participating countries and number of sites: Neuroscience Centre, HiLIFE, University of Helsinki, Finland. Department of Neuroscience and BioEngineering Aalto University, Finland. BioMag laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Finland. Aalto NeuroImaging Infrastructure, Espoo, Finland
Number of subjects: Main study: $N = 800$ with major depressive disorder (MDD). In addition, in the sub-study: $N = 100$ healthy adults

Study objectives:

The study is a comparator-controlled, randomised, double-blinded intervention study aimed at assessing the effects of the investigational device MEL-T01, “Meliora”, on the symptoms of major depressive disorder (MDD). MEL-S01 acts as a comparator. MEL-T01 is a game-based digital-therapeutics (DTx) medical software device developed at Aalto University and is intended to be used as a treatment for MDD together with treatment-as-usual (TAU). MEL-T01 implements personalised cognitive training to alleviate MDD symptoms and improve cognitive performance in MDD subjects.

Arms and interventions:

Arm	Intervention
MEL-T01	Active investigational device MEL-T01 is a digital intervention implemented in a video game with cognitive training components. MEL-T01 is provided together with Treatment As Usual (TAU).
MEL-S01	Active comparator device MEL-S01 is a digital intervention implemented in a video game with reduced cognitive training load. MEL-S01 is provided together with TAU.
TAU	No intervention.

Primary hypotheses:

- MEL-T01 is superior to TAU in alleviating MDD symptoms as measured by the change in subject health questionnaire (PHQ-9) score between time points T0 (before the intervention) and T3 (after a 12-week intervention).
- MEL-S01 is superior to TAU in alleviating MDD symptoms as measured by the change in PHQ-9 score between T0 and T3.
- MEL-T01 superior to MEL-S01 as measured by the change in PHQ-9 score between T0 and T3.

Secondary hypotheses:

- In terms of a score change from T0 to T3,

  MEL-T01 is superior to TAU,
  and MEL-S01 is superior to TAU,
  and MEL-T01 superior to MEL-S01 in:

    - reducing depression symptoms as measured by quick inventory of depressive symptomatology (QIDS),
    - reducing rumination as measured by short-version ruminative response scale (RRS),
    - reducing anxiety symptoms as measured by general anxiety disorder (GAD-7),
    - reducing the disability symptoms as measured by sheehan disability scale (SDS),
    - increasing positive emotions as measured by positive valence systems scale (PVSS),

      and

    - improving well-being as measured by the WHO-five well-being index (WHO-5)

- The effect of the MEL-T01 is mediated by the training dose, as measured by the subject's total game-playing time during the intervention, and evidenced by a positive correlation between MEL-T01 game time and reduction in symptoms as measured by the PHQ-9.
- The effect of the MEL-S01 is mediated by the training dose, as measured by the subject's total game-playing time during the intervention, and evidenced by a positive correlation between MEL-S01 game time and reduction in symptoms as measured by the PHQ-9.
- The effects of MEL-T01 on depressive symptoms as measured by PHQ-9 are mediated by positive game experience as measured by the immersive experiences questionnaire (IEQ).
- The effects of MEL-S01 on depressive symptoms as measured by PHQ-9 are mediated by positive game experience as measured by the immersive experiences questionnaire (IEQ).

Exploratory hypothesis:

- The effects of the MEL-T01 and MEL-S01 on MDD symptoms are sustained in the follow-up period as measured by the change of PHQ-9 scores between T3 and T4.
- The effects of MEL-T01 and MEL-S01 will also emerge in the TAU group once as measured by the change of PHQ-9 between T3 and T4.
- The MEL-T01, MEL-S01, and TAU cohorts are equal in how they are treated for depression over the intervention period aside from the intervention.

- Interventions MEL-T01 and MEL-S01 are not significantly associated with an increase from T0 to T3 in game addiction as measured by the 7-item game addiction scale (GAS).

- The effects of the MEL-T01 and MEL-S01 on depressive symptoms as measured by PHQ-9 are (negatively) mediated by substance abuse as measured by ASSIST-LITE.

- The effects of MEL-T01 and MEL-S01 on depressive symptoms as measured by PHQ-9 are mediated by PTSD symptoms as measured by PTSD checklist for DSM-5 (PCL-5).

- The effects of MEL-T01 and MEL-S01 on depressive symptoms as measured by PHQ-9 are mediated by experiential avoidance as measured by the brief experiential avoidance questionnaire (BEAQ).

Study design:

The subjects (N = 800) volunteering to participate in this investigation are diagnosed with MDD and have an on-going mental health treatment contact with a mental health professional. The subjects are recruited through Helsinki and Uudenmaan sairaanhoitopiiri (HUS) psychiatry and Varsinais-Suomen sairaanhoitopiiri (VSSHP) psychiatry as well as online.

The subjects are randomised into three arms with equal probabilities in blocks of six consecutive subjects. Subjects in the MEL-T01 and MEL-S01 arms are engaged in the intervention for 12 weeks while those in the TAU arm are on a follow-up period during these 12 weeks.

After this 12-week period, the subjects in MEL-T01 and MEL-S01 arms enter a 12-week follow-up period and the subjects in TAU arm engage with either the MEL-T01 or MEL-S01 intervention (randomised at T0 with equal probability) for 12 weeks (See Table 1 below).

The subjects are recommended to play the investigational-device game for a total of 48 hours during the 12 weeks of active intervention with a recommended weekly dose of 4 hours. A minimum of 24 hours is needed for inclusion to hypothesis testing. The subjects are limited to a daily maximum of 1.5 hours of game time.

Prior to the intervention, a clinical interview (MINI) is performed via phone to confirm the subject's MDD diagnosis. The subjects' mental health symptoms and well-being are evaluated through online questionnaires five times: before subjects are randomised into one of the three groups (T0), and then 4 (T1), 8 (T2), 12 (T3), and 24 (T4) weeks after the study has begun.

Subject population:

Criteria for inclusion:

Eligible subjects must fulfil all of the following criteria:

1. Between 18-65 year-old
2. Suffering from major depressive disorder
3. Have an ongoing mental health treatment contact to basic healthcare, specialised healthcare, student healthcare or occupational healthcare
4. Has sufficient eyesight with or without prescription
5. Has a Windows computer with internet connection and mouse
6. Has email and phone number

Criteria for exclusion:

Subjects who fulfil any of the following criteria are excluded from the study:

1. They have threat of self-harm
2. They have addiction to digital games
3. They have psychotic disorders
4. They are pregnant or breastfeeding
5. They have impaired ability in decision making
6. They are prisoner or forensic subject
7. They have neurological disorders such as epilepsy or brain injury

Safety assessments:

MEL-T01 and MEL-S01 have negligible risks to the subject. They are non-invasive cognitive-training-software devices that the subject engages with at home. Pre-clinical evaluation based on internal testing and a pilot study showed no serious adverse effects on the previous version of the game. Adverse effects reported from the population sample of N = 54 were frustration (16.7%) that was almost invariably caused by device deficiencies, i.e., by problems in the technical implementation of the game, boredom due to limited content (14.8%) and anxiety from gameplay pressure (1.8%). Technical implementation of the game has been greatly improved since the previous version hence it is less likely that this kind of adverse effects are reported due to technical problems. More content has been developed into the game.

The version 1.0 made 14.1.2022 has received an approval from the HUS ethical committee (HUS/3043/2021).

Table 1: The overview of the study

Study arms	T0 (Before playing)		T1: T0 + 4 weeks		T2: T0 + 8 weeks		T3: T0 + 12 weeks		T4: T0 + 24 weeks
MEL-T01 intervention		MEL-T01 intervention						Follow-up	
MEL-S01 intervention		MEL-S01 intervention						Follow-up	
Treatment as usual ("TAU")		Treatment as usual						MEL-T01 or MEL-S01 intervention	

3.2 Identification and description of the device

3.2.1 Identification

- MEL-T01
- MEL-S01

Active investigational device MEL-T01 is a digital intervention implemented in a video game with cognitive training components. MEL-T01 is provided together with Treatment As Usual (TAU).

Active comparator device MEL-S01 is a digital intervention implemented in a video game with reduced cognitive training load. MEL-S01 is provided together with TAU.

3.2.2 Description

MEL-T01 ("Meliora"), is a digital intervention, a digital therapeutics (DTx) video game, that is installed and operated on a personal computer with a Windows operating system. MEL-T01 implements a closed-loop cognitive training system that looks and feels like an action video game for entertainment. The game is primarily a first-person action video game with puzzle and strategy elements. The player controls the main character in a fictional 3D landscape.

- The game is a single-player game without online features or social interaction with other players.
- The game is free to play and the player cannot make real- or virtual-currency-based purchases in the game.
- The game has 28 levels that the player passes through following a pre-written narrative and unlocking new game features.
- The game's difficulty is dynamic and adapts to the player's skill level and its changes.

MEL-S01 is derived from MEL-T01 so that the central game mechanics that implement cognitive training are removed. MEL-S01 thus has reduced cognitive training load but remains very similar to MEL-T01, e.g., in terms of action content, progression, and entertainment value (for details, see 3.6.2).

MEL-T01 and MEL-S01 interventions recommend a total of 48 game-play hours during the 12-week intervention period, and at minimum 24 hours during the 12-week intervention period. The subjects are able to play a maximum of 90 minutes per day.

3.2.3 Intended purpose

MEL-T01 is intended to alleviate the symptoms of major depressive disorder (MDD) through adaptive, closed-loop cognitive training delivered through an array of game mechanics.

3.2.4 Manufacturer

Matias Palva Group
Department of Neuroscience and Biomedical Engineering
Rakentajanaukio 2, 02150 Espoo
Aalto University
Finland

3.2.5 Traceability

The developed software is fully traceable with version control tools and any changes to the game can be tracked to the exact changes and to the individual who has made the changes in any given time. All documentation related to the software is stored in a cloud repository with restricted access and complete version history. Documentation is versioned properly for minor and major changes. Program code is stored in a repository with restricted access, version control, and complete version history. Code is produced with Good Programming Practices (GPP). The user access to the development environment is strictly controlled by the game team.

For industry-standard software-development version control we use Plastic SCM. Every update to the files in the system is recorded and can be always traced back to a specific, authenticated developer. Historical data of these updates includes, but is not limited, to usernames, file changes, timestamps and change messages. Every user of the version control has to log in with personal accounts including individual usernames and password. This allows us to trace not only what changes have been made but also who has made changes.

For managing the client-build generation, we use a software build-machine that follows the version control and creates a new software version from every new update to the system. The game version is then automatically uploaded to Steam, the service we are using to deliver the game version to subjects. Every new game version is logged in to Steam as well, meaning that we can monitor the changes made and by whom. Releasing the final game version to the subjects also requires manual triggering within the Steam pipeline that has restricted access. This prevents any unauthorised changes to the game version.

Neither client nor back-end server software are altered during the clinical investigation unless such an unexpected device deficiency is observed that needs to be corrected in order to restore the intended functionality. The process for managing (“patching”) device deficiencies and meeting the associated traceability demands is described in 3.14.2.

3.2.6 Target population

The target population of our device are subjects diagnosed with MDD. In this study we focus on those who, in addition, have an existing treatment contact with a mental healthcare professional. The treatment is not intended for psychotic or suicidal subjects.

3.2.7 Materials coming into contact with the human body

MEL-T01 and MEL-S01 are digital interventions based on a software medical device installed on a personal computer of the subject. The subject is only in direct contact with their own computer, keyboard, and mouse.

3.2.8 Medical or surgical procedures involved in device's use

None. MEL-T01 and MEL-S01 are digital interventions based on a software medical device. The subject receives the device download, installation, and login information from the recruitment website.

3.2.9 Necessary training and experience for its use

No training needed. The software is intended to be used without prior training similarly to commercially-available video games. To ensure this, we provide the subject with comprehensive information on how to install the software, and once they launch the software, the video game includes a comprehensive patient-adaptive tutorial guiding its use.

3.2.10 Background

3.2.10.1 Global burden of the Major Depressive Disorder (MDD) literature review

Major Depressive Disorder (MDD) is a disorder characterised by e.g. depressed mood, loss of interest or pleasure, feelings of worthlessness or excessive guilt, and diminished ability to concentrate or make decisions. The symptoms vary from mild to severe.

MDD is a common global disorder. WHO (2017) estimates that there are over 300 million people who suffer from depression, roughly 4.4% of the global population. Depression is *"ranked as the single largest contributor to global disability"* causing challenges in work performance, studies and home responsibilities. It also leads to nearly 800 000 annual deaths. These make MDD an important research subject both from the individual as well as societal viewpoint.

3.2.10.2 Neurophysiological basis of MDD

MDD symptoms are paralleled neurophysiologically by hyperactive ventro-medial prefrontal cortex (VMPFC) (Drevets et al., 1992); the cortical area that both serves emotional processing and introspective thoughts as a key node in the 'default-mode' brain system (Raichle, 2015). However, an equally salient characteristic of MDD is the hypoactivity of the lateral prefrontal cortex (LPFC) (Biver et al., 1994) that plays a critical role in brain systems underlying attentional and executive control for accomplishing external tasks (Corbetta et al., 2008). Unsurprisingly in this light, MDD subjects have significant deficits in core cognitive functions such as attention and working memory (Christopher & Macdonald, 2005). Nevertheless, several lines of research suggest that cognitive dysfunction is not epiphenomenal in MDD but rather an important and predisposing factor (Engen & Kanske, 2013). This suggests that treatment of the cognitive deficit and restoration of normal brain dynamics in LPFC could be a useful aim (Motter et. al., 2015) and could support the classical treatment that aims to control the negative thoughts (and thus implicitly to suppress the VMPFC).

3.2.10.3 Compromised cognitive functions as a key untreated MDD symptom

The central symptoms of MDD (i.e., negative emotional bias, rumination, a pathological shift from external to internal thoughts, and cognitive impairments) cause difficulties in coping with everyday life. Subjects with MDD also show high lifetime comorbidity with other psychiatric diagnoses such as anxiety.

Although often seen as an affective disorder, MDD is associated with cognitive deficits in many patients. Cognitive impairment is a diagnostic criterion for MDD and both decreases the quality of life and predicts decreased functioning. More specifically, MDD is particularly associated with impairments in cognitive control (Snyder et. al., 2013). Yet, current treatments typically do not ameliorate the cognitive deficits and the deficits persist in remission from mood symptoms. Cognitive deficits also predict poor pharmacological treatment response and the treatment may further worsen them. At present, there are no established treatments that target the cognitive impairment in MDD.

In addition to influencing quality of life directly, cognitive deficits appear to play a role in exacerbating the mood symptoms. Insufficient cognitive control over information in working memory may lead to proliferation of negative information in working memory and to perseverative negative thinking, *i.e.*, depressive rumination and maladaptive emotion regulation (Joormann, et al., 2014). This shows that cognitive control impairments are a vulnerability factor (Siegle et al. 2007) and links them with rumination, a core affective symptom of depression (Nolen-Hoeksema et al., 2008). Cognitive control deficits are most apparent during rumination and these impairments also predict future rumination and the development of new depressive symptoms.

Taken together, several lines of evidence strongly suggest that new approaches to rehabilitate cognitive functioning in MDD are warranted and that they have the potential to ameliorate MDD symptoms both directly through treatment effects on cognitive impairment and indirectly through the resulting alleviation of mood symptoms.

3.2.10.4 The potential of video games as novel media for digital therapeutics

Digital therapeutics (DTx) is an emerging healthcare technology field that aims to offer clinically-validated and high-quality solutions to global health challenges. The Digital Therapeutics Alliance (DTA) defines DTx as *"evidence-based therapeutic interventions that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease."* (DTA, 2019). Within DTx, the usage of games as a media for delivering the treatment has remained scarce but is increasing (Hong et al., 2021).

Johannes et al. (2021) have found that there is a positive relationship between playing entertainment video games and well-being. Playing 10 hours of games per week is, according to this study, related to an increase of well-being rather than the diminishment of it. In the present trial, 10 hours per week is set to be an upper boundary game playing time.

Looking into a particular genre, action games, that is relevant as it is the closest game genre for MEL-S01 and MEL-T01, we can consider the meta-analysis of 82 studies on the effects of video games on cognition by Bediou et al. (2018). Both cross-sectional and interventional data indicate that action video games improve individual performance in multiple domains of cognitive functioning. The researchers conclude: *"Overall, the present meta-analysis confirms a medium size impact of habitual action video game play on cognition and a small-to-medium size effect of training young adults with action video games on a few cognitive domains."*. Two crucial factors limiting the cognitive improvements in these studies were that (i) entertainment games do not implement closed-loop training and (ii) the majority of studies used intervention durations of 10-20 h while the evidence for cognitive training effects was robust and salient only at intervention durations of 30-50 h.

Thus, learning (behavioural level) and neuroplasticity (biological level) can be induced in adults by action video games. In recent years, several studies have shown that the ability to coordinate visual attention and working memory may be enhanced by videogame-like cognitive training in healthy adults (Jaeggi et al., 2008; Green & Bavelier, 2003). In addition to improving higher-level cognitive functions, especially action video games, such as first-person shooters, also improves visual perceptual accuracy (Li et al., 2009). These results hence suggest that generalising experience-dependent-plasticity driven cognitive improvements may also be attained in adulthood under appropriate conditions. The dysfunctional neuronal mechanisms underlying MDD could thus be trained with targeted neurogaming.

Video games could thus emerge as an effective media for novel therapies and influence mood and wellbeing already at the level of entertainment games. Johnson et al. (2013) argue that *"Positive mental wellbeing has been associated with videogame play as a means of relaxation and stress reduction"; "Depressed mood has been found to be significantly lower in the moderate players of video games compared to those who 'never' play videogames and those who play videogames to excess",* and *"Moderate video game play can contribute to positive emotions"*. In a more recent review, Fleming et al. (2017) highlight that computer gaming formats are feasible in offering therapies specifically in the field of mental health: *"Applied games have considerable potential for increasing the impact of online interventions for mental health. However, there are few independent trials, and direct comparisons of game-based and non-game-based interventions are lacking."*

3.2.10.5 First steps towards FDA-approved, prescription DTx games

Pioneering work for using video games as a basis for digital interventions and software medical devices has been achieved by Akili Interactive Ltd.. Kollins et al. (2020) reported a randomised, double-blinded, parallel-group controlled trial for paediatric patients with ADHD for the AKL-T01 game-like digital intervention. AKL-T01 involved 25 minutes of game time per day, 5 days per week, for 4 weeks, and its use had a population mean change of baseline TOVA (Test of Variable Attention) API (Attention performance index) of 0.93 ∓ 3.15 (SD), with an effect size of ~0.3. This finding showed that an objective measure of attention that captures the attentional deficits in ADHD children can be improved by AKT-T01. The research found no serious adverse events or discontinuations. Treatment-related adverse events were mild (frustration 3%, and headache 2%) and compliance was high (83%). This illustrates the potential of using video-game-like digital therapeutic products to ameliorate psychiatric disorders. Akili Interactive Ltd. gained U.S. Food and Drug Administration permission for marketing their device "EndeavorRx" as a prescription digital therapeutic intended for 8-12 year old children with ADHD (FDA, 2020).

3.2.10.6 The importance of intervention duration

The small-moderate effect size of 0.3 observed for AKL-T01 may be limited by the intervention's duration of only ~8 hours. The action-video-game training literature very convincingly indicates that interventions of 30-50 h are needed to achieve robust effects and that interventions of 10-20 h have a significant probability of yielding false negative (or positive) findings (Bediou et al., 2018). Our earlier clinical trial with the predecessor of the present investigational device used a 35-hour intervention and yielded good compliance, a large effect size, and highly significant improvement of visual acuity in adult patients suffering from amblyopia (Huttunen, et al., 2018). In the present investigation, we recommend

the subjects to play 48 h (24-72 h) in order to ensure reliable testing of the efficacy of our investigational device.

3.2.10.7 Alleviation of MDD symptoms by cognitive-control training

Findings of cognitive deficits as a key symptom and unmet treatment need in MDD (see 3.2.10.3) suggest that cognitive functioning could be an important target in the development of novel therapies.

As discussed above, entertainment games are known to alleviate MDD symptoms and lead to improved cognitive functioning (3.2.10.4). Entertainment games, however, can never serve as actual treatments because they deliver cognitive training in an uncontrolled and non-adaptive fashion and, moreover, can be used by players in a multitude of manners depending on individual game and play-style preferences.

To deliver cognitive training in a controlled manner, one may use either "traditional" computerised cognitive training methods developed for research purposes or game-DTx approaches, where the former are likely to suffer from a lack of appeal and retention. The effects of computerised cognitive-control training (CCT) on MDD have been addressed in multiple academic studies. Two recent meta-analyses of these studies (Motter *et al.,* 2016; Launder *et al*., 2021). Motter *et al* (2016) examined $N = 9$ RCT-level trials and report finding significant small-moderate effects of CCT for Symptom Severity (0.43) and Daily Functioning (0.72), and moderate-large effects for Attention (0.67), Working Memory (0.72), and Global Functioning (1.05) were found. No significant effects were found for Executive Functioning or Verbal Memory. Launder *et al.* (2021) examined $N = 24$ academic studies and reported finding a small and significant effect of CCT for overall cognition (0.26) and depressive symptoms (0.24). Benefits of CCT were also found for psychosocial functioning and several domain-specific cognitive functions. In line with our notion in 3.2.10.6, Launder *et al.* (2021) found a moderating effect of dose was found for overall cognition, with larger doses of CCT associated with greater effect size estimates.

The effects of a digital game-DTx intervention, AKL-T03, on MDD have also been initially tested (Gunning et al., 2021). This study reported putative positive effects of AKL-T03 on cognitive-control functioning (here operationalized by sustained attention and working memory) or self-reported symptoms of apathy or depressive mood. However, Gunning et al. (2021) did not employ a comparator or a control (TAU) group, and hence it remains unclear whether these effects were attributable to AKL-T03 or other ongoing recovery from depressive symptoms.

The present investigation aims to fill this knowledge gap and provide a rigorously controlled test of whether cognitive, and especially cognitive-control, training has the potential to lead to novel efficacious treatments of both the mood and cognitive symptoms of MDD.

3.2.11 Current state of the art in clinical care

In Finland, Käypä Hoito recommendations are *"independent, evidence-based clinical practice guidelines. These national guidelines cover important issues related to Finnish health, medical treatment as well as prevention of diseases."* (kaypahoito.fi) The recommendations are widely followed in healthcare. In regards to our study, the most important clinical guideline regards Depression, released on 11.3.2021, and written by the work group of the

Finnish Medical Society Duodecim and the Finnish psychiatry association. (Depressio, Käypä Hoito).

The prevalence of depression in Finland is roughly 5-7%, yet only a minority of subjects with depression actively seek treatment from healthcare. Those who do, have more symptoms, their symptoms are enduring, and the symptoms cause disability. Also, those who do seek treatment have comorbidity with anxiety, personality, or substance abuse disorders.

The beginning of treatment includes depression diagnosis done by a medical doctor through clinical examination. The majority of depression subjects can be treated in primary health care or occupational healthcare. If depression is severe, resistant to psychopharmacological treatment, the subject has severe comorbidities, the subject is suicidal, or the treatment hasn't led to remission, the subject can be guided to specialised healthcare which is in the public field organised by municipal hospital districts.

The treatment of depression is divided in three parts: 1) acute treatment that seeks to alleviate and remove the symptoms, and once this is achieved, the 2) follow-up treatment seeks to prevent relapse, and 3) maintenance treatment seeks to prevent a new disorder period. (Depressio, Käypä Hoito)

There are two main ways to treat depression: psychotherapy and psychopharmacological treatments, or both at the same time. In some cases, other modes of treatment are also used, such as light therapy and transcranial magnetic stimulation (TMS) and other neuromodulatory treatments. In every treatment, the subject is also given psychoeducation. The importance of psychopharmacological treatments increases the more severe the symptoms of depression are.

Currently, video games are not used in Finnish healthcare for the treatment of depression, yet the evidence for using them globally is growing. Our aim is to explore the possibility of including therapeutic video games as a mode of therapy that alleviates the symptoms of MDD.

3.2.12 Proposed benefits of the new device

3.2.12.1 Rationale for the putative core benefits of the device

We hypothesise MEL-T01 alleviates the symptoms of depression by rehabilitating cognitive functioning deficits associated with MDD through broad-spectrum cognitive training that is delivered through MEL-T01 game mechanics and cognitive tasks. We postulated that cognitive training leads to improvements in cognitive performance and executive functions, which are reflected in the patient being able to function better in their everyday life and gaining both psychologically and neurophysiologically improved ability to suppress key MDD mood symptoms, such as rumination and negative bias.

3.2.12.2 Potential for additional benefits

Besides these expected clinical impacts, we consider using video games in mental health has also other benefits such as those proposed by Fleming et al. (2017):

1) Appealing potential. The video game may help address the treatment gap where people suffering from depression do not seek help. Applied games may increase the reach of mental health interventions to underserved populations.

2) Engaging potential. Internet-based interventions have high attrition rates hence using game mechanics may help keep the players with the solution in order for them to deliver their value in interaction.

3) Effectiveness potential. Games offer immersive experiences that are experientially rich and thus have potential to be more effective.

These factors make it likely that both MEL-T01 and MEL-S01 yield positive effects similarly to those obtained with commercial video games for entertainment (see 3.2.10.4). In addition, playing the game attenuates introspective rumination associated with depression by engaging the player in an intense task, offers a meaningful, pleasurable experience that depressed subjects may lack, and fosters feelings of competence. The training regimen also provides structure to the subject's day.

3.2.12.3 Clinical and societal implications

In addition, we consider that software-based approaches have the potential to help address the increasing healthcare costs by offering scalable solutions for a large number of subjects. This means that in addition to alleviating the burden that the symptoms cause to the subjects, MEL-T01 could also yield economic impact and reduce the direct healthcare burden of MDD and its indirect societal effects.

3.3 Risks and clinical benefits of the device

3.3.1 Central risks and summary of risks

Risks are explored in two sections. First, we will consider the most important risks to the subjects and how they are mitigated. Second, we consider lesser risks and how they are mitigated.

3.3.1.1 Adverse events (AEs) in earlier game-based interventions and DTx trials

In our pre-clinical feasibility study in 2019 with a sample of $N = 54$ MDD patients, no serious adverse events (SAEs) were reported. The three most common adverse event (AEs) were

1. frustration (AE reported by 16.7% of subjects)

2. boredom (14.8%)

3. Stress (1.8%)

Frustration was almost invariably caused by objective device deficiencies, i.e., problems in the technical implementation of the game. Boredom was attributed to limited unlockable content (progression levels) in this game version. Stress was defined to arise from the time pressure in the game.

Since this pre-clinical study, we have made considerable improvements to the game and to the investigational device framework. The game has gone through several rounds of testing and quality assurance, which has led to the elimination of all so far discovered device deficiencies

and greatly improved usability and user experience. We believe this effort will lead to significantly lower amounts of frustration AEs in the MelioraRCT trial.

We have also added considerably more content, expanding the prior 14 progression levels into 28, which makes it possible for the subject to enjoy new game elements for well over 25 hours of game time. We believe that this will limit the occurrence of boredom AE.

Finally, time-pressure is an integral part in the design of the investigational device for achieving its therapeutic efficacy. We have improved the device's user interface and communication about the device's goals to mitigate the stress as an AE.

In a previous RCT study on a game-like software-based digital therapeutics for ADHD, Kollins et al. (2020) report that of their 180 subjects 12 had intervention-related adverse events, 5 experienced frustration, 3 headache, 2 had emotional reactions, 1 dizziness, 1 had nausea, 1 had aggression. There were no serious adverse events or discontinuations due to the AEs. Overall, the subjects had exclusively mild treatment-related adverse events.

MEL-T01 and MEL-S01 closely resemble commercially freely-available entertainment video games that are considered safe and widely used as entertainment. In Finland 78% of people play digital games, and, on average, people play 7 hours per week (Kinnunen et al., 2020).

However, as all activities, video gaming also has risks, even if they are mild. These are considered below.

3.3.1.2 Anticipated AEs

In guidelines for good clinical practice E6(R2) European medicines agency defines adverse events (AE) as: *"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment."*

The subjects may have unanticipated or anticipated adverse events during the study. Below, we have identified anticipated AE that may arise in the use of the MEL-T01 or MEL-S01 software. The list is based on possible negative events that may occur from playing entertainment video games (see Playstation, 2022) that closely resemble the MEL-T01 and MEL-S01 software. The adverse events are:

- Frustration
- Boredom
- Stress
- Eye ache
- Headache
- Dizziness
- Nausea
- Neck pain

- Visual disturbances
- Migraine
- Muscle twitching
- Uncomfortable feelings or ache in hands
- Losing sense of time and space

We take measures to mitigate the anticipated AE. We guide the user to pay attention to ergonomics, ensure sufficient lighting, and keep breaks while playing. Should the user encounter any AE, they are guided to stop playing, and report the AE to the researchers either through the in-game link or email. The information to the subjects is included in Appendix 2 (Tutkittavan tiedote) and the information given to the subject is found in Appendix 6 (Investigator's brochure). For AE reporting procedures, see 3.14.

Another risk is the potential addiction that video games may create. To mitigate this risk, we take the following precautions: 1) Digital game addiction is an exclusion criteria for the study. 2) We only recommend playing 45 minutes per day, and the players cannot play the game for more than 90 minutes per day at which point the game locks them out. 3) Our game doesn't include highly addictive features such as so-called loot boxes.

"A very small percentage of individuals may experience epileptic seizures or blackouts when exposed to certain light patterns or flashing lights." (Playstation, 2022). Considering the risk for epileptic seizure, we exclude subjects who have a history of epilepsy from the study to mitigate the risk. We also inform the subject about this (see Appendix 6 - Investigators brochure, 2.2.5.).

3.3.1.3 Unanticipated AEs

Besides anticipated AE, it is possible that the subject encounters unanticipated AE. The subject is encouraged to report all AE, whether unanticipated or anticipated, to the researchers. Subjects' channels for reporting AE are covered in 3.14.

The anticipated or unanticipated AE may or may not be related to the device use which the coordinating investigator assesses case-by-case, see 3.14.

3.3.1.4 Serious adverse events (SAEs)

According to the European Medicines Agency, SAE includes death, threat to life, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

As MEL-T01 and MEL-S01 are software and essentially indistinguishable from many commercially available entertainment video games, the risk for serious adverse effects is very low.

Should SAE occur during the study, the coordinating investigator evaluates all SAE cases for their possible connection with MEL-T01 or MEL-S01, as described in 3.14.

3.3.1.5 Eliminated risks

Eliminated risks include risks that are possible regarding digital video games but which we have eliminated through the device design.

Social conflicts. Many video game softwares have interaction between players which may lead to negative side-effects such as social conflicts and bullying. To negate this risk, MEL-T01 is a single-player game. This means that the player doesn't have any contact with other players which negates the social risk.

Monetary losses. Some entertainment video games today have the potential to make additional purchases within the game which are called microtransactions. This may cause players to use more money on video games than they intended, which may lead to regret and even actual financial challenges. To negate the risk, our game is free to the player and the players cannot make real or virtual purchases in the game.

3.3.1.6 Summary of risks

Overall, we consider that MEL-T01 and MEL-S01 have low risks for the subject: the existing risks are of low impact and many of them are mitigated in the device design. The software is non-invasive, the subject uses it voluntarily with informed consent, and the subject can at any point quit the intervention. The device is similar to many entertainment video games, yet it doesn't include highly addictive features or allow social interaction between players that exist in some video games.

Overall, we consider that the benefits of MEL-T01 and MEL-S01 considerably outweigh the possible risks which we have mitigated. The game offers the player a meaningful experience in their everyday life through engaging, adaptive gameplay, and evolving, hope-inspiring narrative. The game offers the players a chance to relax while simultaneously challenging them. Should our video game prove effective in reducing the symptoms of depression, it may possibly have considerable social benefits. In this case, video games could offer a scalable, supplementary treatment option alongside the existing modes of treatment.

Please find a supplementary ethical consideration in: *Appendix 11 - Ethics Evaluation of the Study*, for a summary of the AE and SAE see 3.3, and regarding AE and SAE reporting see 3.14.

Table 2: Risk assessment table (see also 3.14)

Risk	Likelihood Before mitigation	Likelihood After mitigation	Severity of harm	Mitigation measures
Frustration Boredom Stress Physical AEs: Eye ache Headache Dizziness Nausea Neck pain Visual disturbances Migraine Muscle twitching Uncomfortable feelings or ache in hands Losing sense of time and space	Possible	Possible	Mild	Physical AEs: Health information about safe device usage and prevention of adverse events is available in-game continuously. The subject can stop playing anytime. See 3.14.
Epileptic seizure	Possible	Rare	Severe	History of epilepsy or seizures is an exclusion criteria for the study.
Game addiction	Probable	Possible	Moderate	Playing time is restricted Exclusion of addicted players No highly addictive game features No social interaction in the game No gambling elements in the game

3.3.2 Peripheral risk considerations

The following include other risks that we have considered in the design as well as those that have limited applicability to software devices but are named in REGULATION (EU) 2017/745.

3.3.2.1 Use errors

Like entertainment video games, the investigational device requires minimal knowledge, experience, education, and training in its use. Necessary training is included in the installation

manual and in-game tutorials. Ergonomic factors in the usage environment can affect realisation of adverse effects originating from joint pain and tension which is why we guide the subject to pay attention to their ergonomics. The subjects are instructed to set up an environment where excessive strain on back, neck and wrists are minimised.

3.3.2.2 Device stress under normal operating conditions

The device comprises client software at the subject's personal computer and backend software at the sponsor's backend servers.

The backend server capacity is sized to handle 100 times more concurrent patients than expected at any moment of this clinical investigation, and hence, under normal operating conditions, the backend stress is very unlikely to contribute to net device stress and its risk of failure.

The client software may face performance limitations depending on the CPU and GPU capacity of the subject's personal computer. When running in computers meeting the minimum specification, the client's performance is adequate to achieve the device's intended treatment outcome.

Device stress under normal operating conditions does not adversely affect the health or safety of the subject or any other persons.

3.3.2.3 Chemical, physical and biological properties and interaction

Investigational device is a software thus it does not possess chemical, physical or biological properties hence it does not react to environmental materials and substances. No particles can be released to the subject's body.

3.3.2.4 Substance labelling

The investigational device has no substances thus it does not require such labelling.

3.3.2.5 Compatibility

The investigational device's client application, *i.e.*, the "game" installed on the subject's personal computer, is compatible with the Windows operating system and a wide variety of hardware components as long as the minimum requirements are met. To ensure compatibility, it is advised to use a modern (purchased after 2010) computer with a separate graphics processing unit (GPU). Using an incompatible computer may lead to a compromised user experience or altogether prevent the playing of the game, but it does not cause any risks for the subject's health or safety.

Minimum requirements:

- CPU: Intel or AMD Quad-Core
- RAM: 4 GB
- OS: Windows 7
- VIDEO CARD: GeForce GTX 260 (1 GB) or Radeon HD 4850 (1 GB)

3.3.2.6 Consequent risks

Fault conditions regarding the investigational device do not produce any consequent risks for subjects' health or safety.

3.3.2.7 Diagnostic or measuring functions

The device does not have diagnostic functions. The device has measuring functions for the subject’s cognitive performance evaluation and adaptation of the game to the subject’s individual performance level and changes therein. The measuring functions are designed in such a way that they are not compromised by usage of low performing personal computers as long as the minimum requirements are met.

3.3.2.8 Power shortage

Power shortage regarding the back-end server or on-site operating computer prevents access to the software but it does not cause any risks for the subject's health or safety.

3.3.2.9 Clinical parameters

The investigational device does not have clinical parameters; hence parameters going out of range can not lead to death or severe deterioration, thus there are no alarm systems.

3.3.2.10 Electromagnetic interference

Investigational device being a software, it does not produce electromagnetic interference (EMI) or is affected directly by environmental EMI thus achieving intrinsic immunity to it. Subject’s operating computer produces and is affected by EMI in quantities defined by the manufacturer of the operating computer.

3.3.2.11 Unauthorised access

Signing in to the distribution platform (Steam) requires a personal login account and the game client requires another login account. Considering that the device is operated at the subject's home, these procedures provide adequate levels of unauthorised access prevention. Also, the subjects are informed that they are not to give access to other people as explained in Appendix 3 (Salassapitovelvoite ja käyttöoikeus).

Back-end servers are in secure data centre facilities with multiple security layers and access control.

3.3.2.12 Protection against mechanical and thermal risks

The investigational device is a software, thus it is not directly affected by mechanical, vibrational or thermal energy which could lead to risks for the subject.

3.3.2.13 Noise emission

The investigational device is software, thus it does not directly generate noise other than the audio components of the gameplay. The player can control the volume, turn it off, or use headphones at their discretion.

3.4 Relevance of the clinical investigation

MDD is a considerable, global public health problem that causes considerable personal suffering for the subjects and is a leading cause of disability worldwide.

Medical relevance: Depression is, at worst, lethal. In 2015, there were 788 000 people who died due to suicide (WHO, 2017), and suicide is the cause of 1.5% of deaths globally. Out of all suicides, two thirds are related to depression, and when depression is related to suicide, the subject hasn't often had proper treatment for the disorder (Depressio, Käypä hoito). Thus, developing the existing treatment, treatment pathways, and creating new treatments that can also help reach underserved populations can help treat depression.

Economical relevance: MDD causes considerable economic burden to societies. Globally, depression led to *"a total of over 60 million years lived with disability"* only in 2015, according to WHO (2017). In Europe, the annual cost of MDD is €100B, approximately one eighth of the costs of all brain disorders together and one half of the cost of cancer. In the United States, the annual cost of MDD is $200B.

To address this global mental health challenge, it is thus vital to not only improve existing treatments but to develop novel complementary approaches that leverage the benefits of the digital therapeutics and yield highly-scalable and low-cost treatments.

3.5 Objectives and hypotheses of the clinical investigation

Main objective

The primary objective of this research is to assess the effectiveness of MEL-T01 in reducing MDD symptoms. The subjects are randomised into three research arms (MEL-T01, MEL-S01, and TAU), and their subject health questionnaire (PHQ-9) scores are measured on five occasions (see Table 1).

Research arms

- MEL-T01
- MEL-S01
- TAU

Time intervals

- T0, before subjects in MEL-T01 and MEL-S01 arm begin the active intervention.
- T1, 4 weeks after T0
- T2, 8 weeks after T0

- T3, 12 weeks after T0
- T4, 24 weeks after T0

Primary hypotheses

- MEL-T01 is superior to TAU in alleviating MDD symptoms as measured by the change in subject health questionnaire (PHQ-9) score between time points T0 (before the intervention) and T3 (after a 12-week intervention).
- MEL-S01 is superior to TAU in alleviating MDD symptoms as measured by the change in PHQ-9 score between T0 and T3.
- MEL-T01 superior to MEL-S01 as measured by the change in PHQ-9 score between T0 and T3.

Secondary hypotheses

- In terms of a score change from T0 to T3,

  MEL-T01 is superior to TAU,
  and MEL-S01 is superior to TAU,
  and MEL-T01 superior to MEL-S01 in:

  - reducing depression symptoms as measured by quick inventory of depressive symptomatology (QIDS),
  - reducing rumination as measured by short-version ruminative response scale (RRS),
  - reducing anxiety symptoms as measured by general anxiety disorder (GAD-7),
  - reducing the disability symptoms as measured by sheehan disability scale (SDS),
  - increasing positive emotions as measured by positive valence systems scale (PVSS),

    and

  - improving well-being as measured by the WHO-five well-being index (WHO-5)

- The effect of the MEL-T01 is mediated by the training dose, as measured by the subject's total game-playing time during the intervention, and evidenced by a positive correlation between MEL-T01 game time and reduction in symptoms as measured by the PHQ-9.
- The effect of the MEL-S01 is mediated by the training dose, as measured by the subject's total game-playing time during the intervention, and evidenced by a positive correlation between MEL-S01 game time and reduction in symptoms as measured by the PHQ-9.

- The effects of MEL-T01 on depressive symptoms as measured by PHQ-9 are mediated by positive game experience as measured by the immersive experiences questionnaire (IEQ).

- The effects of MEL-S01 on depressive symptoms as measured by PHQ-9 are mediated by positive game experience as measured by the immersive experiences questionnaire (IEQ).

Exploratory hypothesis

- The effects of the MEL-T01 and MEL-S01 on MDD symptoms are sustained in the follow-up period as measured by the change of PHQ-9 scores between T3 and T4.

- The effects of MEL-T01 and MEL-S01 will also emerge in the TAU group once as measured by the change of PHQ-9 between T3 and T4.

- The MEL-T01, MEL-S01, and TAU cohorts are equal in how they are treated for depression over the intervention period aside from the intervention.

- Interventions MEL-T01 and MEL-S01 are not significantly associated with an increase from T0 to T3 in game addiction as measured by the 7-item game addiction scale (GAS).

- The effects of the MEL-T01 and MEL-S01 on depressive symptoms as measured by PHQ-9 are (negatively) mediated by substance abuse as measured by ASSIST-LITE.

- The effects of MEL-T01 and MEL-S01 on depressive symptoms as measured by PHQ-9 are mediated by PTSD symptoms as measured by PTSD checklist for DSM-5 (PCL-5).

- The effects of MEL-T01 and MEL-S01 on depressive symptoms as measured by PHQ-9 are mediated by experiential avoidance as measured by the brief experiential avoidance questionnaire (BEAQ).

3.6 Design of the clinical investigation

3.6.1 General information

The is a comparator-controlled, randomised, double-blinded clinical intervention study designed to yield reliable, high-quality, and medical-device regulation compliant evidence. The study aims to assess the effects of a novel digital intervention, MEL-T01, on the symptoms of MDD. MEL-T01 has no prior equivalent devices. The closest equivalent is AKL-T01 (Akili Interactive Ltd.) that is the only FDA-approved game-based medical-software device so far and is intended for a different age group (children) and indication (attention deficit hyperactivity disorder, ADHD) (FDA, 2020; Kollins, 2018).

The study design includes primary-endpoint comparisons of the investigational device with both a comparator device and treatment as usual. On one hand, this aims to achieve strong evidence for our hypothesis about the therapeutic potential of specific

cognitive-training-related game mechanics. On the other hand, with the TAU arm, this design assesses the overall clinical relevance and value of MEL-T01 over the spectrum of currently available treatment-as-usual approaches. Finally, the comparison of MEL-S01 with TAU establishes the overall potential of "any" adaptive, closed-loop action-video-game based digital interventions to alleviate MDD symptoms.

The study design leverages randomisation of the subjects into three arms in blocks of six consecutive subjects. Randomisation is a robust and valid method that is typically used in clinical studies to acquire unbiased data. Randomisation in blocks further improves this by essentially eliminating the possibility that temporal variation in recruitment, such as some recruitment sources yielding more patients at some time than others, would bias the results. Possibilities of subject bias are limited by blinding both the subjects and the researchers from research arm randomisation and by using an active comparator that from the subject's perspective is indistinguishable from the investigational device.

The rationale for choosing PHQ-9 as the outcome measure for the primary endpoint is that PHQ-9 has been proven to be a valid and reliable measurement of depression severity (Kroenke et al., 2001; Kroenke et al. 2002). In their meta-analysis, Manea et al. (2012) found PHQ-9 to have acceptable diagnostic properties for detecting MDD. In addition, PHQ-9 is mentioned by the Finnish Käypä Hoito for depression, and the questionnaire is widely used in Finland.

For the secondary endpoints, we sought to use clinical outcome measures that describe comprehensively the complex symptomatology of MDD. To corroborate our results with our primary outcome measurement, PHQ-9, we also employ another depression questionnaire (QIDS). As Finnish Käypä Hoito recommendation mentions, many patients that suffer from depression also suffer from anxiety (measured in our study by GAD-7), and we evaluate the potential of the interventions to influence symptoms of anxiety. Depression is also associated with rumination (measured in our study by RRS), that we hypothesise our intervention may reduce. Anhedonia, or the lack of positive emotions associated with depression (measured in our study by PVSS) may also be influenced. We also examine how depression influences disability in the subject's everyday life (as measured by SDS) and measure the subjects' general well-being (as measured by WHO-5). We also predict that the impact of our game is mediated by the degree the player immerses themselves into the game (as measured by IEQ).

Finally, the exploratory endpoints assess the post hoc comparability of patient cohorts and seek to identify factors mediating intervention success. These include substance abuse (as measured by ASSIST-LITE), post-traumatic stress disorder (measured in our study by PCL-5), and experiential avoidance, tendency to avoid negative experiences (measured in our study by BEAQ). We also evaluate whether the interventions influence game-addiction (measured in our study by GAS). For details regarding the clinical questionnaires, see section 3.6.5.1.

3.6.2 Investigational device and comparator

The investigational device MEL-T01 is a digital intervention based on an action-video-game-like software medical device for cognitive training (see 3.2). MEL-T01 and the active comparator MEL-S01 are similar with the exception that MEL-T01 includes real-time-strategy game mechanics and several forms of adaptive cognitive tasks, which have been removed from MEL-S01 (Table. 3). The absence of these game mechanics in MEL-S01 is accounted for by slight changes in enemy encounters in order to maintain as similar as

possible subject action levels and game pacing. The investigational device and comparator are thus very similar in terms of sensori-motor- and attentional-processing demands as well as engagement, arousal, reward processing, agency, narrative, and overall activation. This facet has been suboptimally realised in essentially all prior game-intervention research. Here, a rigorous comparator enables the possibility of drawing strong inferences about the mechanistic role of cognitive training in achieving the hypothesised therapeutic effect, thereby increasing the value of this investigation in forming a basis for future development of digital therapeutics for MDD and other brain disorders.

Table 3: Device features

Feature	**Investigational device (MEL-T01)**	**Comparator (MEL-S01)**
3D navigation	Yes	Yes
Gameplay tutorial	Yes	Yes
Enemy encounters	Yes	Yes
Narrative	Yes	Yes
Spellcasting	Yes	Yes
Environment interaction	Yes	Yes
Avatar abilities	Yes	Yes
Gameplay feedback	Yes	Yes
Avatar	Yes	Yes
Real-time strategy (RTS)	Yes	No
Cognitive tasks	Yes	No

3.6.3 Subjects

3.6.3.1 Inclusion criteria

Eligible subjects must fulfil all of the following criteria:

1. Between 18-65 year-old (self-reported)
2. Suffering from MDD (self-reported and corroborated by clinical interview, see 3.6.5.2.)
3. Have an ongoing mental health treatment contact to basic healthcare, specialised healthcare, student healthcare or occupational healthcare (self-indicated and confirmed by CSC)
4. Has sufficient eyesight with or without prescription (self-reported)
5. Has a Windows computer with internet connection and mouse (self-reported)
6. Has email and phone number (self-reported)

The subject MDD is indicated by a self-reported diagnosis and confirmed by a clinical MINI interview (see 3.6.5.2).

The criteria are also found in Appendix 1 - Rekrytointi-ilmoitus, which is given to the subjects. Only subjects who fulfil the inclusion criteria are admitted to study.

3.6.3.2 Exclusion criteria

Subjects who fulfil any of the following criteria are excluded from the study:

1. They have a threat of self-harm (evaluated by the clinical interview, see 3.6.5.2.)
2. They have an addiction to digital games (self-reported)
3. They have psychotic disorders (self-reported)
4. They are pregnant or breastfeeding (self-reported)
5. They have impaired ability in decision making (self-reported)
6. They are prisoner or forensic subject (self-reported)
7. They have neurological disorders such as epilepsy or brain injury (self-reported)

Should the subject indicate that they have suicidal thoughts, they are evaluated by the clinical subject coordinator in the clinical interview for the severity of suicidality. If the subject has a threat of harming themselves (See 3.6.5.2 for procedures), they are excluded from the study.

The criteria are also found in Appendix 1 - Rekrytointi-ilmoitus which is given to the subjects. Only subjects who do not fill the exclusion criteria are admitted to study. To further ensure that the subjects do not meet the exclusion criteria, we contact them through the phone prior to the intervention.

The exclusion criteria are compliant with the law concerning medical research in Finland (Laki lääketieteellisestä tutkimuksesta, 9.4.1994/488; 2 luku) with respect to specific protected categories of subjects:

- Elderly (2 luku, §7)
- Underaged (2 luku, 8 §)
- Those with impaired ability to make decisions (“vajaakykyinen”), (2 luku 7 §)
- Those pregnant or breastfeeding (2 luku, 9 §)
- Prisoners or forensic psychiatric subjects (2 luku, 10 §)

3.6.3.3 Evaluation of inclusion and exclusion criteria

The subjects are presented in written form the exclusion and inclusion criteria in the recruitment phase (Appendix 1 - Recruitment notice) and in the information regarding the study (Appendix 2 - Participant information and consent form).

After the subject has signed up to the study and filled the first set of questionnaires (T0), the clinical subject coordinator (CSC) calls them via phone to confirm they meet the inclusion and do not meet the exclusion criteria (Appendix 5 - Clinical Subject Coordinator phone call). See section 3.6.5.2.

3.6.3.4 Discontinuation criteria

The coordinating investigator may discontinue the study for the subject if

- Subject has an adverse event (AE) related to the device use
- Subject violates the Appendix 3 (Confidentiality obligation and right of use)
- Subject’s mental health deteriorates in a way that they are not fit for continuing in the study. This includes, for instance, psychotic symptoms, hospitalisation, and suicidality.

If the subject has a serious adverse event (SAE) their participation in the study is discontinued. For more information on the protocol regarding adverse events and serious adverse events, see section 3.14.5.

3.6.3.5 Subject monitoring

The subject answers to the clinical questionnaires are monitored. Particularly if the subject answers that they have suicidal ideation, they are given support text as indicated in Appendix

11 (Ethics evaluation of the study) and contacted by the clinical subject coordinator for support and guidance towards healthcare and other support resources.

3.6.3.6 Size of investigation population

Pirkola et al. (2005) found that prevalence of MDD in Finland is 4.9% in a representative adult sample ($N = 6005$).

According to Statistics Finland, there are 3 119 000 people between 20 and 64 years of age on 31.12.2020. This means that there are 153 000 20-64-year old people who suffer from MDD in Finland. This is the maximum size of the investigation population, considering that we focus on the Finnish population, and this maximum population is further reduced when other inclusion and exclusion criteria are applied.

We aim to reach the investigation population through contacts with HUS psychiatry and VSSHP psychiatry as well as through online recruitment using, for intance, Mielenterveystalo.fi webpages.

3.6.3.7 Representativeness of investigation population in relation to target population

Our target population are people who suffer from MDD. We believe that through our recruitment process, we are able to reach a relevant population sample. Through HUS and VSSHP psychiatry we are able to recruit subjects who have more severe MDD symptoms. Through online recruitment we are able to reach subjects who have lesser MDD symptom severity.

We also gather demographic information with background questionnaires through which we can analyse the representativeness of the sample gathered and compare it in demographic terms of age, gender and education to see how well it represents the population (see 3.7.1.1.).

3.6.4 Measures to minimise bias

3.6.4.1 Blinding

In order to ensure minimum bias, the main study is double-blinded so that neither the subjects nor the investigators, CSCs in particular, know whether any given subject is randomised to the MEL-T01 or MEL-S01 study arm. Investigators are aware of which subjects are randomised to the TAU arm but will be blinded to the subsequent intervention of the TAU-arm subjects with MEL-T01 or MEL-S01 after their initial follow-up period has ended.

3.6.4.2 Randomisation

The recruited MDD subjects are randomised into the MEL-T01, MEL-S01, and TAU arms in blocks of six consecutive subjects so that two subjects are allocated into each arm and so that one subject in the TAU arm will receive MEL-T01 and the other TAU subject MEL-S01 at the end of their initial 12-week follow period.

3.6.4.3 Investigation data exempt from blinding

For the purpose of **subject monitoring**, the CSCs and excluding all other investigators, will have access to the gaming-time and questionnaire-completion-status data of individual identifiable subjects. This information will be available to the CSCs for AE report, email, or

phone call interactions with the subjects so that the CSCs are able to make informed inferences, e.g., about the subject's study compliance. Notably, the CSCs will also have access to the suicidality-related questionnaire responses for subject monitoring as specified in 3.6.3.5. The CSCs remain blinded to all other investigation data, and especially the data about the study arm, game performance, and all other questionnaire replies of the subjects.

For the purpose of **study monitoring**, the investigators, excluding the CSCs, will have access to the gaming-time, questionnaire-completion-status, and study-arm data of individual but unidentifiable subjects. These data will enable the assessment of whether the criteria for the interim analysis or study completion are met.

- These data are needed because the interim analysis (see 3.7.5) is triggered when each arm has 33 subjects that have completed the intervention (specifically, the 12 first weeks, which are follow-up for the TAU arm) and meet the inclusion criterion (see 3.7.2) to data analysis.
- Conversely, termination of the investigation (see 3.7.4.2) will be triggered when each arm has 133 subjects that have completed both the intervention and the follow-up period and meet the inclusion criterion (see 3.7.2) to data analysis.

3.6.5 Clinical procedures and diagnostic methods

3.6.5.1 Questionnaires

We use the following questionnaires in gathering data about the subjects. For details regarding the questionnaires, see 3.7.1.

- Questionnaire regarding their state of care
- Patient health questionnaire (PHQ-9)
- Quick inventory of depressive symptomatology (QIDS-SR16)
- General anxiety disorder questionnaire (GAD-7)
- Positive valence systems scale (PVSS)
- The ruminative response scale short-version (RRS)
- Alcohol, smoking and substance involvement screening test lite (ASSIST-LITE)
- PTSD checklist for DSM-5 (PCL-5)
- Brief experiential avoidance questionnaire (BEAQ)
- Sheehan disability scale (SDS)
- Well-being index (WHO-5)
- 7 item game addiction scale (GAS)
- Problem gambling severity index (PGSI)

The immersive experiences questionnaire (IEQ, Jennett et al., 2008) measures the subjective experience of being immersed while playing a video game. It has 31 questions on a scale of 1-7, which require the subject to answer according to how they felt at the end of the game. One additional question - “How immersed did you feel?” - on a scale of 1-10, let’s the researcher evaluate whether the IEQ reliably reflects the participant’s immersive experience. Scores for five immersion factors can then be computed: challenge, control, real world dissociation, emotional involvement and cognitive involvement.

The questionnaire regarding state of care (Appendix 7) determines if there have been any changes in the subject’s treatment during the preceding four weeks. If the subject reports changes to have occured, they are then asked the same questions regarding treatment status as in the background questionnaire part 2: Mental health (see Appendix 7), excluding the open question regarding diagnoses.

The patient health questionnaire (PHQ-9, Kroenke et al., 2001) is a self-report measure of MDD and a component of the longer PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 scores each of the nine DSM-IV criteria for MDD from “0” (not at all) to “3” (nearly every day), providing a 0-27 severity score of depression.

The quick inventory of depressive symptomatology (QIDS-SR16, Rush et al., 2003) is a self-report measure derived from the 30-item Inventory of Depressive Symptomatology (IDS). It has 16 questions on a scale of 0-3 which assess the severity of depressive symptoms.

The general anxiety disorder questionnaire (GAD-7, Spitzer et al., 2006) is a 7-point screening tool for generalised anxiety disorder and its severity (scale 0-3).

The positive valence systems scale (PVSS, Khazanov et al., 2020) is a 21-item measure of the Positive Valence Systems domain of the National Institute of Mental Health's Research Domain Criteria. The scale (1-9) measures responses to a wide range of rewards: food, physical touch, outdoors, positive feedback, social interactions, hobbies, and goals. It is more strongly related to reward than punishment sensitivity, positive than negative affect, and depression than anxiety. Scores have been found to discriminate depressed from nondepressed individuals and predict anhedonia severity even when controlling for depression status.

The ruminative response scale (RRS) is a subscale of the response styles questionnaire (RSQ, Nolen-Hoeksema & Morrow, 1991). This study uses an 8-item short form of the RRS, which has been found to capture within-person variation in depressive brooding and reflection well (Brose et al., 2020).

The alcohol, smoking and substance involvement screening test lite (ASSIST-LITE, Ali et al., 2013) is a short-form screening tool of the original test (ASSIST), first developed for the World Health Organisation. The tool covers the misuse of and dependency on alcohol, tobacco, cannabis, stimulants, sedatives, opioids and other psychoactive substances including non-prescribed medicines. It is used to identify subjects whose alcohol and drug use and smoking may be increasing their risk of physical, psychological or social harm.

The PTSD checklist for DSM-5 (PCL-5, Weathers et al., 2013) is a 20-item self-report measure that assesses the 20 DSM-IV symptoms of PTSD. Subjects give their response on a 5-point scale according to how much they have been bothered by certain symptoms during the past month.

The brief experiential avoidance questionnaire (BEAQ, Gámez et al., 2014) is a short version of the multidimensional experiential avoidance questionnaire (MEAQ), which consists of 16 5-point Likert scale items. The BEAQ assesses experiential avoidance on six subscales: behavioural avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance.

The Sheehan disability scale (SDS, Sheehan, 1983) is a brief measure of functional impairment. It is used to evaluate the impact of treatment on disability in a number of psychiatric disorders. The scale consists of five questions designed to assess the extent to which a subject's disorder or health problem interferes with their everyday life. The subscales of SDS - work disability, social life disability, family life disability - can be scored independently or combined as a score of global impairment.

The well-being index (WHO-5, WHO, 1998) is a brief measure of subjective psychological well-being. The index contains five positive statements which the subject rates from 0-5 according to how well the statements have applied to their life in the past two weeks. Raw scores are converted into percentages, with 0 reflecting the worst imaginable well-being and 100 the best imaginable well-being.

The 7-item game addiction scale (GAS, Lemmens et al., 2009) is a shortened version of the scale, which measures game addiction on seven criteria: salience, tolerance, mood modification, relapse, withdrawal, conflict and problems. GAS was developed before the publication of DSM-IV and partially covers the criteria of Internet gaming disorder (IGD). Subjects rate on a scale of 1-5 how often they have felt, thought or behaved a certain way in the last month.

Finally, the problem gambling severity index (PGSI) consists of nine of the 18 items from the Canadian problem gambling inventory (CPGI, Ferris & Wynne, 2001). It is a tool used for identifying and quantifying risk and problem gambling in the general population. Items are not focused on diagnostic criteria but rather assess gambling behaviour and the financial, social and health repercussions of gambling. The total score indicates non-problem gambling (0), low-risk gambling (1–2), moderate-risk gambling (3–7), or problem gambling (8+). Reports of lower levels of severity are to be interpreted cautiously (Miller et al., 2013; Samuelsson et al., 2019).

3.6.5.2 Clinical interview

A clinical interview is conducted after the subject has enrolled in the study but prior to the beginning of the intervention. The aim of the clinical interview is to evaluate the subject inclusion and exclusion criteria.

The subject's MDD diagnosis is evaluated using the MINI International Neuropsychiatric Interview Module A, Major Depressive Disorder (Sheehan et al., 1998). We use MINI version 6.0 that has been translated into Finnish. Only the patients who fulfil the criteria for MDD are included in the study.

We are aware that the inclusion criteria for study is MDD of which the symptoms by definition include suicidal thoughts. At the same time, the threat of self-harm is an exclusion criteria for the study. Should the patient indicate suicidal thoughts or deeds in the interview, they are pursued further in order to evaluate whether the subject meets the exclusion criteria for threat of self-harm.

If the subject has suicidal thoughts but the subject is aware of the thoughts and it is clear that they are not intending to act on them, the subject may be included in the study. If the suicidal thoughts are excessive, the subject is considerably hopeless, has explicit plans or intention of suicide, they are excluded from the study.

If the CSC is not certain whether to include the subject into the study or not, MINI Module B, Suicidality, is conducted. A score of 17 or more points is used as a definitive cut-off point, yet the CSC may use a lower score at their discretion.

The exclusion criteria "They have addiction to digital games" includes addiction to both entertainment games and gambling, and CSC asks the subject of both. If CSC is uncertain whether the subject suffers from gambling addiction, they conduct the Problem Gambling Severity Index (PGSI) as an interview holding 8 points as absolute exclusion criteria, however, they can use a lower cutoff point based on their evaluation. If CSC is uncertain about a subject's addiction to digital games, they conduct Game Addiction Scale (GAS) as an interview, holding four or more answers of "sometimes" or more frequently as absolute exclusion criteria, however, the CSC may hold a lower threshold if necessary.

When needed, the subjects are guided towards their healthcare providers and other health resources as needed.

Also other inclusion and exclusion criteria are evaluated in an interview with the subject. If the subject does not meet the inclusion criteria or that they do meet the exclusion criteria, the subject is not admitted further to the study.

The clinical interview is conducted by clinical subject coordinators (CSCs) who are licensed healthcare professionals. The CSCs are trained to use MINI and have an in-depth understanding of the clinical investigation plan. The clinical interview is described in Appendix 5 - Clinical subject coordinator phone call.

3.6.6 Monitoring plan

3.6.6.1 The rights and well-being of our human subjects

The rights and well-being of our human subjects are protected. They are informed of their rights and how their data is stored. They participate in the study voluntarily. (See Appendix 2 - Participant information and consent form). We exclude vulnerable people whose ability to participate in the study (as detailed in 3.6.3).

The software is noninvasive, built to minimise possible risks to the subject, and akin to many freely available commercial video games for entertainment (see 3.14 and Appendix 11 - Ethics evaluation of the study). The subjects have contact channels with the clinical subject coordinators (CSC) and the coordinating investigator.

3.6.6.2 The reported trial data are accurate, complete, and verifiable from source documents

The study is conducted primarily online so that the subjects play the game and complete online questionnaires along predefined instructions, progression, and scheduling dictated by backend server software. Thus, a vast majority of actions and data acquisition during this trial take place automatically and in a manner that is fully traceable in terms of data sources and

time stamping. This alleviates the monitoring burden that is significant for the present trial that is carried out as academic, non-commercial research.

The trial data is gathered online using digital tools that have been developed through Good Programming Practises (GPP) and tested to verify that they produce accurate and complete data. As the subjects enter their information, the information is stored to servers in secure data centres, and their answers can be verified through a database query by an authenticated user inside a dedicated shield server.

The game infrastructure has two server entities:
1. Registration server
2. Game server

Registration server is responsible for the subject registration pipeline, questionnaires and following subjects game time limits. This server is being backed up according to best practises. Database of the registration server is being copied once a week and saved to an external back-up location to preserve the historical accuracy of the data. This guarantees that the data is intact and unchanged over time.

Each of the subjects is assigned a pseudonymised unique username and password upon registration ensuring that only the specified user participates in the intervention. With this username and password combination we can track and validate each of the subjects from the data. The game server uses only the unique pseudonymised username and password.

Game server is responsible for the adaptation of the game. Subjects log in with their unique account credentials and the game client sends and receives data from the game server. Data sent to the game server from the client is time stamped and tracked per user credentials. Data on the game server is being also backed up according to best practises and saved to an external location.

3.6.6.3 Trial compliance

The trial will be conducted in compliance with the currently approved protocol and the present amendment, as well as possible upcoming amendments. This compliance will be ensured by

1) **Training** of the investigators, CSCs, data analysts, and software developers to operate in the context of GCP-compliant RCT research. All staff participating in the conductance of the research are trained to be intimately aware of the CIP and design, and thus the appropriate investigational methods and practises, described in detail in CIP.

2) **Documentation** of, especially, subject- and data-related actions before, during, and after trial. In particular, the actions carried out in patient interactions and investigation monitoring will be documented and deviations from the CIP identified and acted on as described in section 3.10. Similarly, the data processing actions associated with interim and final analyses, and the actions triggered by these events (possible changes to trial structure and reporting demands, respectively) will be carried out in a CIP- and GCP-compliant manner.

3) **Effective communication.** The research team has internal communication channels to facilitate daily, low-threshold communication within the team. The researchers hold recurrent team meetings weekly where the compliance with the CIP is actively reflected.

The trial compliance from the perspective of CIP, GCP, and associated regulations is monitored actively during the study. All research and clinical staff are encouraged to engage in good-faith reporting in case of detection of deviations from CIP or GCP to the coordinating investigator. If a staff violation is detected, the coordinating investigator will follow it up, creating a written report on the incident. Necessary disciplinary actions are taken, the incidence is reflected internally, and research processes are improved to avoid such deviation in the future. A full evaluation of the CIP compliance, cross-referencing the items in this CIP, is conducted annually completed with a written report.

3.7 Statistical considerations

3.7.1 Data descriptors and frequency

Data for the analysis of the clinical study will be collected in the forms of:

1. **Sign-up process.** The online sign-up process is done once at the beginning of the study where the subject gains information regarding the study, signs an informed consent form, and background information is gathered.

2. **Clinical questionnaires.** The subjects fill questionnaires prior to the intervention (T0), and 4 (T1), 8 (T2), 12 (T3), and 24 (T4) weeks from the beginning of the research.

3. **In-game questionnaire.** An in-game questionnaire is presented to the subject after each game level, up to a total of 27 times, please see Appendix 7 - Tutkimuksessa kerättävät tiedot

4. **In-game behaviour.** Behavioural performance scores that are acquired from each completed game.

5. **Clinical interview.** The subjects are interviewed for the inclusion and exclusion criteria before the intervention begins.

6. **Experiential interview.** The subject may opt in to an interview conducted online.

3.7.1.1 Sign-up process

The sign-up is done completely online.

When the subject enters the online study recruitment site, they are first guided to read the recruitment information (Appendix 1 - Recruitment notice). Then, they are guided to read the information regarding the study (Appendix 2 - Participant information and consent form) and asked to read the user agreement (Appendix 3 - Confidentiality obligation and right of use). Should they agree and be willing to participate in the study, they are guided to sign an informed consent form (Appendix 2 - Participant information and consent form).

Then, the subject is asked for their contact information, demographics, mental health history, digital game playing history, and they are asked for their interest to participate in the interview and brain imaging sub-study.

The sign-up process is presented visually in the table 4 below, and the questions are in detail in Appendix 7 - Data collected in the study.

Table 4: Sign-up process (filled once)

	Pre-game period		**Playing intervention**			**Follow-up**
Content	Sign up and background questionnaires	T0 Before playing	T1: T0 + 4 weeks	T2: T0 + 8 weeks	T3: T0 + 12 weeks	T4: T0 + 24 weeks
Welcome to to the depression study recruitment page. ("Appendix 1 - Recruitment notice")	x					
Participant information ("Appendix 2 - Participant information and consent form")	x					
Confidentiality obligation and right of use ("Appendix 3 - Confidentiality obligation and right of use")	x					
Study consent form ("Appendix 2 - Participant information and consent form")	x					
Background 1: Contact information and background	x					
Background 2: Mental health	x					
Background 3: Gaming history	x					
Background 4: Brain imaging and interview	x					
Summary of background information	x					

3.7.1.2 Clinical questionnaires

The subjects fill questionnaires prior to the intervention (T0), and 4 (T1), 8 (T2), 12 (T3), and 24 (T4) weeks from the beginning of the research. All questionnaires are answered online.

The subject must fill the questionnaires at T0 before they are randomised into one of the three research arms: the intervention doesn't begin before the subject has filled the questionnaires. At T1, T2, T3 and T4, the subjects have two weeks to fill the questionnaire from the beginning of the time point. If the subject doesn't fill the questionnaire within one week, they are followed up with a phone call.

ASSIST-LITE, PCL-5, and BEAQ are filled only once at T0. The state of care questionnaire is filled in T1, T2, T3, and T4. IEQ measures game experience and is filled only after the subject has played the game. Other clinical questionnaires are filled at T0, T1, T2, T3, and T4. (see also Table 5).

The questionnaires include:

- Immersive experiences questionnaire (IEQ)
- Questionnaire regarding their state of care
- Patient health questionnaire (PHQ-9)
- Quick inventory of depressive symptomatology (QIDS-SR16)
- General anxiety disorder questionnaire (GAD-7)
- Positive valence systems scale (PVSS)
- The ruminative response scale (RRS)
- Alcohol, smoking and substance involvement screening test lite (ASSIST-LITE)
- PTSD checklist for DSM-5 (PCL-5)
- Brief experiential avoidance questionnaire (BEAQ)
- Sheehan disability scale (SDS)
- Well-being index (WHO-5)
- 7 item game addiction scale (GAS)

For details when the subjects are asked to fill the questionnaire, see table 5. For the questionnaire descriptions see 3.6.5.1, and for questionnaire content, see Appendix 7 - Data collected in the study.

Table 5: Clinical questionnaires

	Content	Sign up and background questionnaires	T0 Before playing	T1: T0 + 4 weeks	T2: T0 + 8 weeks	T3: T0 + 12 weeks	T4: T0 + 24 weeks
1	Immersive experiences questionnaire (IEQ)			MEL-T01 MEL-S01	MEL-T01 MEL-S01	MEL-T01 MEL-S01	TAU
2	Treatment status -questionnaire			x	x	x	x
3	Patient health questionnaire (PHQ-9)		x	x	x	x	x
4	Quick inventory of depressive symptomatology (self-report) (QIDS-SR16)		x	x	x	x	x
5	General anxiety disorder questionnaire (GAD-7)		x	x	x	x	x
6	Positive Valence Systems Scale (PVSS)		x	x	x	x	x
7	Short-version ruminative response scale (RRS)		x	x	x	x	x
8	Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-LITE)		x				
9	PTSD Checklist for DSM-5 (PCL-5)		x				
10	Brief experiential avoidance questionnaire (BEAQ)		x				
11	Sheehan disability scale (SDS)		x	x	x	x	x
12	The world health organisation -five well-being index (WHO-5)		x	x	x	x	x

3.7.1.3 In-game questionnaire

The in-game questionnaire occurs after each level achieved by the player. It asks two questions on a seven point scale: 1) does the subject enjoy the game; 2) how difficult did the subject find the game? In addition, the subject is able to mention other aspects considering their play experience. The questions (in Finnish) can be found in Appendix 7 - Data collected in the study.

3.7.1.4 In-game behaviour

The investigational device feels and displays as a video-game to the subject. Subject navigates in an interacting 3D environment by using keyboard and mouse. The subject's interactions with the game made with keyboard and mouse are stored in game logs. Subject experiences 28 tutorialized game levels that include performing various cognitive tasks that target specific cognitive functions. Purpose of any given game round is to conquer all the monuments. This includes defeating the opposing forces, solving tasks and overcoming challenges.

Performance values from these cognitive tasks, like reaction time, correct answer and execution time, are stored in the game logs and are used in evaluating gameplay performance values. These performance values are evaluated after each game and used for adapting the task difficulty individually to achieve the training effect.

The game includes a narrative and the subject receives feedback from their game progression to support learning. Subject has an avatar that yields magical, non-violent abilities. These include skills that can be used e.g. to alter temporal structure globally or locally, teleport to a location, cast a damaging beam of light or freeze enemies. Use of abilities is stored in game logs. Avatar has also the ability to command up to three friendly allies with defensive and offensive capabilities. Commands assigned to friendly allies are stored in game logs. These performance values are evaluated after each game and used for adapting the task difficulty.

3.7.1.5 Clinical interview

The clinical interview is conducted prior to the intervention. The aim of the interview is to evaluate whether the subject meets the inclusion and exclusion criteria. The clinical interview is described in 3.6.5.2, and in Appendix 5 - Clinical subject coordinator phone call. The clinical interview is conducted remotely by a trained, clinical professional.

3.7.1.6 Experiential interview

Qualitative research is ever more frequently used in randomised controlled trial (RCT) studies to explore the feasibility and acceptability of the intervention (Cooper et al., 2014). Using video games as a therapeutic modality is most likely a new concept for the majority of our subjects, and it is vital to gain insight into how they perceive the intervention.

To complement the questionnaire and in-game data gathering, we conduct interviews to the subjects who indicate their interest in participating in an interview. The aim is to interview approximately 20 subjects.

The interview is conducted online and it takes 1-1.5h. The aim of the interview is to understand 1) how the subjects view playing video games as a treatment modality; 2) explore how the player experiences playing Meliora, and 3) explore possible effects the game may have had.

For details on the interview protocol, see Appendix 8 (Appendix 8 - Interview study).

3.7.2 Data-analysis-inclusion criteria and handling of missing data

To be included in the analysis of the primary hypothesis, the subject has to

- Have played the game version A or B at least 24 hours (50% of the recommended 48 hour game time) during the 12 weeks.
- The subjects must have answered all of the PHQ-9 items on both T0 and T2 or T3.

Handling of missing data:

- Primary endpoint evaluation will be based on the comparison of scores acquired ~~at~~ between T0 and T3.
- When the subject has played the MEL-T01 or MEL-S01 for 24 hours, but the T3 PHQ-9 score is missing, we will use the T2 PHQ-9 score.
- If the subject has accumulated ≥ 24 hours of intervention use and then ceased the use, we will use the first PHQ-9 score after the cessation of use.
- Subjects that do not meet these criteria are excluded from the analysis.
- In regards to our secondary hypotheses, missing data are handled similarly.

3.7.3 Hypothesis tests and multiple comparisons

Primary and secondary objectives in this clinical study are to demonstrate a statistical difference on outcome measure mean change scores between the following groups:

1. MEL-T01 and MEL-S01
2. MEL-T01 and TAU
3. MEL-S01 and TAU

We will first assess whether we use a parametric or non-parametric test.

- Using the Shapiro-Wilk test we explore if MEL-T01, MEL-S01, and TAU model residuals are normally distributed regarding PHQ-9.
- Using Levene's test we test whether the variance of MEL-T01, MEL-S01 and TAU model residuals are equal regarding PHQ-9.
- If both tests are $p > 0.05$, we will use a repeated measures Linear Mixed Model;
  If either test is $p < 0.05$, we will use a repeated measures Linear Mixed Model with robust standard errors.
- For primary endpoint evaluation (PHQ-9), we will conduct a one-tailed test for the arm pairs MEL-T01-vs.-MEL-S01, MEL-T01-vs.-TAU, and MEL-S01-vs.-TAU. We

are using a significance level of 0.05. Using Holm-Bonferroni correction, we find the multiple-comparison corrected $p = 0.05/3 = 0.0167$.

Change scores are defined as the scores obtained between the pre-intervention (T0) assessment and the during/post-intervention assessments. The general formulation of the null and alternative hypotheses are

$$H_0: \mu_x = \mu_y$$

$$H_1: \mu_x \neq \mu_y$$

where H_0 is the null hypothesis, H_1 is the alternative hypothesis and $x, y \in \{A, B, TAU\}$, $x \neq y$.

3.7.4 Power and sample size

3.7.4.1 Power analysis

A power analysis was conducted to determine appropriate sample size for the study to detect a statistical difference between change scores for the primary hypothesis in a two tailed, repeated measures t-test. Assuming that our samples are independent and identically distributed with normal distribution (see 3.7.3), we analyse the required sample size as follows:

- We conduct sample size analysis using G*Power 3.1.9.7
- We use a two-tailed t-test.
- Cohen (1988) suggests a small effect size is 0.20 and medium effect size is 0.50. As a point of comparison, a meta-analysis of internet-based treatments for adult depression have reached an average effect size of 0.41 (Anderson & Cuijpers, 2009). Meanwhile, Motter et al. (2016) found in their meta-analysis that computerised cognitive training had an effect size of 0.43 on depression symptom severity. Thus, we use an effect size $d = 0.40$.
- We use an alpha error probability of 0.0167 that corresponds to an alpha level of 0.05 with Bonferroni correction for the three primary endpoint tests.
- We use power of 0.80
- We allocate subjects equally to the three arms, leading to allocation ratio of 1:1:1

This leads to a total sample size of 133 per arm and with three arms this equals 399 subjects, which we round to **400 subjects** that we aim to have in T3.

Karyotaki et al. (2015) explored the dropout in self-guided web-based interventions for depression using different psychotherapeutic approaches. While their approach is based on psychotherapies, and ours on cognitive training, the medium of training is the same

(web-based), the intervention is self-guided, and they target people with depression. Karyotaki et al. found that in 10 RCTs 59% of the subjects dropped out before completing half the treatment modules.

Meanwhile, Torous et al. (2020) explored dropout rates for app interventions for depression. Considering publication bias, they found a dropout rate of 47.8%.

Considering the above, we assume a dropout rate of 50%. Thus, we aim to recruit up to 400 subjects / 0.50 = 800 subjects to begin the study.

3.7.4.2 Recruitment and investigation termination condition

Once we have 133 subjects in each of the three research arms that fulfil the data analysis criteria as explained in 3.7.2, we will close the recruitment for the study. The subjects who are already recruited at this moment will carry on with the intervention. We will consider the gathered sample complete when these subjects have completed their intervention period up to time T3. When no subjects remain in either intervention or follow-up periods, we will terminate the investigation.

3.7.5 Interim analysis

Interim analysis in clinical trials is an analysis, and hence unblinding, of partially acquired data, which is conducted before the data collection has been completed. This can be performed to assess whether the investigational device can be proven to be (i) clearly beneficial or (ii) harmful compared to the comparator, or to be (iii) obviously futile.

We will use a pre-defined and pre-programmed interim analysis to assess these three conditions and thereafter infer whether the investigation should be stopped early or if the investigation plan warrants a change in terms of the to-be acquired cohort size. If evidence for one alternative is acquired, such modifications allow the saving of resources and subjects' efforts.

The interim analysis will be conducted when each arm has 33 or more subjects that have completed the 12 first weeks of the investigation and meet the inclusion criterion to data analysis (see 3.7.2).

3.7.5.1 Criteria for "clearly beneficial"

We will consider MEL-T01 to be clearly beneficial if it the it reaches the primary endpoint so that:

> The reduction in PHQ-9 score from T0 to T3 is
>
> greater for MEL-T01 than for TAU
>
> AND
>
> greater for MEL-T01 than for MEL-S01.

If both superiority conditions are met in a one-tailed t-test (or in a one-tailed Wilcoxon test if the conditions defined in 3.7.3 for using a parametric test are not met) with an alpha-level of 0.025, the recruitment will be carried on until the next 33 data-analysis-qualified subjects have

been recruited to each of the three arms. After this recruitment goal has been achieved, the investigation will be terminated with the same process that is defined for the main termination condition (defined in 3.7.4.2).

Thus, if evidence for MEL-T01 being clearly beneficial is observed, we will acquire a replication cohort to corroborate this observation and terminate the study.

3.7.5.2 Criteria for "harmful"

We will consider the digital interventions (MEL-T01 or MEL-S01) to be harmful if TAU is superior to either intervention so that:

> The reduction in PHQ-9 score from T0 to T3 is
>
> greater for TAU than for MEL-T01
>
> OR
>
> greater for TAU than for MEL-S01.

If either of the superiority conditions are met in a one-tailed t-test (or in a one-tailed Wilcoxon test if the conditions defined in 3.7.3 for using a parametric test are not met) with a Bonferroni-corrected (N_{tests} = 2) alpha-level of 0.0125, we consider the digital intervention as harmful to the subjects and terminate the investigation immediately.

Here, it is important to note that, at the discretion of the investigators, it is also possible to halt or terminate the investigation on the basis of harmfulness also at times other than that of the Interim analysis. As described in 3.15.2.2, evidence for such harmfulness could be excessive AEs in many subjects or an SAE that is related to the investigational device and may potentially be experienced by other than the subject first reporting it.

3.7.5.3 Criteria for "futile"

The study may be considered futile, if it becomes clear that the subjects are not interested in the devices under investigation, or the investigation is too burdensome for them. These may be indicated by (i) considerable difficulty in recruiting subjects to the investigation, (ii) there is an excessive amount of subjects that drop out, or (iii) the subjects indicate that they are not interested or willing to play the game for more than a few hours. In these cases, at the joint discretion of the principal and coordinating investigators, the investigation may be terminated prematurely.

3.7.5.4 Otherwise

If the investigational device is not clearly beneficial, harmful, or futile, the investigation will be continued as planned in this CIP.

3.8. Data management

3.8.1 General information

The subject data is managed responsibly, securely, and with the informed consent of the subject. The access to data is only with designated researchers. Managing the data is described in detail in Appendix 4 - Privacy notice and impact assessment.

The subject is given informed consent of their rights regarding the data, including their right to withdraw their consent. The subject rights are described in detail in Appendix 2 - Participant information and consent form.

3.8.2 Data validation

Access to the server system and to the data folder is given only to authorised personnel under password verification through two security layers. All data analysis will be performed in the custom-made data-analysis platform that keeps an audit-trail of the performed data-analysis. Data validation or data cleaning procedures are designed to assure validity and accuracy of clinical data. Data validation consists of manual reviewing during data entry and computerised edit checks and queries for identifying data values that are out of range, protocol violations, incomplete or inconsistent.

When errors in clinical data are discovered during data entry, a discrepancy is created. Discrepancies are created when information is missing or is illegible and needs further clarification. Discrepancy forms are sent to the coordinating investigator.

3.8.3 Record keeping and archiving

The study specific essential documents must be retained until at least 15 years after the completion of the study. The investigator must not destroy any study specific documentation before receiving written permission for this from the sponsor.

3.9 Amendments to the CIP

The beginning of this document includes a version history where possible amendments are made visible. The previous versions of the CIP are stored and recoverable.

3.10 Follow-up and management of deviations from the CIP at investigational sites

Bhatt (2012) differentiates deviation from violation in that deviation has less significant consequences than violation. It is possible that CIP deviation or violation occurs due to the subjects or the researchers.

3.10.1 Subjects deviations or violations

The majority of human made deviations are mitigated because the majority of the intervention is digital: answering questionnaires as well as playing the game. Wherever possible, we have mitigated the possibility for the subject to deviate from the CIP.

Before the subject is included in the research, they complete the signup process (see 3.7.1.1), first set of clinical questionnaires (see 3.7.1.2), and their MDD diagnosis is confirmed through clinical interview (see 3.7.1.5). Only then the subject is randomised to MEL-T01, MEL-S01, or TAU group, and they are given access to the intervention (for groups MEL-T01 and MEL-S01). Thus we mitigate the risk of the subject not meeting the inclusion/exclusion criteria.

When the subject arrives at T1, T2, T3, and T4, they are emailed the instructions to complete clinical questionnaires. In addition, the reminder to complete the questionnaires is shown to the MEL-T01 and MEL-S01 group in the game, and they are not able to make progress until they have completed the questionnaires. The questionnaires are filled online. If the subject doesn't fill the questionnaires in 7 days from the onset of T1, T2, T3, or T4, they are followed up with a phone call by the CSC.

The subject is recommended to play the game for 48 hours during the 12 week play period. To be included in the sample we require 24 hours of gameplay. When the subject is contacted by the CSC, the CSC has access to the subject total game time and number of weeks played (but they do not know the subject group). If the subject total game time divided by the number of weeks played is less than 2 (the minimum required), the CSC kindly discusses the topic with the subject encouraging them towards reaching 24-48 hours of playing time during the 12 week play period.

3.10.2 Research staff deviations and violations

The nature of clinical investigation is double-blinded. The information regarding the subject group is withheld from all researchers, including the CSC who are in direct interaction with the subjects as well as from the researcher conducting the experimental interview. Thus, we mitigate the risk of breaking the blind. The rest of the interactions between the subject and the researchers is avoided. If the subject contacts the researchers or coordinating investigator, the researchers are not aware of the subject group.

The CSC are trained in using MINI to ensure the inclusion and exclusion criteria are met. There are at least two CSC to ensure sufficient human resources to keep contact with the subjects.

The subjects are encouraged to report all AE and SAE to the researchers, and they have multiple channels to do so: in-game link, email, and phone calls.

After randomisation, the subjects are randomised to three groups. The groups are handled automatically to prevent mishandling samples.

3.11 Accountability

3.11.1 Control of access to the device

Access to the software is only available as long as the digital key is valid. The digital key can be activated and deactivated remotely by the researchers. Only one install is possible with one digital key. Deactivated key prevents launching the software. The researchers can deactivate the subject's key if the subject doesn't follow the researchers instructions. Access to the game requires login to the distribution channel (Steam) and login to the game client itself.

Access to the MEL-T01 and MEL-S01 software is restricted to subjects who have completed the signup pipeline, T0 questionnaires, and gone through the clinical interview by the CSC. After this, the subjects are randomised to one of the three groups.

Whether in TAU, MEL-T01, MEL-S01 group, the access to the training is 12 weeks from the beginning of the intervention. For 2 weeks after the intervention has ended, the access to the training is denied from the user, but they can access the main menu through which they can complete the questionnaire T3 (groups MEL-T01 and MEL-S01) or T4 questionnaire (TAU group).

After the two weeks are over, the access to the software is denied, and the subject can uninstall it from their device. See Table 6 for a detailed outline of the access to the device.

Table 6: Access to the device

Access to the device

Study arms	T0 (Before playing)		T1: T0 + 4 weeks		T2: T0 + 8 weeks		T3: T0 + 12 weeks	T3 + 2 weeks		T4: T0 + 24 weeks	T4 + 2 weeks.	After T4 + 2 weeks
MEL-T01 intervention	T0 begins after CSC confirms the subject is eligible to the study. The subject is randomised to one of the three groups.	MEL-T01 intervention						Access to menu only.	No access to the device.			
MEL-S01 intervention		MEL-S01 intervention						Access to menu only.	No access to the device.			
Treatment as usual ("TAU")		Treatment as usual						Access to MEL-T01 or MEL-S01 intervention			Access to menu only.	No access to device.

3.11.2 Follow-up in relation to the device used in the clinical investigation

When the access to the device is denied, the subject is no longer able to access it via the Steam platform as the software locks the player out. The subject can then uninstall the game from their device.

3.11.3 Return of unused, expired or malfunctioning devices

The device is a software with a digital key that makes installation possible. Subjects can anytime choose to uninstall unused, expired, or malfunctioning software instances.

3.12 Compliance with the recognised ethical principles

3.12.1 Independent ethics committee (IEC)

The study is performed according to the Declaration of Helsinki and in line with local ethical regulations. The study will not commence until a favourable opinion has been obtained from the appropriate institutional ethics committee (IEC). Any significant alterations affecting ethical issues a formal protocol amendment will be issued and submitted to relevant IEC/IRB (institutional review board) for approval. The amendment will not be implemented until IEC/IRB approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the subjects.

3.12.2 Guidelines and regulations

The trial will be conducted in compliance with the protocol, International Conference of Harmonisation (ICH), Good Clinical Practice (GCP), the applicable regulatory requirement(s) and the Declaration of Helsinki.

3.12.3 Subject confidentiality

The investigator(s) will respect and protect the confidentiality of the subject in all possible ways. Subject personal information is pseudonymised. Only the investigator and the persons authorised to verify the quality and integrity of the study will have access to subject records where the subject can be identified. See also Appendix 2 - Tutkimuksen tiedote ja tutkittavan suostumus, and Appendix 4 - Privacy notice and impact assessment.

3.13 Description of the Informed consent process

The subjects that have read the recruitment information (Appendix 1 - Recruitment notice) and confirmed that they fulfil the criteria for the study, are guided to read information regarding the study (Appendix 2 - Participant information and consent form) that has been written in accordance to the Finnish law medical research act (9.4.1999 / 488).

Research subjects are entitled to withdraw their consent at any point prior to the completion of the research. They are informed of this before the start of the research. Withdrawal of consent and resulting withdrawal from the research shall not involve any negative consequences for the research subject which they are informed of. For other details regarding informed consent, please see Appendix 2.

After reading information about the study, the subject is asked to read a user agreement (Appendix 3 - Confidentiality obligation and right of use).

After reviewing both Appendix 2 and Appendix 3, the subject signs the informed consent digitally. For information regarding the safe storage of digital materials, please consult Appendix 4 - Privacy notice and impact assessment.

3.14 Safety reporting

3.14.1 Safety reporting procedures and timelines

For AE and SAE definitions, see 3.3.

The subjects are given health information regarding the device in the game (see Appendix 6 - Investigator's brochure). Should the subject experience an anticipated or unanticipated AE or an SAE, or an assumed or observed device deficiency, they are able to report them through the channels below. The subjects can:

- Provide any free-form feedback in in-game questionnaires presented 28 times during the intervention, which are monitored by the CSCs.
- Report game-related issues digitally into a Jira-based system that is accessible through the in-game main menu which is monitored by the CSCs.
- Describe their concerns in both subject-initiated and pre-scheduled (weeks 0, 4, 8, 12, and 24) phone calls with the CSCs.
- Send email to CSCs by using an email address presented both in the game main menu and in the subject's informed consent form.

The CSCs actively monitor these channels on a daily basis from Monday to Friday between 9-17 o'clock. When the subject indicates an AE, SEA, or device deficiency, the event is recorded into a secure, traceable digital system.

Timelines. The summary report for AE is delivered to the coordinating investigator on a weekly basis for review. AE that merit investigations are reported immediately to the coordinating investigator. All SAE are reported immediately to the coordinating investigator both verbally as well as in written reports.

Records. Coordinating investigators keeps a full digital record of any AE, SAE, and device deficiency. The coordinating investigator is responsible for evaluating whether the AE or SAE has a causal connection with the device use. The causality is evaluated on a scale of **possible**, **probable**, and **definitive**. In addition, the AE is evaluated for its severity from **mild** effects that are easily tolerated, **moderate** where there is discomfort, and **severe** that has significant effects. All device deficiencies are evaluated for the possibility of AE and SAE.

Follow-up. The coordinating investigator will follow the AE, SAE, or device deficiency with examining its connection with the device use. When necessary, a patch process is undertaken as described in 3.14.2 The AE and device deficiency are reported to regulatory bodies, including FIMEA and HUS ethical board, according to regulatory schedules. SEA are reported without delay and within a maximum of 7 days to the relevant regulatory bodies as well as research sites.

3.14.2 Device deficiencies and patch process

It is possible that the software bugs cause the program to function in an unintended way such as preventing the subject from making progress in the game or causing the program to shut down. These effects may or may not cause AE, such as frustration, to the subject.

The subject can report their complaints of device deficiencies digitally at any point in the channels indicated in 3.14.1. Like AE and SAE, device deficiency is recorded digitally. Device deficiencies are also considered whether they have led to AE for the subject.

In the case of a critical issue in the game version that, for example, prevents the subjects from using the game as intended, we are able to deliver targeted “patch” versions that fix the critical issue. These patch versions are divided into two categories: server patches and game version patches.

Patching is a normal industry procedure for fixing critical issues. A server patch is a correction at the server side. It may or may not need a game version patch along with it. Server patches include but are not limited to correcting game difficulty or correcting error situations that may prevent subjects from using the software. The principal reason for a server patch is to adjust issues that can not be adjusted with a game version patch.

Game version patches focus on correcting issues on the game client installed on the subject’s PC. This includes but is not limited to fixing game breaking error situations where the subject is no longer able to use the software because of a software issue.

The patch process always targets a specific issue and does not change the overall behaviour of the software described in this protocol. If an issue has been deemed necessary to patch, we will track all the changes to the game code and game version as described in section 3.2.5. This includes but is not limited to file changes, date, author, version number and game versions. This process ensures that the changes made are targeted correctly to fix the desired issue and that there are no undesired changes. The patching process will never change the intended device functioning or lead to any changes to the functional and technical features of the device, which are reported in this protocol.

In the case that a subject notifies us about a critical issue in the game version via phone, email, customer support tool or any other means, we will follow the following procedure. First these issues will be documented in a complaints log by the clinical subject coordinator. These complaint logs are managed in a cloud document repository as described in section 3.2.5. Next the situation will be analysed by the game team to make sure that it is a valid issue, meaning the issue requires a change to the game itself. We will then proceed to creating a patch version either to the game or to the server. The patch version will go through rigorous and documented testing before being released to the subjects to validate the patch has fixed the issue and to ensure that the rest of the game remains unaffected.

3.15 Criteria and procedures for follow-up

3.15.1 Subjects following the end

The MEL-T01 and MEL-S01 have a 12 week follow-up period after the playing intervention between T3 and T4. TAU has a playing period between T3 and T4.

All subjects are emailed after they have filled the T4 questionnaire when the study period ends for all of the groups. In this email, the subjects are told about the randomisation as well as which group they belonged to as explained in Appendix 2 (Participant information and consent form). The subject is informed that the research results will be published later. The

subject is asked for feedback regarding the study, and their questions regarding the study are answered. The subject is thanked for their participation. The subject is asked for feedback regarding the study, and their questions regarding the study are answered via email or phone.

The subject is compensated for their participation based on Social and health ministry 82/2011 §2: 50€ if they have played the game for at least 24 hours and answered all questionnaires; or 120€ if they have played the game at least 48 hours and answered all questionnaires.

3.15.2 Temporary halt or early termination of an investigation

3.15.2.1 Halt or termination for one subject

As per 3.6.3.4, the coordinating investigator may discontinue the study for the subject if

- Subject has an adverse event (AE) related to the device use
- Subject violates the Appendix 3 (Confidentiality obligation and right of use)
- Subject's mental health deteriorates in a way that they are not fit for continuing in the study. This includes, for instance, psychotic symptoms, hospitalisation, and suicidality.

If the subject has serious adverse events (SAE) their participation in the study is discontinued. If the study needs to be terminated early for a subject, the subject is contacted through the phone, and the reasoning for discontinuation is discussed with them.

3.15.2.2 Halt or termination of the investigation for all subjects

By design, the investigation will continue until the termination condition (see 3.7.4.2) is met unless the results of the interim analysis lead to an earlier termination (see 3.7.5). In addition to these termination conditions, we consider the following adverse-event-related conditions.

If MEL-S01 or MEL-T01 is deemed to be a probable or definitive cause for an SAE that another subject may face as well, or to cause unduly AEs in a larger subset of subjects, the whole study may be halted or terminated early to protect other subjects. Halting is warranted if a specific correctable device deficiency can be identified as the cause and in this case the halt continues until said deficiency is patched and validated to be corrected. If no such identification or correction is possible, the trial will be terminated. The decision is made by the principal investigator without delay upon communication from the coordinating investigator.

An early termination of the investigation may also be triggered if the Interim analysis identifies the intervention to be harmful (see 3.7.5.2) or at the time of the Interim analysis, the investigators find the investigation to be futile (see 3.7.5.3).

If such a decision is made, all the subjects are informed of the reasons for the study to be halted or terminated prematurely, and their access to the software is denied. The subjects are followed-up to evaluate the impact of the device on them leading to a full, written investigative report delivered to the relevant regulatory bodies.

The investigation may also be prematurely ended either immediately or by cessation of recruitment if the Interim Analysis indicates a high probability of MEL-T01 or MEL-S01 causing harm to the subjects.

3.15.3 Subjects withdrawing their consent

The subjects may withdraw their consent to participate in the study at any point without negative consequences or without giving a reason. Yet, the subject is free to discuss their reasons with the CSC or the coordinating investigator if they wish.

The subject's access to the software is then denied and they can no longer open it,
and they are free to uninstall it from their device.

3.16 Taking care of subjects after the clinical investigation

The subjects of our study have an ongoing treatment with a mental healthcare professional as described in the "3.6.3 subjects". After the clinical investigation, their treatment continues with their healthcare provider. Based on our assessment of the risks of the device and its use, we do not expect our subjects to require taking care after the investigation.

3.17 Clinical Investigation Report and Publication of Results

The publication of study results will be agreed between the sponsor and the investigator(s). The sponsor is interested in publishing the results of the study but to prevent publication of any confidential information, the sponsor retains the right to review all publications and presentations before they are made public. This trial will yield high quality and highly novel clinical findings and we expect them to be publishable in top level scientific journals. After the termination of the trial, a clinical investigation report will be prepared and the results are also published in clinicaltrials.gov service where the trial pre-registration is handled.

3.18 Technical and functional features of the device

The digital intervention MEL-T01 and the investigational medical device comprise a DTx software software solution that is designed to alleviate depressive symptoms by targeted training of those cognitive functions that are compromised in MDD. The main software is the game client that renders the 3D environment where subjects can interact in various ways. The game client is made with Unity 3D game development environment in C# programming language and has been written solely with Good Programming Practices (GPP). Program code is stored in a version controlled repository that allows traceability of any changes. For subjects it feels and looks much like an entertainment action video game.

Distribution of the software is handled through Steam gaming platform that is available to consumers via online download. Steam streamlines the distribution of the software with an intuitive and easy to use interface and registration process. Operation of the software is done

with the subject's own computer at home. Subjects' ability to interact with non-study related applications is not restricted.

The software is designed to train cognitive functions. This is achieved by analysing player in-game performance in various domains and then adjusting the challenge of the game after each complete game round. The performance evaluation and adaptation is performed on a dedicated and secure back-end server that is accessible only for approved users inside Aalto University shield server.

Communication between game client and back-end server is encrypted and follows https protocol. This communication is effectively invisible to the subjects and happens during loading screens.

The technical and functional features of the device are described in table 6.

Table 6: Technical and functional features

Technical and functional features of the device	*Covered by the investigation?*
MEL-T01-specific game mechanics, incl. real-time-strategy elements and cognitive tasks	Yes, tested against MEL-S01
MEL-T01 and MEL-S01 shared game mechanics (see Table 3)	Yes, tested against TAU
Challenge-level adaptation system	Yes, tested against TAU
Audiovisual execution of the game	No
Performance of Steam platform	No
Performance of Unity game engine	No
Performance of the subject’s personal computer	No
Performance of backend server soft- and hardware	No
The usage of phone and email communication channel	No

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