RESEARCH PROTOCOL

0-phobia: towards a virtual cure for specific phobias

(March 27, 2017)

PROTOCOL TITLE '0-phobia: Towards a virtual cure for specific phobias>'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
ANOVA	**Analysis of variance**
App	**application**
AR	**Adverse Reaction**
AQ	**Acrophobia Questionnaire**
CA	**Competent Authority**
CBT	**Cognitive Behaviour Therapy**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUS	**System Usability Scale**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
VR	**Virtual Reality**
VRET	**Virtual Reality Exposure Therapy**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Specific phobias, such as intense fear of flying, heights, or spiders, are the most common form of mental health disorders worldwide. Specific phobias have a lengthy history of clinical research and very effective exposure treatment exists (Wolitzky-Taylor et al., 2008). However, due to high costs, stigma, and long waiting lists, access to evidence-based therapy is currently limited. Meta-analyses on treatment effectiveness for people suffering from specific phobias have shown that Virtual Reality Exposure Therapy (VRET) is as effective as traditional forms of exposure therapy (Marino et al., 2015; Parsons and Rizzo 2008; Powers and Emmelkamp 2008; Opris et al., 2012). VRET, however, involves relatively high costs and limited accessibility which make it prohibitive for the larger part of the population. This project capitalizes on novel technology and recent scientific advances to develop an affordable treatment modality that is available for anybody, anywhere. Specifically, 0-phobia, a self-help VRET for fear of heights, that is delivered through a smartphone application (app) in combination with rudimentary cardboard Virtual Reality (VR) Google Cardboards will be developed and tested. We hypothesize that 0-phobia is effective in reducing anxiety symptoms and is user-friendly to use.

Objective: To determine (1) the clinical effects of 0-phobia to reduce fear of height anxiety symptoms at post-test and follow-up, (2) the user-friendliness of the intervention and 3) effects on depression, general anxiety and mastery.

Study design: This study will be a randomized controlled trial with two arms: the intervention condition (0-phobia) and a waitlist condition.

Study population: 154 individuals (18-65 years) who experience fear of heights symptoms will be recruited from the general population to participate in the trial.

Intervention: The intervention 0-phobia is 6-week self-help VRET for fear of heights, that is delivered through a smartphone application (app) in combination with rudimentary cardboard VR goggles. 0-phobia includes modules of psychoeducation, case examples, exposure through VR, cognitive techniques, monitoring of symptoms, and a relapse prevention module. Participants in the waitlist condition will be offered the intervention directly after post-test.

Main study parameters/endpoints: The main study parameters are the post-test differences in anxiety symptoms between the experimental and control condition, and follow-up differences in anxiety symptoms between baseline and follow-up in the experimental condition.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden of participation consists of completing online baseline questionnaires (15 minutes) and performing the intervention (3 weeks x 5-20 minutes and

daily VR exposure practice during 2 weeks of 10 minutes). In addition, participants will be asked to complete an online post-intervention assessment immediately after completion of the last module of 0-phobia (less than 5 minutes), the intervention (20 minutes) and a follow-up after 3 months (20 minutes) (experimental condition only). There is minimal risk involved and the burden to participants is limited.

1. INTRODUCTION AND RATIONALE

Specific phobias are intense and irrational fears for a particular object or situation that poses no objective threat (Ledoux, 2015). Think, for example, of fear of spiders, heights, needles, or flying. People with a specific phobia recognize that their fear is excessive and unreasonable, yet are unable to overcome it. The object or situation causes the person suffering from the phobia to endure intense anxiety and distress, which can significantly interfere with his/her ability to function in their private and working lives. With a lifetime prevalence nearing 10%, specific phobias stand at the top of the cost hierarchy of all mental disorders (Smit et al., 2008). More than 500.000 people in the Netherlands currently suffer from one or more specific phobias and each year there are 75.000 new cases with a specific phobia diagnosis (De Graaf et al., 2012). The estimated annual societal cost of specific phobias is €168 million (De Graaf et al., 2012). Due to high treatment costs, long waiting lists, and a general reluctance to seek treatment, access to evidence-based therapy is currently limited. Only around 20% of people with a specific phobia currently had access to treatment in 2012 The Netherlands (De Graaf et al., 2012). As specific phobia treatment is not covered by health insurance in The Netherlands anymore, the current percentage of people who receive treatment may even be lower. If left untreated, specific phobias can become chronic and increase the risk of developing other mental disorders, such as anxiety and depression. Given the psychological burden phobias carry, along with increased risk of developing comorbid depressive and anxiety disorders, and the heavy economic burden for society (Kessler, 2005), there is a need for affordable and scalable self-help interventions.

Specific phobias have a lengthy history of clinical research and very effective treatment exists (Wolitzky-Taylor et al., 2008). So-called exposure therapy refers to a form treatment in which a person is gradually exposed to the object or situation of his/her fear. Over the past decade, a new type of treatment based on these same principles has emerged but now making use of virtual reality (VR) rather than exposure ‘in vivo’. In virtual reality exposure therapy (VRET), artificially created computer-generated environments replace in vivo therapy to expose clients to the object of their phobia. Meta-analyses on treatment effectiveness for people suffering from anxiety disorders and specific phobias in particular have shown that VRET is as effective as traditional forms of exposure therapy (e.g. Goncalves et al., 2012; Morina et al., 2015; Parsons and Rizzo, 2008; Powers and Emmelkamp, 2008; Opris et al., 2012) in reducing anxiety and other outcomes, such as depression. In a review of 14 studies (Morina et al., 2015), participants in the VRET condition for specific phobia improved significantly on behavioral assessments after VRET from pre- to post-test (aggregated uncontrolled effect size g = 1.23) as well as when

compared with wait-list control subjects (*g* = 1.41). Furthermore, there were no significant differences between VRET and exposure in vivo at post-test and follow-up (g= -0.09 and 0.53 respectively). In another meta-analysis of Opris et al. (2012), results demonstrated that VRET has better outcomes than wait-list controls, similar efficacy between VRET and C(B)T, and no difference in dropout rate between VRET and exposure in vivo. This research shows that virtual environments can be usefully employed as substitutes for real-world settings (Slater et al., 2006, 2013). Aside from demonstrated effectiveness for anxiety disorders and specific phobias in particular, VRET has a number of additional advantages over traditional 'in vivo' treatment, such as the possibility to conduct it within the confines of the therapist's office rather than having to go outside. Furthermore, VRET offers more flexibility in terms of sequencing and intensity of treatment and graduality of exposure. That is, people can practice more often and with a larger variety of scenarios compared to in vivo exposure. In spite of its advantages over traditional in vivo therapy, VRET still involves relatively high costs and limited accessibility which make it prohibitive for the larger part of the population. Existing VRET often also requires heavy graphic processing capabilities not found in ordinary computers and mobile devices. Additionally, existing VRETs still require the intervention of a therapist.

Research into mobile apps as a method to intervene for psychiatric disorders are promising (e.g. Donker et al., 2013; Eysenbach et al., 2011; Saeb et al., 2015). App-based mental health interventions based on e.g. CBT principles have shown to be effective in reducing mental health symptoms with within-group and between-group intention-to-treat effect sizes ranging from *d*=0.29-2.28 and 0.01-0.48 at post-test and follow-up, respectively in a review of Donker et al. (2013). Advantages are better accessibility and participant retention, real-time progress monitoring, portability and flexibility. As far as we know, one study has investigated the effectiveness of VRET using a mobile application for fear of spiders. Results showed a reduction in anxiety levels (Piercey et al., 2012). Another study in which the effectiveness of VRET on a smartphone compared with traditional one-session exposure therapy for subjects with spider phobia is currently being evaluated (Miloff et al. 2016). To our knowledge, no studies yet have explored the feasibility and efficacy of VRET delivered through a smart phone app using Google cardboards for fear of heights. The aim of this project is to test a low cost, scalable, and evidence-based solution for fear of height symptoms through exposure therapy by integrating VR technology with a smart phone app. The fear of heights intervention will be tested for its effectiveness in reducing anxiety symptoms and user-friendliness using a randomized controlled trial (RCT) design amongst adults from the general Dutch populations with fear of heights symptoms.

2. OBJECTIVES

Primary Objective: To determine the clinical effects (a reduction in anxiety symptoms – fear of heights at post-test [between the experimental condition and controls] of 0-phobia, and whether effects are sustainable at follow-up [a reduction in anxiety symptoms between baseline and follow-up for those in the experimental condition])
Secondary Objective(s): To determine the user-friendliness of 0-phobia and effects on mastery (locus of control), depression and general anxiety of subjects.

3. STUDY DESIGN

A randomized controlled design will be carried out, in which the effectiveness and user-friendliness of an online app-based VR self-help treatment '0-phobia' will be evaluated. In this study, 154 participants from the Dutch general population will be randomized over 2 conditions: the experimental condition (0-phobia) and a waitlist condition. The duration of the intervention will be 3 weeks. Measures will be taken at baseline, directly after the intervention (3 weeks) and at 3 months (follow-up). All measures will be completed online. Subjects in the wait-list condition will receive the intervention after completion of the post-test. Randomization (block-randomization) will be performed by an independent researcher. Figure 1 presents the flow chart of the study.

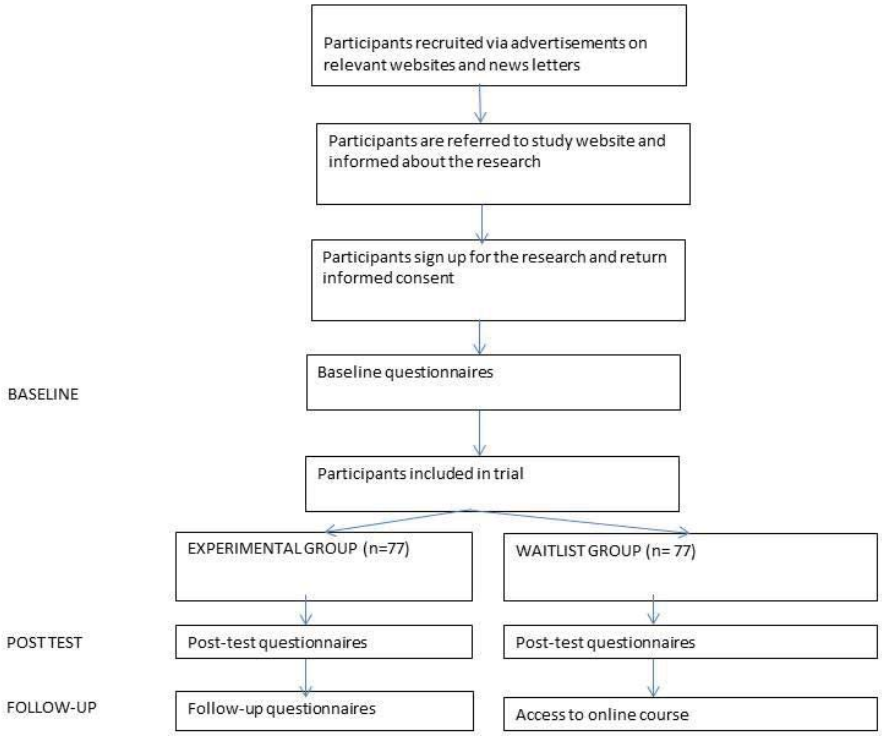
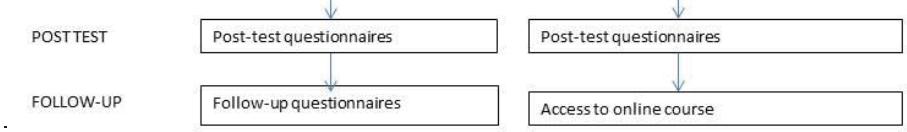


Figure 1



4. STUDY POPULATION

4.1 Population (base)

A sample of 154 individuals (18-65 years) with symptoms of fear of heights will be recruited in the Dutch population.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

-are between 18-64 years old

-scoring above 45.45 on the AQ-Anxiety (one standard deviation below the mean of a previous acrophobic sample; Cohen, 1972; Steinman and Teachman, 2011)

-have access to a smart phone (Android) and internet

-willing to participate in the research study and providing informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

-present with symptoms of severe depression or suicidality respectively as measured with the PHQ-9; total score > 19 or a score 3 on the suicidal ideation question of the WSQ, (Donker et al. 2009)

-have insufficient knowledge of the Dutch language

-are under current treatment for specific phobia or psychotropic medication (unless on stable dosage for the previous 3 months and no changes planned during the study period).

4.4 Sample size calculation

The primary outcome measure, the AQ, has been used for the power calculations. In previous RCTs using the AQ as an outcome measure, effect sizes of 0.79-1.42 (Emmelkamp et al.,2002; Krijn et al., 2004) were demonstrated. However, as we will use Google cardboards instead of expensive head-mounted displays, we will use a conservative estimation of a post-treatment effect size of 0.50 on the AQ for the current study. To be able to detect a difference between the experimental and control condition with a standardised effect size (Cohen`s d) of 0.50 (two-sided), an alpha of 0.05 and statistical power (1-Beta) of

0.80, we need 64 participants in each condition (128 participants in total). With a drop-out of 20%, we need 154 participants in total.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

0-phobia is based on the principles of virtual reality exposure therapy (VRET) and Cognitive Behavioral Therapy (CBT), which currently is the most researched and used treatment for anxiety disorders. 0-phobia is developed by the VU and In-Session. The content is developed by both, In-Session is responsible for app-programming and VR development. 0-phobia has been tested by persons with fear height symptoms throughout the process of development. In a recent 0-phobia user-test the VR environment was tested in 10 healthy participants. Results showed that the VR environment was rated as realistic and that subjects felt they were present in the environment. Among those who had symptoms of fear of height, the level of anxiety raised with increased levels of difficulty of the VR environment. Anxiety reduced afterwards.

The 0-phobia fear of heights intervention is an app-based intervention consisting of six modules that can be followed according to a user's own tempo and timing and without the intervention of a therapist. The participant will download the app on his or her smartphone. The program can be viewed from their mobile phone. Only when practicing in the VR environment (1 module) participants will put their mobile phone into Google cardboards to be able to experience the VR environment. Participants are allowed to keep the cardboards after finishing the study.

The therapy consists of six consecutive modules, each taking between 5 to 20 minutes to complete:

1. Psychoeducation: Explanation of a specific phobia and 0-phobia
2. Facing your Fears: Setting your goals, explanation about exposure and the fear curve.
3. Exposure Therapy: Practicing in virtual reality and exposure feedback
4. Cognitive Therapy: Detecting automatic thoughts
5. Cognitive Therapy: Developing helping thoughts
6. The Next Steps…..: Facing your fears in daily life

Ad 1) **Psychoeducation**: Explanation of what a specific phobia exactly entails, how it can emerge and what the potential consequences are.
Ad 2) **Facing your fears:** In this module, the participant will define his/her goals for the treatment. Furthermore, the treatment principles underlying exposure are explained
Ad 3) **Exposure in VR**: in this module, the VR content is explained and how to access it. Participants will practice in a practice-environment with VR before commencing the exposure

therapy. After practice, the actual exposure takes place. With the virtual reality environment, participants get a series of assignments to perform in the virtual theater. After that, subjects can practice with non-interactive 360 degrees VR videos of height situations. Based on his/her fear levels and performance the user receives feedback. S/he can return to practicing in virtual reality as often as s/he likes and gradually expose him-/herself to different heights and fear intensities. Only during the exposure sessions will the participant use the Google cardboard.

Ad 4 and 5) **Cognitive therapy**: In these modules according to the well established principles of CBT, users identify and evaluate their catastrophic thoughts regarding heights (e.g., “I am bound to fall” or “I will jump”).

Ad 6) **The Next Steps**: This module contains information on how the user can continue his/her practice and further reduce his/her fear and prevent relapse. This includes developing an individualized fear hierarchy. A fear hierarchy contains the necessary steps that need to be taken to reach one’s goals in the therapy. Explicit attention is devoted to motivation and encouragement.

The program further consists of:

1) Instructions

Instructions in each of the modules are provided using animated doodles, i.e., drawn 2D animations with a voice-over. The animation underlines the core elements of the therapy.

2) Case examples

The animations contain a returning character, “Louise”, who had suffered from fear of heights and had overcome her specific phobia. Over the course of the modules Louise describes how her phobia emerged and developed, what the consequences were for her and how she overcame it, i.e. through exposure therapy. Louise also provides user feedback and motivates the user to continue with his/her therapy program.

3) Virtual reality

The prototype immersive VR environment consists of a 3D theater. The user is an employee of the theater (see Figure 2). To prepare the theater for the night’s performance s/he needs to complete a number of assignments in the virtual theater. These assignments involve different levels of exposure to heights (from standing on a ladder to fixing the curtains high above the stage). Participants are also able to go to balconies with different levels to see the stage from there. They can also access non-interactive 360 degrees VR videos in which they

e.g. walk on a high bridge or do a bungee jump. With these environments the entire exposure spectrum is covered, from very low to very high intensity exposure.

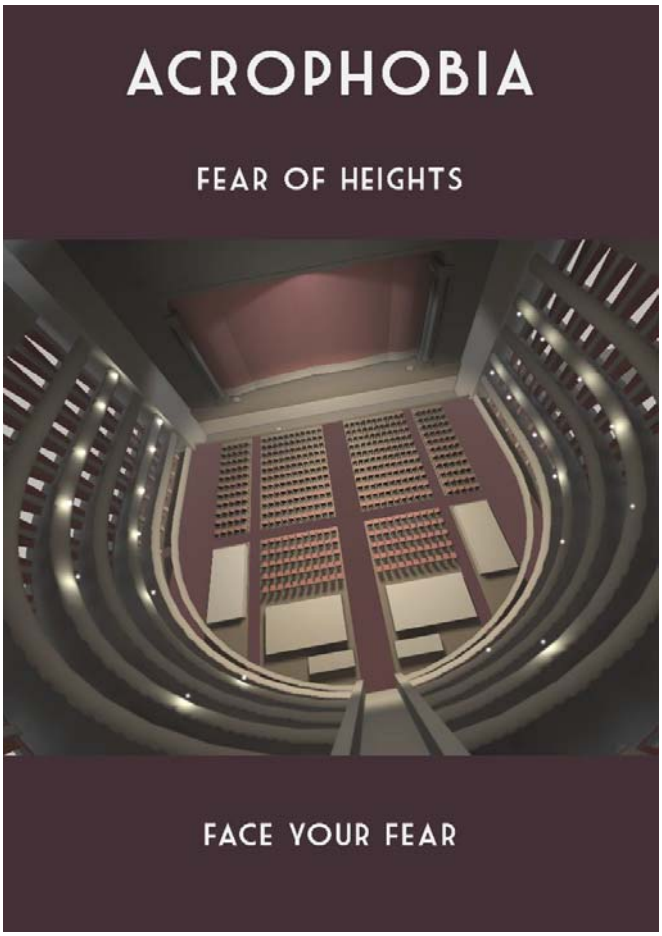


Figure 2: VR content: theatre

4) Ecological momentary assessment

Participants will be asked about their fear levels before, during and after the exposure VR: *How high is your fear at this moment? Please rate from 0 (no fear) to 10 (very high fear).*

5.2 Use of co-intervention

This study will not interfere with care-as-usual. 0-phobia is offered to the participants, and can be followed in addition to care as usual if needed.

5.3 Escape medication

Not applicable.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

The 0-phobia application is a VR exposure-based intervention for smartphones (Android) and consists of six modules, each taking for about 5-20 minutes to complete. The objective of the intervention is to reduce subjects fear of heights symptoms through VR exposure using Google cardboards. At the end of each level the participant can increase, decrease or keep the difficulty of the VR environment the same, in such a way that VR exposure is taxed optimally (e.g. not too difficult so that anxiety levels will not raise too high and not too easy so that anxiety levels are too low for exposure to be effective).

6.2 Summary of findings from non-clinical studies

Not applicable. No non-clinical studies have been conducted regarding 0-phobia. For an overview of clinical studies see 4.3 (page 19).

6.3 Summary of findings from clinical studies

The working mechanism behind exposure therapy is based on Pavlov`s learning theory of classical condition (Pavlov, 1927; Rescorla & Wagner, 1972). Numerous recent studies show that exposure therapy, virtual reality exposure therapy (VRET) and mobile app based therapies are effective in reducing symptoms of anxiety.

1) (Meta-analytic) Studies of exposure therapy have repeatedly demonstrated to reduce anxiety levels of specific phobias in different settings (e.g. Kaczkurkin & Foa, 2015; Wolitzky-Taylor et al., 2008). Exposure therapy is among the most effective treatments (Wolitzky-Taylor et al., 2008).

2) VRET has shown to reduce anxiety and depression levels of participants with specific phobias with similar effectiveness compared to exposure therapy (Goncalves et al., 2012; Krijn et al., 2004; Morina et al., 2015; Opris et al., 2012; Parsons and Rizzo 2008; Powers and Emmelkamp 2008; Raghav et al., 2016; Slater et al., 2006, 2013). Self-help VRET has also shown positive results (e.g. Piercey et al. 2012).

3) Recent research has demonstrated efficacy of mobile app based therapies for anxiety and depression (Bakker et al., 2016; Donker et al., 2013). Research into mobile apps as a method to intervene for psychiatric disorders are promising (e.g. Eysenbach et al., 2011; Saeb et al., 2015).

Above studies demonstrate the extensive research that has been done on exposure therapy and VRET in particular. The application of exposure therapy as an effective treatment of specific phobia indicates that there is no risk involved in offering VRET as an intervention and that the burden to participants is limited.

6.4 Summary of known and potential risks and benefits

The risks associated with offering 0-phobia to individuals who have symptoms of fear of heights is minimal. In the undue case, participants may experience elevated distress, cyber sickness or fall (see chapter 8 for a more detailed description regarding the risks). Potential benefits of following 0-phobia are a decrease in anxiety and depression symptoms.

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

7.1 Name and description of non-investigational product(s)

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main parameter will be the 40-item of the Acrophobia Questionnaire (AQ, Cohen; 1977). The AQ has a 7-point Likert scale ('not anxious' to 'extremely anxious'), total score 0-120. The questionnaire is widely-used and has good psychometric properties (Cohen, 1977). This measure will be given at baseline, post-test and follow-up and takes less than 5 minutes to complete. To be considered for inclusion, individuals have to score at least a 45.45 on the AQ-Anxiety (one standard deviation below the mean of a previous acrophobic sample; Cohen, 1972; Steinman and Teachman, 2011).

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary parameters are:

- The Attitudes Towards Heights Questionnaire (ATHQ; originally Abelson & Curtis, 1989, with minor modifications to the wording reported in Coehlo, Santos, Silvério, & Silva, 2006) is a 6-item measure in which individuals read pairs of dichotomous adjectives describing ways people may feel about heights (e.g., "Good/Bad," "Safe/Dangerous"), and rate how they feel about elevated places on a scale of 0 (which corresponds with the first adjective) to 10 (which corresponds with the second adjective). The ATHQ has been used in several height fear treatment studies and is sensitive to treatment effects (Coehlo et al., 2006; Emmelkamp, Bruynzeel, Drost, & van der Mast, 2001). Reliability is good (Steinman & Teachman, 2014).
- Beck Anxiety Inventory (BAI; Beck et al., 1988) is a 21-item self-report questionnaire assessing symptoms of anxiety. Patients record how much they have been bothered by each symptom during the past week, including the day the questionnaire is administered. Each item is rated on a 4-point Likert scale ranging from 0 = not at all to 3 = severely: I could barely stand it. The total score ranges from 0 to 63. The following guidelines are recommended for the interpretation of scores: 0–9, normal or no anxiety; 10–18, mild to moderate anxiety; 19–29, moderate to severe anxiety; and 30–63, severe anxiety. Internal consistency is high (0.90-0.94) and convergent validity is good (Brown et al., 1997).
- System Usability Scale (SUS; Bangor et al., 2008): 10 items about user friendliness of the app. The SUS is composed of 10 statements that are scored on a 5-point scale of strength of agreement. Final scores for the SUS can range from 0 to 100, where higher scores indicate better usability. This means that products that are at least

passable have SUS scores above 70, with better products scoring in the high 70s to upper 80s. Truly superior products score better than 90. Products with scores less than 70 should be considered candidates for increased scrutiny and continued improvement and should be judged to be marginal at best. Reliability is good (Bangor et al. 2008). This questionnaire will be completed at post-test.

- Igroup Presence Questionnaire (IPQ; Schubert, Friedmann and Regenbrecht 2001), a 14-item questionnaire which assess realism and "presence" in the VR environment. Each of the items has five response categories from fully disagree (1) to fully agree (5). Chronbach`s alpha is good (α = .73). This questionnaire along with some open questions about user experience of the VR environment will be completed at post-test.
- Mastery (Pearlin Mastery Scale; Pearlin and Schooler, 1978), 7 items to measure self-experienced control over a situation. Each of the 7 items has five response categories from 1 (totally disagree) to 5 (totally agree). The questionnaire has good psychometric properties. (Pearlin & Schooler, 1978). This questionnaire will be completed at baseline, post-test and follow-up.
- The nine-item mood module of the Patient Health Questionnaire (PHQ-9 ; Kroenke et al, 2007) is used to screen subjects with depressive disorders. The 9 items are each scored 0–3, total score range is 0–27. In a review of Wittkampf et al. (Wittkampf et al., 2007), a sensitivity of 0.77 (0.71–0.84) and a specificity of 0.94 (0.90–0.97) was found for the PHQ-9. This questionnaire will be completed at baseline, post-test and follow-up.
- One question about suicidal ideation from the Screening Questionnaire (Gega et al., 2005) and translated for the Dutch population in the WSQ (Donker et al., 2009): "has the idea of harming yourself, or taking your own life, recently come into your mind?" Answer options are" (1) Definitely not; (2) I seriously considered it but I stopped myself"; (3) "I would do it given the opportunity
- Assessment of current anxiety level directly before and after exposure (see section 3.1, Ecological momentary assessment).
- The GAD-7 (Spitzer et al., 2006) is a 7-item self-report questionnaire to asses generalized anxiety symptoms. Each of its 7 questions is rated 0 - 3 ("not at all" to "nearly every day"), and the total score range is 0 - 21. Psychometric properties are good (Donker et al., 2011; Spitzer et al., 2006). This questionnaire will be completed at baseline, post-test and follow-up.

8.1.3 Other study parameters (if applicable)

One question at post-test and follow-up about whether participants have attended professional treatment for their specific phobia during the 0-phobia study and follow-up.

8.2 Randomisation, blinding and treatment allocation

The allocation scheme will be created by an independent researcher with a computerized random number generator (Random Allocation Software) at an allocation ratio 1:1. Participants will be randomized into two groups: 0-phobia or wait list condition. The researchers are blind for treatment allocation. Due to the nature of the study, double blinding for treatment allocation is not possible.

8.3 Study procedures

Advertisements with a call to participate in a VR mobile app study for fear of heights will be posted on several websites (e.g. Fonds Psychische Gezondheid, Angst Fobie en Dwangstichting, Google Adwords, Facebook) and in magazines (e.g. UWV Perspectief). When a person is interested to participate in the study, s/he can use the URL of the website provided in the advertisement to be directed to the study homepage of 0-phobia. On this page, information about the study is provided including eligibility criteria. If the person thinks s/he fulfills the inclusion criteria and is interested to participate in the study, s/he will be directed to a secured online environment to fill in a short screening questionnaire (including name and email-address, the AQ, PHQ-9 and WSQ-suicide) to check eligibility to participate in the study. If eligible, participants are automatically directed to a webpage where they can leave their personal contact details (address and telephone number, for sending the information letter and informed consent form, and the Google cardboard in a later phase of the study). After consent, they fill in baseline assessment consisting of demographic variables (age, gender, level of education, marital level), ATHQ, Mastery and GAD-7 (duration: 20 minutes for screening and baseline assessment). The research assistant will sent the patient information letter and informed consent form to their home address with a return envelope. If necessary, the researcher will remind them by email to complete the informed consent and baseline measurement (2 reminders in total).

If the person is not eligible to participate, an email will be sent with an explanation of the reason(s) of exclusion and, if needed (high level of depression) to contact their GP in case their depression levels are too high. In case that suicidality is present (those who answer “I would do it given the opportunity” on the WSQ-suicide question “has the idea of harming yourself, or taking your own life, recently come into your mind?”) are contacted by telephone

by the research assistant. The person will be asked to give permission for contacting their general practitioner.

After completing the online baseline assessment and returning written informed consent, the participant receives an e-mail from the research assistant to inform him/her in which condition s/he is randomized: the intervention condition or the waitlist condition. If in the intervention condition, the research assistant will sent the Google cardboard to the participant by postal delivery along with an usage instruction of the cardboard. The research assistant will email the participant with an instruction how to download the 0-phobia app to his/her smartphone. The app is locked with an individual code which will be given to the participant at the start of the intervention. Participants can then begin the 0-phobia intervention which they can follow for 3 weeks (5-20 minutes per week, in addition to 2 weeks of VRET which is recommended to do each day for 10 minutes). When practicing in VRET, participants are asked to fill in one question about their anxiety level before, during and after VRET (duration: 5 seconds). Participants can follow the intervention at their own pace. Participants will receive weekly automatic reminder emails to begin or continue the intervention from the research assistant. If needed (e.g., with a question about how to use 0-phobia or in the unlikely case of distress) they can contact the research assistant.

If in the wait-list condition, the participant will wait for 3 weeks and after assessment of post-test, will undergo the same procedure as participants in the intervention condition.

Immediately after completion of the last module of 0phobia, participants are asked to complete the AQ online (less than 5 minutes). After 3 weeks, an online post-test will take place which consists of the AQ, ATHQ, BAI, IPQ, SUS, Mastery, PHQand GAD-7 (duration: 20 minutes) and open questions about the VR environment. At 3 month follow-up, participants are asked to fill in the AQ, ATHQ, BAI, Mastery, PHQ and GAD-7 questionnaires (duration: 20 minutes) and one question about whether they have attended professional treatment for their specific phobia. All assessments are programmed with Survalyzer software. For an overview of measurements, see Table 1. If desired, general information about the outcomes of the study will be send to the participant after completion of the study.

Table 1: Overview of measures

Measures				
	Aim	**Baseline**	**Post-test (6w)**	**Follow-up (3m)**
Demographics	Characteristics of sample	x		
AQ	Symptoms of acrophobia	x	X (and immediately after completing the last 0-phobia module)	x
ATHQ	Symptoms of	x	x	x

	acrophobia			
BAI	Symptoms of anxiety	x	x	x
SUS	User-friendliness		x	
IPQ	VR experience		x	
VR user experience	Open questions about VR experience		x	
PHQ	Symptoms of depression	x	x	x
WSQ suicidal ideation,	Exclusion criteria	x		
Mastery	Coping	x	x	x
GAD-7	Symptoms of anxiety	x	x	x
Professional treatment	To control for a possible confounding variable		x	x

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. In case a participant prematurely terminates his/ her participation, he/ she will be asked to give permission that the data that were collected until that time point may be included in the ITT-analyses. If the participant refuses to give permission, his or her data will be destroyed.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Not applicable

8.6 Follow-up of subjects withdrawn from treatment

When subjects are withdrawn from treatment, either because they decided or the research staff decided, they will still be followed-up. All participants will be included in the intention-to-treat (ITT)-analyses.

8.7 Premature termination of the study

The study will only be prematurely terminated in case of a serious adverse event (SAE, see point 6.9.1) that is the direct result of the study. In this case the accredited METC and the subsidising party will be informed without undue delay. Participants who have completed the study or are in the control group will be informed by email, the content will be individual to the specific reason of termination. Participants who are still in the active treatment conditions will receive a notification through email explaining that the study has stopped due to unforeseen circumstances and access to all modules will be blocked. All participants will receive information on where they can seek help for their mental health problems. In addition, the study can be terminated prematurely due to ethical concerns, or insufficient participant recruitment.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to 0-phobia. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;

- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The principal investigator (TD) will report all SAEs to the subsidising parties without undue delay after obtaining knowledge of the events.
The SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC (VUmc), within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the investigator has first knowledge of the serious adverse events.

9.2.3 Serious adverse device events (SADEs)

The principal investigator (TD) will report all SADEs to the subsidising parties without undue delay after obtaining knowledge of the events. The SADEs will be reported through the web portal *ToetsingOnline* to the accredited METC (VUmc) and the IGZ, within 2 office days of first knowledge for SAEs that result in adaptation or withdrawal of 0-Phobia and within 3 months with other types of SAE`s.

9.2.4 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

The principal investigator (TD) will report all SAEs to the subsidising parties without undue delay after obtaining knowledge of the events at 3 month follow-up.
The SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC (VUmc), within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other

SAEs will be reported within a period of maximum 15 days after the investigator has first knowledge of the serious adverse events.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Based on the low risk of participation in the study (see also section 10: Structured Risk Analysis), a data safety monitoring board (DSMB) is not required and will not be set up.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The primary outcome measure (AQ) will be treated as a continuous outcome. Continuous variables will be presented as mean, standard deviation, and minimum and maximum number of observations. Descriptive statistics of demographics and clinical outcomes will be compared between the experimental and control condition. The quantitative analysis of the primary and secondary endpoints will be performed on an intention-to-treat basis following the per protocol analysis. Comparisons will be made between and within the groups before and after measurements. Intention-to-treat analysis will be used on continuous scales using repeated measures analysis of variance (ANOVA). Missing values will be carried forward. Per protocol analysis will be performed by independent sample t-tests. Standardized effect sizes (Cohen's d) and confidence intervals will be calculated. SPSS version 21 will be used for the analyzes. A *p*-value <0.05 will be considered to indicate statistical significance.

10.2 Secondary study parameter(s)

Continuous variables (PHQ, IPQ, SUS, Mastery, GAD-7) will be presented as mean, standard deviation, and minimum and maximum number of observations. Categorical variables will be presented in terms of frequency numbers and percentages. Descriptive statistics of demographics and clinical outcomes will be compared between the experimental and control condition. The quantitative analysis of the primary and secondary endpoints will be performed on an intention-to-treat basis following the per protocol analysis. Comparisons will be made between and within the groups before and after the intervention. Intention-to-treat analysis will be used on continuous scales using of repeated measures analysis of variance (ANOVA). Missing values will be carried forward. Per protocol analysis will be performed by independent sample t-tests. Standardized effect sizes (Cohen's d) and confidence intervals will be calculated. SPSS version 21 will be used for the analyzes. A *p*-value <0.05 will be considered to indicate statistical significance.

10.3 Other study parameters

Not applicable

10.4 Interim analysis (if applicable)

No interim analyses will be performed.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Concerning the reporting of results, we will follow the latest version of the Consolidated Standards of Reporting Trials guidelines (CONSORT 2010; Moher et al., 2010). Reports will be provided as outlined under 10.4. The co-principal investigator (AvS) is currently following the basic course on regulations and organisation for clinical researchers (Dutch: Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers, BROK®).

11.2 Recruitment and consent

Advertisements with a call to participate in a VR mobile app study for fear of heights will be posted on several websites (e.g. Fonds Psychische Gezondheid, Angst Fobie en Dwangstichting, Google Adwords, Facebook) and in magazines (e.g. UWV Perspectief). When a person is interested to participate in the study, s/he can use the URL of the website provided in the advertisement to be directed to the study homepage of 0-phobia. On this page, information about the study is provided including eligibility criteria. If the person thinks s/he fulfills the inclusion criteria and is interested to participate in the study, s/he will be directed to a secured online environment to fill in a short screening questionnaire (including name and email-address, the AQ, PHQ-9 and WSQ-suicide) to check eligibility to participate in the study. If eligible, participants are automatically directed to a webpage where they can leave their personal contact details (address and telephone number, for sending the information letter and informed consent form, and the Google cardboard in a later phase of the study). After consent, they fill in baseline assessment consisting of demographic variables (age, gender, level of education, marital level), ATHQ, BAI, Mastery and GAD-7 (duration: 15 minutes). The research assistant will sent the patient information letter and informed consent form to their home address with a return envelope. This is at least 24hrs. It

will be clearly indicated that participation in the study is entirely voluntary and refusing to take part is without any negative consequences.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

Participants may benefit from their participation in terms of expected reductions in anxiety and depression levels. It is expected that participation will help improving clinical care. The risks associated with participation are minimal, since a similar intervention previously showed to reduce anxiety and symptoms of specific phobia after VRET through a mobile application (Piercey et al., 2012). Furthermore, research into mobile apps as a method to intervene for psychiatric disorders are promising (e.g. Donker et al., 2013; Eysenbach et al., 2011; Saeb et al., 2015).Note that this study recruits participants who have symptoms of fear of heights. Severely depressed and suicidal participants will be excluded from the study and participants will not be withheld the regular care.

Previous studies in similar samples have shown that studies with VRET can safely be carried out, without a significant risk for unwanted effects (e.g. Bouchard et al., 2006; Emmelkamp et al., 2002; Krijn et al., 2004; Piercey et al., 2012). The VR exposure environment uses gradual exposure. This means that subjects start with relatively easy levels of height situations which induces a small amount of fear. When this situation becomes less fearful, they move on to the next level. In this way, fear levels are manageable. It is nevertheless possible that participants may get distressed or cyber sickness, or feel they will lose their balance and fall during the intervention. In these cases, participants are instructed to remove their cardboards. By removing them, levels of high distress, cyber sickness or the feeling of out of balance are immediately reduced.

Participants may experience distress while completing questionnaires. However administering these instruments is crucial to draw conclusions about the feasibility and effectiveness of the intervention. In case of an undesirable emotional reaction both during the intervention as well as during the follow up assessments, the researcher assistant and at least one experienced clinician (TD) can be contacted by the participant and will be available to provide support if necessary or desirable.

11.5 Compensation for injury

The sponsor does have a liability insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage

to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

No incentives will be provided for taking part in this study. The free provision of treatment is already to the benefit of the participant.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The data will be handled confidentially. All data will be collected at VU University Amsterdam (Section Clinical Psychology) by a staff member. Data (baseline, post-test and follow-up data: name and address, primary and secondary outcome measures) will be captured electronically in a secured online survey platform (Survalyzer B.V., Amsterdam, the Netherlands; www.survalyzer.com). Survalyzer (formerly NetQuestionnaires) is frequently used by university researchers and meets all safety requirements. The data are hosted in an ISO 27001: 2005-certified data center in the Netherlands. With respect to data security, data loss is virtually impossible thanks to an intelligent security system that consists of several steps and a logical wisconcept. The servers are protected against unauthorized access by biometric access control, video surveillance and 24-hour physical security. To protect the best possible safety, Survalyzer pays specific attention to the general safety risks. The ownership of the data collected by Survalyzer lies solely with the VU.

No personal data will be collected through the app. Name, address, telephone numbers and email addresses will not be collected through the app. Thereby, privacy of participants is guaranteed. Data from the 0-phobia app is restricted to anxiety level measures during VR exposure and three exercises: setting goals for the intervention, evaluating anxiety provoking thoughts and creating a personal fear hierarchy. This information is sent from the app to a server which then stores it in a database on a secure (SSL) website. All communication between the app and the database is encrypted by means of a certificate. By this, data between the application and the server is secured, because the data is encrypted. Another benefit of the certificate is a guarantee that the app always communicates with the same server. To prevent others (non-participants) contaminating the database with data, there are a number of keys defined to validate the addition of new data. Adding new data is only possible if the correct key is sent by one of the participants in the study. This data will then be coded and captured electronically in a secured online database which is hosted on the VU server (SciCloud). SciCloud has a mysql database for receiving data. The VU IT for research department is responsible for protection of this data and the virtual server. The data will be uploaded into the IBM SPSS database. All data will be kept in separate databases and

merged into a master database only after data collection is completed and each individual database is locked. The data will be anonymized but linked with the trial identifier consisting of 4 numbers. Data will be coded and the key connecting names to numbers will be kept in a separate, secure location in the principal investigator's office. Coded data will be electronically stored at the VU Amsterdam, separate from identifying information. Access to data will be password-protected. Only the principal investigators and trial researchers will have access to the final dataset. All collected data will be used only for the purposes of this research. The project group will analyze the data, and both positive and negative trial results will be disclosed. Results will be submitted for publication to peer-reviewed scientific journals. They will be kept for the required number of years after publication, and will then be destroyed. The publication policy is in agreement with the publication statement of the CCMO (see: www.ccmo.nl).

12.2 Monitoring and Quality Assurance

As participation in this study is of low risk (see also section 10), a monitoring plan will not be needed. The online platform Survalyzer ensures a minimum degree of data quality by allowing certain answers only to be answered in the appropriate format (e.g. in- and exclusion criteria, when asked for their age, participants can only enter numbers etc.).

9.2.1 Incidental findings and emergencies

Interested individuals who show symptoms of severe depression as measured with the PHQ-9; total score > 19) at baseline will be contacted through email by the researcher assistant and informed about the findings, explaining that they cannot enter the study, that they are recommended to seek out psychological treatment and are referred to their GP for local mental health treatment possibilities. In case of suicidality (a score of 3 on the WSQ-suicide), the research assistant will contact the person to inform him/her about these findings, to recommend to seek psychological treatment and to ask permission to contact their GP. Participants have the opportunity to contact the researcher assistant if they would like to discuss this information. The researcher assistant is a psychologist and can discuss scores and subsequent communication with a licensed healthcare psychologist (the principal investigator, TD). Participants can also contact the healthcare psychologist directly if desired. Note that this study targets healthy individuals who have symptoms of fear of heights. These symptoms are part of the specific phobia fear of heights, which is considered as the mildest disorder amongst the DSM-V psychiatric disorders. There will be no incidental findings, since we only collect data on (fear of heights) anxiety, depression (including suicidal ideation) and coping skills.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.
All amendments (substantial and non-substantial) will be notified to the METC and to the competent authority.

12.4 Annual progress report

The principal investigator, TD, will notify the accredited METC about the start of the study and will also submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The principal investigator, TD, will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The project group will analyze the data, and both positive and negative trial results will be disclosed, unreservedly. Results will be submitted for publication to peer-reviewed scientific journals.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The working mechanism behind exposure therapy is based on Pavlov`s learning theory of classical condition (Rescorla & Wagner, 1972). See section 4.3 for an overview of the literature that supports the mechanism behind the 0-phobia application.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

In a recent 0-phobia user-test the VR environment was tested in 10 healthy participants. Results showed that the VR environment was rated as realistic and that subjects felt they were present in the environment. Among those who had symptoms of fear of height, the level of anxiety raised with increased levels of difficulty of the VR environment. Anxiety reduced afterwards.

A mobile app self-help intervention using VR for spider phobia showed a reducation in anxiety levels (Piercey et al., 2012). In the same line a number of (meta-analytic) studies have shown that (self-help) VRET reduces anxiety levels in participants with specific phobias (e.g. Krijn et al., 2004; Morina et al., 2015; Parsons and Rizzo 2008; Powers and Emmelkamp 2008; Raghav et al., 2016; Slater et al., 2006, 2013). Furthermore, research into mobile apps as a method to intervene for psychiatric disorders are promising (e.g. Donker et al., 2013; Eysenbach et al., 2011; Saeb et al., 2015). In addition, extensive meta-analytic research has demonstrated effectiveness of exposure therapy (Kaczkurkin & Foa, 2015; Wolitzky-Taylor et al., 2008).

Furthermore, extensive research has been done regarding the working mechanism, namely classical conditioning (e.g. Bouton, 2016; Brink, 2008; Pavlov, 1927; Rescorla, 1988; Rescorla & Wagner, 1972).

Above studies demonstrate that extensive research has been done regarding the underlying mechanism of the 0-phobia application.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

No.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable

e. Analysis of potential effect

Participants may benefit from their participation in terms of expected reductions anxiety levels. The risks associated with participation are minimal, since a similar intervention

previously showed to reduce anxiety levels after VRET (Piercey et al., 2012). Note that participants with severe depression or suicidal ideation will be excluded from the study and that participants will not be withheld the regular care. It is nevertheless possible that participants get distressed, experience cyber sickness or feel out of balance during the intervention. A description on how to handle such a situation is given in section J.

f. Pharmacokinetic considerations

Not applicable

g. Study population

The study population consists of adult individuals with heightened levels of anxiety for fear of heights. Individuals with symptoms of severe depression or suicidal ideation that need imminent specialized treatment will be excluded.

h. Interaction with other products

Not applicable

i. Predictability of effect

Not applicable

j. Can effects be managed?

Participants may experience some anxiety distress or cyber sickness during the intervention while practicing in the VR environment. However, this level of anxiety is needed for exposure to be effective (Wolitzky-Taylor et al., 2008). Participants will practice with a hierarchy of fear situations using gradual exposure (from low fear situations to high fear situations) in which participants learn to manage their anxiety so their anxiety levels will be tolerable. First, participants are instructed to sit during VR exposure. If the participant does not feel any anxiety anymore, the participant is instructed to stand during VR exposure to minimalize safety behavior in order for the intervention to be effective. The risk of falling will be minimized by safety instructions: participants are requested to remove all sharp objects in their surroundings and to hold themselves to a heavy object. Note that elderly (above 65 years of age) who are more vulnerable if they fall, are not included in the study. The risk of cyber sickness is being minimized by optimalization of the framerate. Furthermore, there will be no quickly moving objects and it will not be possible for the user to move quickly through the VR environment. Participants are instructed to remover their cardboards in case they experience cyber sickness, high distress or if they feel out of balance. By removing them, levels of high distress, cyber sickness or out of balance are immediately reduced. Previous studies in similar samples have shown that studies with VRET can safely be carried out, without a significant risk for unwanted effects (e.g. Bouchard et al., 2006; Emmelkamp et al.,

2002; Krijn et al., 2004; Piercey et al., 2012). Furthermore, research into mobile apps as a method to intervene for psychiatric disorders are promising (e.g. Donker et al., 2013; Eysenbach et al., 2011; Saeb et al., 2015). In case of an undesirable emotional reaction during the intervention, the participant can contact the research assistant who will be available to provide support if necessary or desirable. Severely depressed and suicidal individuals will be excluded from the study.

13.2 Synthesis

Previous studies (see section 4.3) have demonstrated that the working mechanism behind the 0-phobia application involves minimal risk. Based on these studies one can assume that offering the 0-phobia application to individuals, who have fear of heights, carries low risk. In the undue case of an undesirable emotional reaction, the research assistant and principal investigator (TD) is able to provide adequate support if needed.

Participants may experience distress during the interview or while completing questionnaires. However administering these instruments is crucial to draw conclusions about the feasibility and effects of the intervention. In case of an undesirable emotional reaction both during the intervention as well as during the follow up assessments, the research assistant and at least one experienced clinician will be available to provide support if necessary or desirable.

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