The effectiveness of virtual reality-assisted hypnosis against itch: the creation and evaluation of a new therapeutic concept

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Abstract

Chronic itch is a disabling condition with currently limited treatment options. Virtual reality (VR) is an approach that takes people to another place and has demonstrated to temporarily reduce itch. Hypnosis, which is a state of relaxation, has been applied with more long-term relief of itch in the specific case of severe eczema. However, hypnosis tends to depend on an individual's susceptibility, or ease to come into hypnosis. A combination of VR and hypnosis (VRH) has been proposed, since it may combine the longer-lasting effects of hypnosis with VR, making the hypnosis more accessible by facilitating imagination. Even though VRH is promising, it has never been investigated in itch. This study focusses on the patient-guided development and evaluation of a novel VRH-based treatment scheme - including the design and programming of a VR-environment, and the creation of the accompanying hypnosis scripts - directed at chronic itch. On top of that, we here propose an interventional study to assess the effectiveness of the VRH and VR in reducing itch and its psychological burden in individuals with chronic itch. In this randomized controlled trial, a VRH and a VR treatment will be studied for their potential to reduce clinical itch from baseline till after 8 sessions and at follow-up (6 weeks after the end of treatment). Secondarily, the VRH and the VR treatment groups are compared. The medical treatment need, itch sensitivity and overall wellbeing of the participants are also assessed. Patient inclusion is expected around late summer/autumn 2023. If effective, this technique may be further optimized to provide an on-demand treatment option to alleviate itch (independent of its origin) and its associated burden of disease.

Keywords: (*chronic) itch, virtual reality (VR), hypnosis, top-down inhibition, psychodermatology, therapeutic design, focus group, (heuristic) evaluation*

Introduction

Chronic itch is a condition with high burden and currently often limited treatment perspectives. Patients with chronic itch often suffer from being locked in an itch scratch cycle [Rinaldi et al., 2019], accompanied by, amongst others, sleep disturbances and a significantly lower quality of life [Simpson et al., 2018]. Itch may even trigger depression and suicidal ideation [Thyssen et al., 2018].

Itch has been demonstrated to be temporarily reduced through virtual reality (VR) immersion compared to audiovisual distraction only. Leibovici et al. (2009) found itch intensity to be significantly decreased compared to baseline at 10 minutes after VR exposure (Cohen's d 1.12; p=0.01), compared to no significant decrease for audiovisual distraction. VR as such specifically relies on the concept of sense of presence and may as such enhance patient wellbeing more effectively than 2D approaches, at least on the short term. A higher score on sense of presence in VR is expected to be independently associated with a better outcome of VR-based treatments [Malloy and Milling, 2010].

More recently, it has furthermore been shown that even exposing patients with clinical itch to an individually chosen "antipruritic" color in immersive VR [Baschong et al., 2021] is effective at reducing itch perception. After 10 minutes of exposure to the subjective, individually chosen "antipruritic" color, the clinical itch intensity on average decreased with -1.2 ± standard deviation (SD) 1.6 on a 0-10 NRS compared to baseline itch levels rated at 5.8 ± SD 1.8 (Cohen's d 0.64; p=0.001). It remains to be seen however whether it is the color, or rather the "antipruritic" suggestion and subsequent focus, or trance state, that results in the observed effect.

This trance state may also be called hypnosis, another strategy that has been successfully applied to mitigate itch and enhance overall well-being in children and adults suffering from atopic dermatitis [Stewart & Thomas, 1995]. Hypnosis has been described as a "*state of consciousness involving focused attention and reduced peripheral awareness, characterized by an enhanced capacity for response to suggestions*" [Elkins et al., 2015]. As such, the hypnotic response relies on three pillars which will be further explained below: hypnotic susceptibility, hypnotic induction, and hypnotic suggestion [Landry et al., 2017].

Hypnotic susceptibility can be defined as the ease with which a person can enter a state of hypnosis. This ease can be quantified by numerous scales, amongst which the Stanford Hypnotic Susceptibility Scale C [e.g. Näring et al., 2001].

Hypnotic induction is the actual first stage of each hypnosis session and focusses on achieving progressive relaxation. This relaxation may be achieved through multiple techniques, including (most often) a count down and a plethora of interactive induction techniques. A proper induction is important as it determines the achieved hypnotic depth, which determines the individual's openness to suggestions, or suggestibility, in the next stage of the hypnosis session [Shor, 1962].

Hypnotic suggestions are directed at the desired outcome and may take on different forms, from direct suggestions such as *you cannot feel itch* [e.g. Thompson et al., 2019], to what are called indirect suggestions as *you might find the itch to slowly ease away* [e.g. Maurer et al., 1993].

Previous studies applying hypnotic suggestions to pain (which is alike itch, also a signal of potential threat), show promising results regarding both pain relief and medication use with up to 42% of pain relief upon the use of direct analgesic suggestions [Thompson et al., 2019]. The study population size and follow-up of hypnosis in itch management specifically remains limited however. Stewart & Thomas (1995) found a significant reduction in steroids use for itch management of more than 40% over 16-weeks follow-up after only three therapy sessions. Based on literature on the use of verbal suggestions in relation to itch (not under hypnosis), there is no doubt that suggestions can modulate perceived itch intensity [e.g., van Laarhoven et al., 2011; Evers et al., 2019]. The combination of hypnosis and itch suggestion is thus promising.

All in all, the advantage of VR over hypnosis in the management of itch is that it appears to be effective independently of the individual's hypnotic susceptibility [e.g. Patterson et al., 2006]. Hypnosis, on the other hand, has longer lasting effects [e.g. Stewart & Thomas, 1995]. To combine the universal applicability of VR with the longer established effects of the hypnosis, the combination of hypnosis and VR has been coined. It is especially the hypnotic induction phase that has been proposed to make hypnosis challenging for poorly hypnotisable individuals. This hypothesis led Holroyd et al. (1996) to call for making the hypnotic induction *"less effortful*". Whether VR may play a role here has not been affirmed yet due to scarce literature and small sample sizes [Rousseaux et al., 2020]. The primary aim of this study is to design, develop, and evaluate a novel virtual reality-assisted hypnosis (VRH) therapy as first step towards an interventional study we propose.

Materials & Methods

Focus group

An online 1,5-hour focus group was held with people suffering from chronic itch – independent of its origin – for at least 1 year. The participants were recruited through convenience sampling within the network of the author. Upon expression of interest, participants received an information letter and signed informed consent forms prior to participation in the focus group (see Appendix A).

The focus group was guided by a moderator to lead the discussion, and a note taker was present. The format of the focus group followed a semi-structured questionnaire with four distinct categories: (1) general associations with itch, (2) itch relief and general concepts such as color, objects, situations, etc., (3) itch relief and voice/sound, (4) itch relief and movement/action. Within each category, open questions were asked, images could be shown, and audio could be presented. All ideas generated were closely noted down in word webs by the note taker during the discussion and were then reviewed by the moderator of the focus group and analyzed using graphical depictions in *KeyNote*. See also Appendix B for an overview of the focus group design and unprocessed word webs.

Upon completion of the focus group, the participants each received €15. The study was approved by the Psychology Research Ethics Committee (CEP) of Leiden University.

Conceptual Design

Graphics & User Interface

Based on the concepts generated in the focus group, a primary conceptual design was made using *Procreate*® to sketch envisioned VR-environments and UI elements. User interfaces were sketched for both the VRH intervention and the VR control intervention. Start scenes were sketched, along with several intermediate scenes, and a concluding scene. Also, a “pause” screen was created in case someone might start to feel unwell during the treatment. Scenarios for the different weeks of treatment were written down concurrently.

This design was subsequently translated into a 3D environment using *Unity’s* open-source *High-Definition Rendering Pipeline* for an as realistic graphical representations as possible. The *River Auto Material 2019* and *NatureManufacture Assets* packages were used to facilitate the design of a realistic natural graphical environment.

Accurate rendering was secured by a laptop conforming to *Vive's* and *Meta's* minimal computer specifications [Meta, 2023; Vive, 2023]. See Appendix I for an overview of the computer specifications.

The VR-environment and UI interfaces were subsequently heuristically evaluated according to the description in the section "*Heuristic evaluations*".

Hypnosis scripts

The hypnosis scripts were written according to modern hypnosis techniques, such as used by Milton Erickson [Bandler et al., 1975]. Hypnotic inductions were chosen to vary to prevent participants from getting too anticipated on (and perhaps bored by) the inductions. The suggestions were chosen to be direct and focused on itch and overall wellbeing. A count was scripted for deduction at the end of each session. The scripts were reviewed by experienced hypnotherapists before they were recorded, and subsequently heuristically evaluated as described in the section "*Heuristic evaluations*".

Home exercises

The design of the home exercises for the VRH intervention was based on self-hypnosis and followed a similar pattern as the design of the hypnosis scripts. To maintain treatment adherence, the duration of the home exercises was aimed at ±5 minutes a day. For the subsequent design of the home exercises for the VR control intervention, two major design criteria were identified and implemented in the design: (1) the duration and nature of the recordings need to match the home exercises of the VRH intervention, (2) the home exercises need to be and stay interesting to maintain treatment adherence. The resulting audio recordings were then also heuristically evaluated as described in the section "*Heuristic evaluations*".

Audio recording

The Voice Memos app was used to record the hypnosis audio recordings and home exercises. The audio database *Pixabay* was screened for royalty-free music to match the topics covered in the focus group. The obtained sounds were implemented as background sound in the interventions. The open-source AI-software *Songpeel.com* was used to convert the audio files to 8D-audio. Finally, iMovie was used for sound editing. A band-pass filter was applied to the audio fragments to reduce background noise. Remaining murmur, sighs or crackling sounds were carefully cut out of each fragment. In the end, the fragments were matched to the timing of the VR-environment.

Heuristic evaluations

According to the optimal number of heuristic evaluations as described by Nielsen [Nielsen, 1994], five individual on-site 1 to 1,5-hour heuristic evaluations were arranged with both healthy participants and with people suffering from chronic itch – independent of its origin. The participants were recruited through convenience sampling within the network of the author. Upon expression of interest, participants received an information letter and signed informed consent forms prior to participation in the heuristic evaluation (see Appendix A).

The heuristic evaluations were structured according to a semi-structured questionnaire consisting of two parts: (1) evaluation of the VR-environment (on 2D desktop screen version) and storyline based on the evaluation principles described by Sutcliffe et al. (2004), (2) evaluation of the home exercises and hypnosis scripts. The evaluations were recorded in Qualtrics, if desired by the participant with an observer to assist in noting down the feedback during the experience.

For the evaluation of the hypnosis-audio recordings, a new 7-item metric was designed to identify aspects relevant to the functionality of the audio recordings focusing on the intonation of the voice, the tempo, the extent of unrelaxed mind wandering, the extent of achieved relaxation, the total duration, the applicability of the given suggestions, and the expected own therapy compliance. Additionally, three questions were asked regarding the evaluators' views on the necessity of a physically present hypnotherapist for hypnosis over audio-based hypnosis, on the therapeutic confidence in home exercises provided by a practitioner versus self-selected relaxation exercises, and the expected own therapeutic compliance. Before the heuristic evaluations, two experienced hypnotherapists already provided their feedback on the hypnosis scripts. See also Appendix G & H for an overview of the heuristic evaluation design and content.

Upon completion of the heuristic evaluations, the participants with history of chronic itch each received €15. This study was also approved by the Psychology Research Ethics Committee (CEP) of Leiden University.

Results

Focus group

Three people suffering from chronic itch were invited to participate in the focus group. One of them withdrew due to illness, leaving two itch experience experts. Both were male with an age of 35 and 55 respectively. Both had completed higher education and had been diagnosed with atopic dermatitis as cause of the itch. One had been diagnosed with trichotillomania additionally. Itch intensity had been 6 and 7 out of 10 over the preceding 4 weeks and 3 and 6 at the start of the focus group respectively.

During the focus group itch relief was approached from 6 different themes: (1) itch mitigating activities, (2) itch mitigating environments, (3) itch mitigating colours, (4) itch mitigating objects, (5) itch mitigating movements, and (6) itch mitigating sound. The themes and the concepts belonging to them as identified in the focus group are depicted in *figure 1*. Within each theme, general concepts (dark gray) were identified and distinguished from more specific examples (light gray).

In terms of activities, personal care, relaxation, distraction, and cooling were identified as important concepts in itch relief, aside from the act of scratching itself. Examples of activities mentioned in relation to itch relief thereby include making music, engage in rewarding experiences in general, affection, and performing acts like meditation.

From an environmental design perspective, a holiday-site with sun, high humidity, yet also a bit of cold, along with the presence of the sea were identified with itch relief. Examples of specific places that would meet these criteria include a ski-site and a sauna.

Colours in itch relief were preferred to be natural cold colours, pastels, without busy patterns and above all: natural. Examples of important colours mentioned in the focus group are blue, brown, grey and green.

Objects that were appreciated in relation to itch relief concerned mainly cooling and scratching items. Movements would mostly focus on hand movement, scratch-like movements such as barbed wiring, and “mindful” movement. Preferably no sweating would be involved, as this was associated with itch induction. Touch on the other hand was mentioned as an important itch distractor.

Lastly, natural, uncomplex low tones that were used in a context congruent manner, were appreciated most. Binaural beats/8D audio were mentioned as an example technique to make the sound more interesting to listen to and perhaps in this way enhance itch distraction.

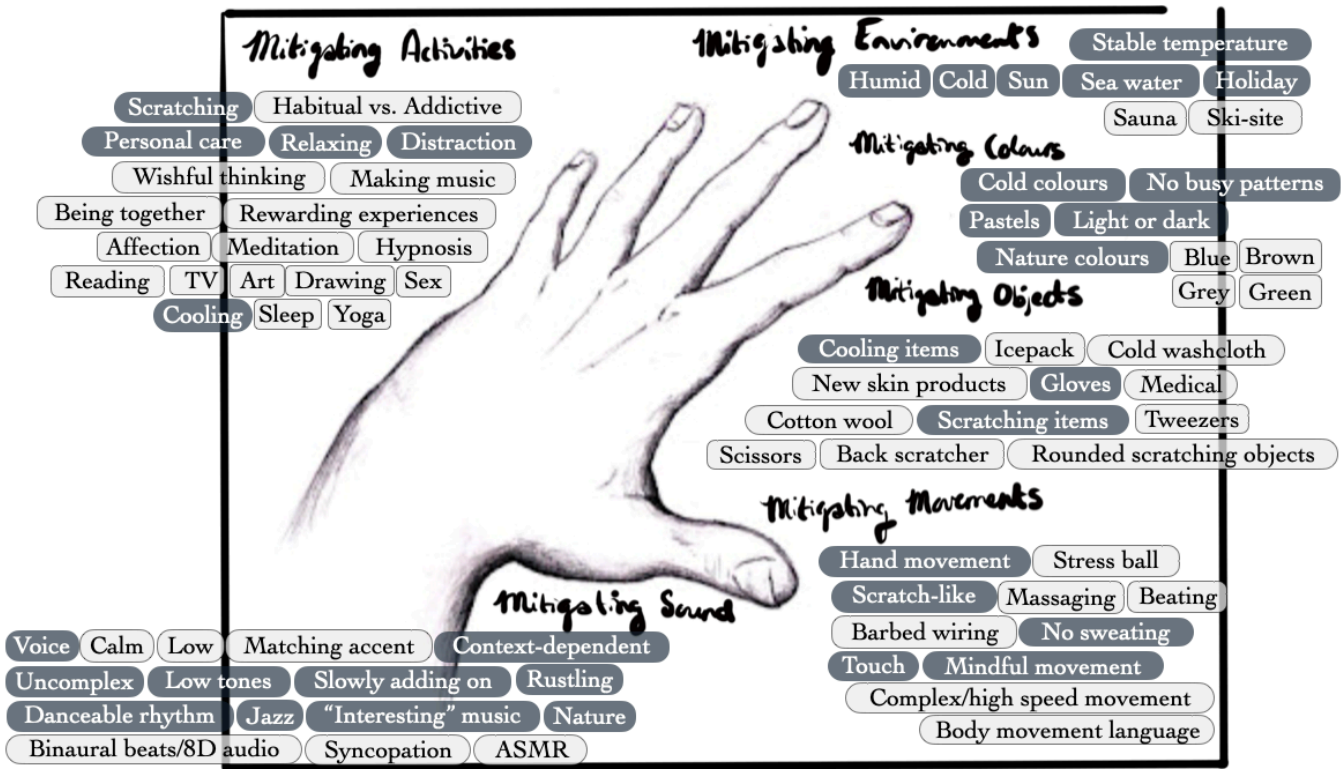

Figure 1. Mindmap focus group design concepts

Graphic design

Based on the concepts identified in the focus group, an example design could be envisioned, centered around a natural-looking environment with different facets: from icy mountains to a sunny beach, allowing people to choose their own favorite place. Relaxation focused instructions and activities, e.g. mindful tasks that also keep the hands busy may augment the design along with spatial audio to increase the experiential immersivity. This concept was used as a starting point for the scenic sketching performed as initial phase in the VR design. Some example sketches are included in Appendix C.

From the example sketches, a VR design was created, as depicted in *figure 2*. In this 3D design, special attention was paid to light reflections, shading, and wind to allow the users to have a comparably realistic natural experience.

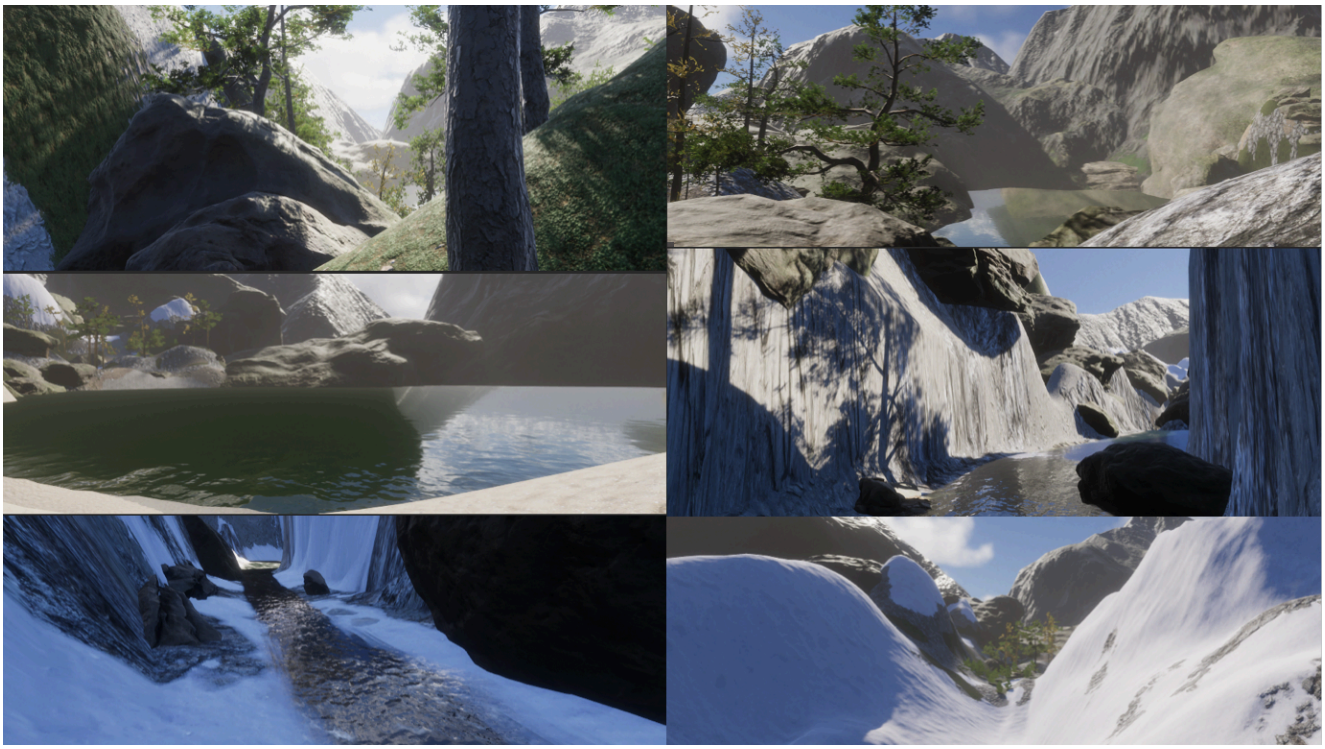

Figure 2. Example scenes from the virtual reality design

User Interface design

The user interface was sketched to suffice several key patient safety factors: (1) clear start instructions, (2) clearly instructed user control over time-out and/or restart throughout the experience, (3) key operating keys highlighted throughout the experience, (4) instructions access throughout the experience. These instructions should of course not come at the expense of the perceived immersion. Hence, it was chosen to structure the user interface as depicted in *figure 3*. At the start of the experience, an instructions panel is depicted, which people can close when finished reading. Additionally, in the right corner, a bar is shown which gives a subtle indication of the time left to spend in the environment. In the left corner, an overview is given of the buttons/keys to be used for the most important tasks, i.e. turning the screen black (e.g. when having tired eyes), restarting (e.g. should one get stuck in the environment), or retrieving the information panel.

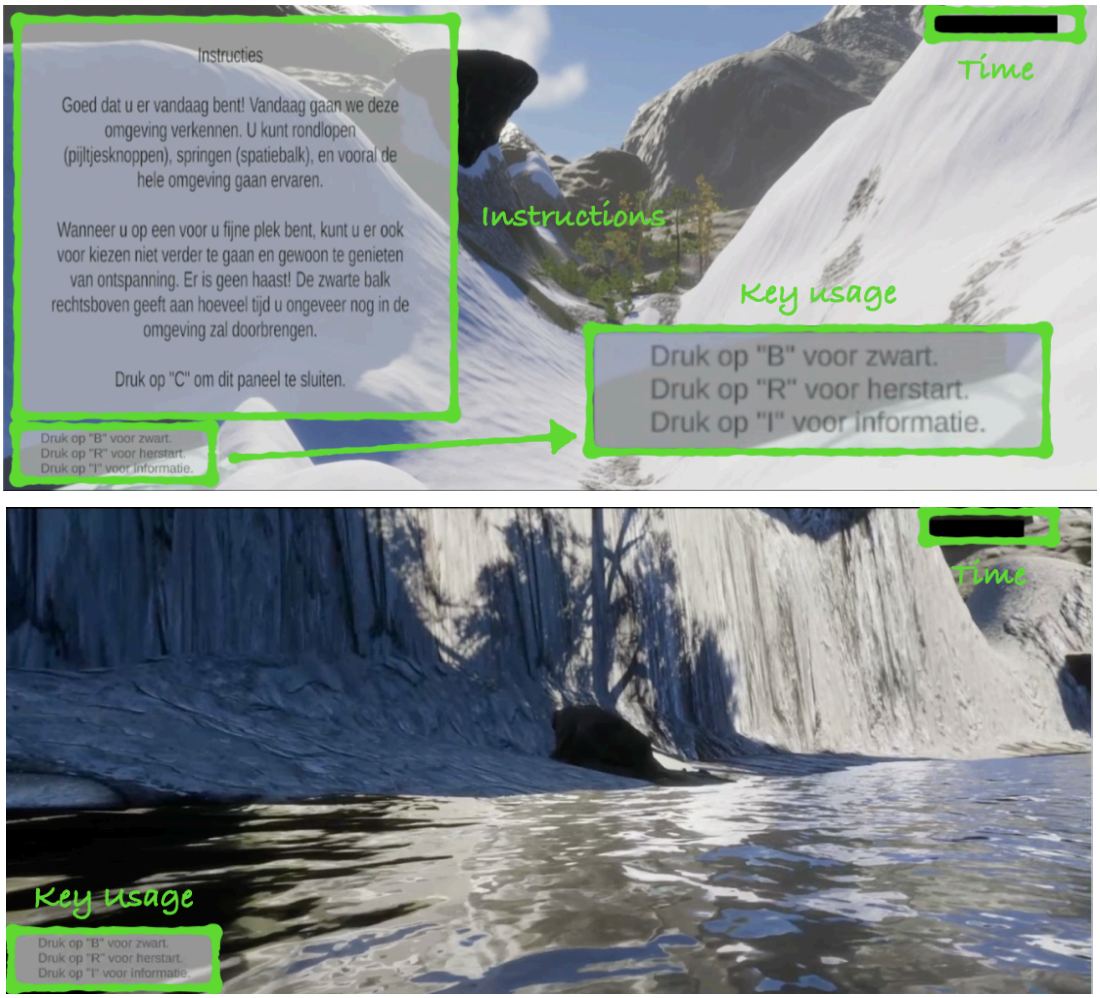

Figure 3. Overview of user interface elements

Designing the intervention: VRH and VR

The virtual reality hypnosis intervention (VRH) was designed as a ca. 15-20 min experience per weekly session adding to eight sessions in total. The individual treatment duration was based on earlier research on hypnosis as applied to pain [Thompson et al., 2019], taking also into account fatigue that may occur as a result of the VR experience within 30 min [e.g. Lei et al., 2023]. It was chosen to provide the treatment in eight sessions based on the average treatment scheme for irritable bowel syndrome, for which hypnosis is already a common treatment in regular medical care, generally consisting of four to twelve sessions [e.g. Gonsalkorale et al., 2005].

For the VRH condition, in the initial phase to induce the state of relaxation or hypnosis, the hypnotic induction, the participants will experience the VR environment while listening to instructions to

progressively relax. A floating island is programmed in the VR environment to allow the participants' eyes to move along an "infinity" pattern controllably, allowing for an induction of type butterfly. Alternatively, participants are instructed to focus on their breath and walk down imaginary stairs until they open their eyes and experience the VR environment. Similar hypnosis inductions were used in the online hypnosis treatment as designed by Brooks et al. (2022).

After the induction, parallel to the VR environment, the participants are instructed to close their eyes while they will continue to listen to the recorded hypnotic script developed based on general hypnotic principles as amongst others described by Yapko (2013). Direct antipruritic suggestions are used such as "your skin will feel so soft, relaxed and cool, it is fully at ease". After these suggestions, the participants are alerted again. Participants are seated at all times during the intervention. An example hypnosis script is attached in Appendix E.

The VR control condition was designed to match the VRH in time, lasting about 15-20 min per session as well. For the VR condition, participants will experience the same VR environment while listening to relaxing music/sounds without the hypnotic induction and suggestions. Within this control intervention, participants are also seated at all times.

Overall design ideas and considerations

To optimise the treatment experience, many design considerations were made. An overview of design considerations made is provided below:

- Unity's High-Definition Rendering Pipeline was chosen for the most realistic graphics for this initial testing phase. In case the testing will be promising, the environment could be adapted to Unity's Universal Rendering Pipeline for WebGL export to allow people to experience the session at home.
- A timing bar was implemented to provide a global idea of time/analogous extent of relaxation, to allow for some orientation. The bar was designed not to provide exact timing, to prevent people from focussing too much on the timing.
- To enhance VR immersivity, hands were included in the VR, to allow grabbing of objects.
- Clickable buttons were omitted due to the impact they may have on the perceived immersion. Keys people could use were chosen to be instructed separately.
- The most essential instructions, i.e. how to turn to black screen, how to restart, and how to make the information panel appear, were chosen to be visible at all times.

- It was chosen to incorporate multiple routes to stop the treatment. Simultaneous desktop and XR controls were programmed, allowing both the researchers and the users/participants to control the environment at the same time. People are instructed that they can either close their eyes, take off their headset, instruct the researcher to stop it (using a single button), and/or click the key for “black screen” themselves. With each VR(H)-experience, the participants are instructed on what to do should they start to feel unwell. In the hypnosis fragments, furthermore several sentences are incorporated to actively ask how the patient feels at different time points, to keep the interaction during the session to assess safety.
- The “*fixed update*”-method was used for reduced camera jittering and reduce motion sickness e.g., when jumping. For this reason, the gravity was also reduced to -4 m/s^2 instead of the regular -9,81 m/s^2, to allow for easier movement over hills, for having a feeling of free weightlessness, and possibly allowing for less motion sickness as may also be enhanced by quick movements.
- The environment was chosen to include some heights for a sheltered feeling. To account for people with fear of heights, it was chosen to explicitly mention the goal of finding a place where one feels best, which can be within a non-mountainous area.
- To enhance immersion, the audio files were attached to the player in 8D format. It was chosen not to attach audio files to different objects to prevent sounds from different objects from mixing.
- It was chosen to make the hypnosis audio fragments play separately from the VR to ensure continuation of the script when people just want to restart the VR or just want a black screen for the time being. In case people would want to also stop the hypnosis audio, they are instructed they can take off the headset.
- Counters in relation to certain tasks were omitted to prevent invoking stress about completing tasks.

Designing the home exercises

Home exercises were scripted to last about 5 minutes per day and to be practiced at any moment of the day at almost any comfortable place. These exercises are audio records the participants can listen to on their phone or computer. For the VRH intervention, the exercises consist of hypnosis records that are structured similarly to the on-site hypnosis experiences described in the section “*Desiging the intervention: VRH and VR*”.

For the VR control intervention three different types of control home exercises were envisioned: (1) informative podcasts about nature and technology, (2) mock hypnosis exercises, (3) general

relaxation exercises. The informative podcasts would most likely allow for the largest distinction between the interventions, comparing a fully relaxation focused VRH intervention with a mostly informative control intervention. Scripts were written to focus on general natural topics. However, not everyone comprehends and enjoys the same informational content, risking dropouts. Another option would be to allow participants a free podcast choice, which however in turn could be seen as incomparable, both because people listen to different content, and because the podcasts are not similarly provided by the researchers. This difference could possibly interfere with the outcomes, inducing a form of the placebo effect related to trust in the researchers.

Secondly, mock hypnosis exercises were envisioned, i.e. hypnosis recordings containing the full hypnotic induction, deepening and deduction, but without the symptom-directed suggestions. This control intervention however, appeared to be too similar to the VRH intervention records, indirectly providing hypnotic suggestions focused at relaxation, which is also an outcome measure in the present study. Therefore, lastly, for the control intervention it was chosen to opt for general relaxation exercises, e.g. focusing on breathing. In this way both home exercises are comparable, but different in whether they contain hypnotic elements or not. Moreover, because both interventions' home exercises are aimed at relaxation, for both interventions we could expect an effect. This in turn may enhance treatment compliance, especially given the pressing need for additive treatments as becomes clear from amongst others the requests the Department of Medical, Health and Neuropsychology receives for itch treatment.

Heuristic evaluations and improvements

Five people participated in the heuristic evaluations upon invitation. Three out of five were female, and the average age was 51.8 ± 11.9 year. One participant had a primary school background, the other participants had received higher education. All but one participant suffered from chronic itch. Three had been diagnosed with a skin condition such as atopic dermatitis as cause of the itch, one had had no clear diagnosis. Itch intensity had been 1.6±1.2 out of 10 over the preceding 4 weeks and 2.0±2.6 at the start of the evaluations respectively. The self-estimated digital ability was 5.2±1.9 out of 10.

Evaluation of the VR environment

Due to a limited availability of VR set ups, it was chosen to evaluate the environment in a 2D desktop version. During the heuristic evaluations of the VR environment no uncomfortable bright light flashes, extreme distortions, or too loud sounds were experienced. One person experienced the ground texture consisting of little twigs with an itchy sensation. This participant also experienced some motion

sickness, when the total screen time had passed 25 minutes and she focussed intensely on the tasks. Overall, the participants showed a strong preference for having no tasks. One participant particularly enjoyed playing with the cubes, stating that the interaction in particular provided distraction. It was recommended to open de environment with the sentence "*This is not a game, but a relaxation exercise*", and to subsequently only provide optional elements to interact with.

The instructions were evaluated as clear and well visible. Only the keys for navigation were requested to be displayed in a panel continuously (e.g. arrow keys = walking, mouse = looking around, space = jumping). All but one participant preferred to walk the environment with keys instead of having the opportunity to teleport.

The appreciation of the sounds was positive, showing a highly individually determined preference equally divided over the bird sounds and the instrumental music. The bird sounds however may be most relaxing, when they would be unpredictable and different all the time.

The sense of presence was rated high with an 8.6±1.7 out of 10. The environment was furthermore rated high on the expected ability to reduce itch with an 8.0±1.0 out of 10. Some suggestions to improve antipruritic associations were the addition of more forest and increasing the amount of wind. The environment was rated well for the appreciation of repeated experiences. All ratings on the virtual reality evaluation heuristics adapted from Sutcliffe et al. (2004) are displayed in *figure 4* (the full questionnaire can be found in Appendix H).

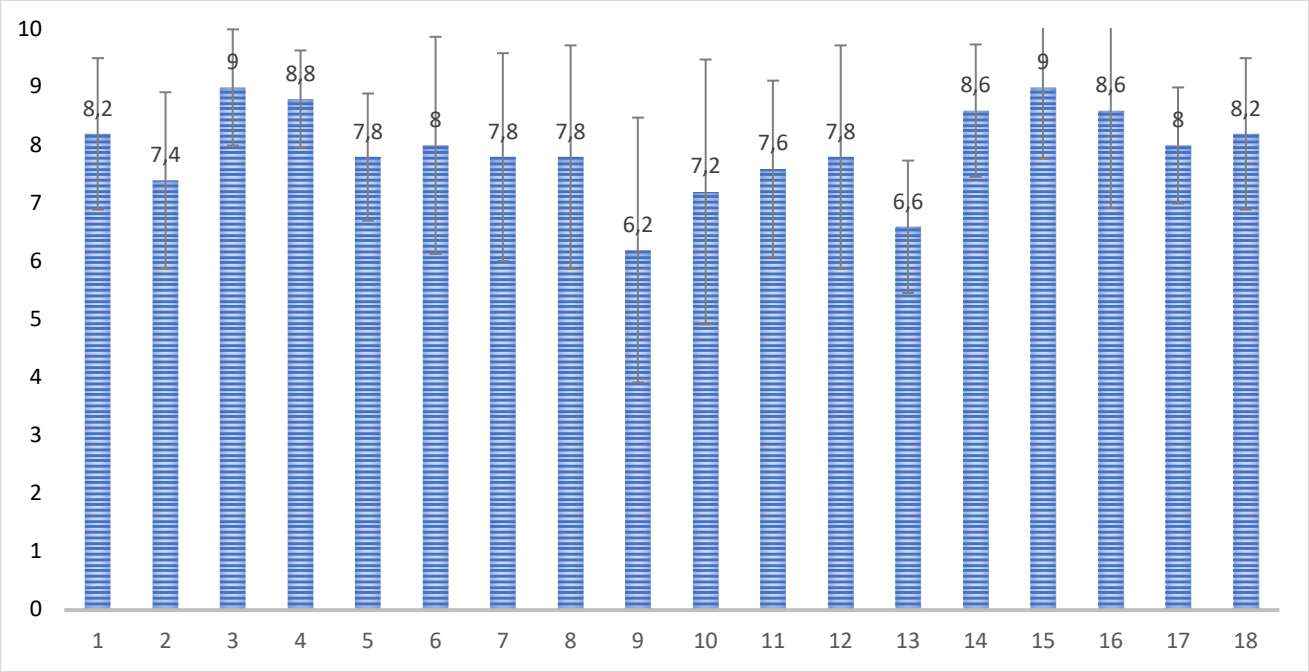

Figure 4. Overview of the ratings of the VR environment in the heuristic evaluations on a scale from 0-10, with 0 meaning "Not at all" and 10 "Very much". The x-axis contains number related to the following topics (full questions can be found in Appendix H): 1: overall experience, 2: instructions clear, 3: screen text large enough, 4: amount of text, 5: action facilitation, 6: enough to do, 7: overview over tasks, 8: sense of satisfaction, 9: naturalness of activities, 10: smoothness of navigation and orientation, 11: accessibility, 12: pleasantness of height difference, 13: overview over environment, 14: visuals, 15: relaxing nature of sounds, 16: sense of presence, 17: expected itch reducing capabilities, 18: pleasantness of repeating the same environment.

During and after the evaluations, the evaluators made notes of the problems they encountered. One of the identified problems includes the possibility of "*falling off the land*" at some borders. Also, the navigational speed was identified as a little too high. An overview of the problems identified by the evaluators is given in *table 1*. Here, also a rating is given to which extent the problem may annoy the user, along with the design modifications that have been made, or could be envisioned.

Table 1. Overview of design problems identified through the heuristic evaluations with a rating indicating the extent to which the problem may annoy the user (0, meaning "Not at all", 10, meaning "Very much"), and the subsequent modifications that have been made or could be envisioned.

Feature	**Problem description**	**Problem rating (Out of 5)**	**Design modification**
Graphics	Ground texture twigs may enhance itching	2	The ground texture was changed.
	Little too mountainous	2	The environment was smoothened for height.
Presence	-	-	-
Interaction	Lack of overview	1	Helicopter view was added *(by grabbing a cube and then pressing the navigational arrow key forward).*
	The tasks were too strenuous.	4	Tasks were made optional.
	Tired eyes	3	The option to close the eyes was mentioned explicitly.
	The visible instructions could include all keys for navigation.	3	An information panel was added to always display the navigation keys.
Environmental features	At the borders there were some possibilities to *"fall off the land".*	3	Colliding planes were added at borders (restart options were already present too).
Controls	The navigation speed was too high.	3	The navigation speed was reduced.
Hardware	Some rendering issues resulted in planes sporadically distorting the view.	1	Instructions are envisioned on not looking down too much.

Quotes noted down by the evaluators include the following (first the original Dutch quote, then the English translation):

"Ik ben echt in een andere wereld geweest. Ook na de ervaring merk ik nu echt nog alsof ik in mijn hoofd mijn lichaam ontstijg. Ik denk dat dit ook voor andere aandoeningen, bijvoorbeeld trauma verwerking goed zou kunnen werken." – Participant 1 (NL)

"I have really been in a different world. Even after the experience, in my head, I still feel like I transcend my body. I think this could also work well for other conditions, such as trauma processing." – Participant 1 (ENG)

"Ik vond het heel mooi gemaakt en oprecht rustgevend, veel meer dan ik had verwacht." – Participant 2 (NL)

"I found it very beautifully made and genuinely soothing, much more than I had expected." – Participant 2 (ENG)

Evaluation of the scripts and audio fragments

Secondly, the audio fragements were evaluated, showing an almost dichotomous appreciation for, or aversion of relaxation exercises in general. One participant declared at the start to not believe in relaxation exercises. Another participant indicated to quickly find relaxation exercises too spiritual. On the other side of the spectrum were two participants who already had positive experiences with mindfulness exercises, and one participant who had previously had positive experiences with hypnosis.

The overall listening experience to the voice and its pace were both appreciated with a 7.8 (±1.6 and 0.4 respectively) out of 10. As such, the audio fragments could relatively well capture the evaluators' attention, scoring only 4.0±3.7 out of 10 on unrelaxed mind wandering (with 0 indicating no unrelaxed mind wandering, and 10 continuous unrelaxed mind wandering).

The degree of achieved relaxation with the exercises was rated with a 6.2±1.9. One participant indicated it would not have been possible to achieve better relaxation upon listening to the self-hypnosis audio fragments. Another participant indicated the hypnotic staircase metaphor to work for him, while the other relaxation exercises made him a bit agitated. It was suggested to make people choose individually which audio fragments they like best to listen to. In this way, people can individually choose fragements that suit them and that they do not find too spiritual or annoying in

another way. It was furthermore suggested to allow people to choose themselves whether they want to sit or lay down during each exercise, and it was recommended for people to optionally hold a pillow on their lap for an extra protected feeling.

The total length of the home exercises was on average 7 min and 22 seconds, which was evaluated with a 6.6±1.1 out of 10 for the duration. With this duration, the evaluators estimated their own expected therapy compliance would be 7.0±2.1 out of 10 (0, meaning "*I would probably do no home exercises at all*", and 10 meaning "*I would practice the home exercises every day*"), corresponding to doing the home exercises about 4 out of the 6 times per week. Barriers indicated by the evaluators include the amount of time involved in doing exercises in general, along with an absence of direct result. One of the evaluators however did indicate to feel a direct result. Lastly, the possibility that you are annoyed by the voice or the exercise was mentioned as a barrier with the suggestion to make people choose between provided fragments.

Finally, the content of the suggestions was rated for its expected effectiveness with a 6.2±2.7 out of 10. One participant mentioned that the explicit mentioning of "*cool and calm rest*" was highly effective for her. Another participant indicated that the less explicit the exercise phrases the suggestions, the more spiritual it appears, resulting in less therapeutic confidence. An overview of all ratings of the audio fragments is given in *figure 5*.

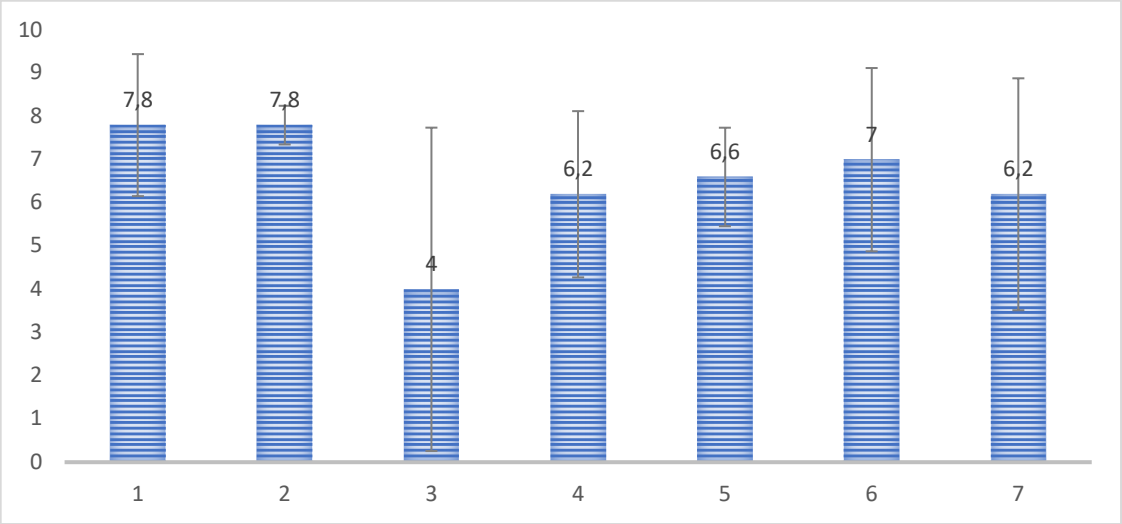

Figure 5. Overview of the ratings of the audio fragments in the heuristic evaluations on a scale from 0-10, with 0 meaning "Not at all" and 10 "Very much". The x-axis contains numbers related to the following topics (full questions can be found in Appendix H): 1: pleasantness of listening to the voice, 2: pleasantness of the pace, 3: extent of unrelaxed mind wandering, 4: extent of relaxation, 5:

appreciation of total length home exercises, 6: expected own therapy compliance, 7: extent of suggestion applicability.

The evaluators furthermore indicated to overall have as much confidence in a physical hypnotherapist as a hypnosis audio fragment for bringing them under hypnosis. Since most evaluators had no experience with hypnosis, they tended to find this question difficult to answer. When it comes to the provider of the exercises, most evaluators (3 out of the 5) regarded exercises provided by their practitioner to be more effective as part of their medical treatment than self-chosen exercises.

Final game

An overview of the environment with some of the programmed game elements can be viewed in the following movie (password: VR): https://vimeo.com/835212965?share=copy.

Upon request an appointment can be scheduled with the author to experience the game in real life and/or to get access to the full stack of audio files. Also, for more information about the clinical trial, including patient letters etc., please send an email to: jardmattens@live.nl.

An overview of the risk assessment and management plan is given in Appendix J. Furthermore, in Appendix K, a short version of the clinical trial proposal is depicted.

Conclusion

With the design of this top-down therapeutic intervention aimed at mitigating itch and its psychological consequences, a new step has been taken towards improving the health and wellbeing of individuals suffering from chronic itch. Parallel to this design study, a clinical trial has been set up - at the time of writing still under review by the medical ethical committee – which may in the near future give a final indication of the actual clinical effectiveness.

Discussion

The design process founds its origin in literature and was soon taken to the intended user population of people with chronic itch in the initial focus group. In this way, the development process was informed by the user from early on. In total, there were two moments of interaction with the intended

users: during the initial focus group and during the heuristic evaluations of the VR environment. These two moments were chosen to induce a minimal patient burden while receiving feedback at the most essential points of development, as was approved by the Psychology Research Ethics Committee (CEP) of Leiden University.

Due to a limited availability of VR set ups and expected similarity in general usability factors, the evaluations were chosen to be performed in 2D fashion instead of in virtual reality. This means the environment was created in two versions: a VR version and a desktop version. Only the exact interactive keys/buttons are different, along with most likely the perceived immersion (e.g. in the VR version amongst others grabbing hands have been incorporated), allowing the performed heuristic evaluations to give a comparably adequate outlook on the intervention in VR as well.

The number of evaluators was chosen in accordance with the suggested optimal number by Nielsen (1994). A drawback of this number of evaluators, however, is that some usability problems may not be found to the extent this may depend on the inhomogeneity of the evaluator population. One could example given imagine that a person of 80 years without any digital experience may have different needs and may therefore find different usability problems than a digitally skilled person of 30 years, and the other way around. For this research, it was chosen to approximately match the evaluator population to the intended user population in terms of age and estimated digital ability to find the most relevant usability problems.

The effectiveness of providing hypnosis therapy in the form audio recordings - in comparison with providing hypnosis therapy by a physically present hypnotherapist - has been widely disputed. In terms of costs, audio recording-based hypnosis may constitute a significant relief on the healthcare system. Forbes et al. (2008) however claim audio recordings to be less effective. A postulate corroborated by one of the evaluators in the present study, who likewise indicated to believe that the hypnosis should be tuned to an individual's breath and state in real life. This means that the cost-effectiveness of the treatment should be evaluated at subsequent stages, allowing space for the hypnosis to be provided by a hypnotherapy-trained care giver using the virtual reality as an assistive device. Nevertheless, more recent studies hint at non-inferiority of audio-based hypnosis comparted to therapist-led hypnosis treatments at least for children up to 6 years after treatment [e.g. Rutten et al., 2017; Rexwinkel et al., 2022], providing a hopeful future for the cost-effectiveness of VR-assisted hypnosis interventions as well.

Within the presently designed treatment, it can moreover be envisioned to have a multiplayer variant and/or the presence of animated characters using Unity's *Animation Track*. In this way, example given a "physically present hypnotherapist" could be created in the VR environment to possibly enhance the feeling of immersion and perhaps even trust and/or treatment confidence.

Not everything works for everyone. The design process applied within the present study was aimed at catering for as many people as possible. This generalized strategy is important for comparability in research practices, but may overall be less effective for the individual. For future designs, it could be envisioned that AI-based rendering of VR environments is used. In this way, individuals could input their own associations with itch relief as training set consisting of images and words, with which subsequently endless amounts of different VR designs could be generated. At the time of writing, Unity is developing an AI-rendering pipeline, addressing this topic for effective individualized future designs.

This process of individualized rendering may also apply to the generation of hypnosis scripts and audio records. ChatGPT was tried to generate hypnosis scripts, which already showed promising results. These scripts were however still limited in the variability in suggestion content and were therefore not yet used in the present design. Also, voice rendering can be achieved using AI these days to allow for a more flexible choice of the hypnotherapist's voice on the record and higher cost-effectiveness.

Finally, the addition of haptic feedback is a promising avenue for future designs. In hypnosis, often different cues - involving different senses - are used simultaneously. The power of synchronization of our different senses is also demonstrated by the well-known rubber hand experiment where vision is synchronized with touch to result in the misleading conception of ownership over a rubber hand [e.g. Kammers et al., 2009]. The focus group also brought forward the concept of mindful movement or body movement language, which focusses on making movements in interaction with computer visuals. These concepts were intentionally not integrated in the present study to prevent cases of disbalance, falling and/or other additional complications with haptic feedback in this only preliminary study, but may for the reason of integration of the senses be promising future additions for optimal clinical effectiveness.

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Overview appendices

A. Information letters and informed consent forms
B. Focus group questions and word webs
C. Conceptual design sketches
D. Concept storyline VR control group
E. Example VRH script
F. Example VRH and VR home exercises with instructions
G. Heuristic evaluation principles virtual reality
H. Heuristic evaluation questions
I. Computer specifications
J. Risk analysis and risk management plan for clinical trial
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Appendix A: Information letters and informed consent forms (focus group & heuristic evaluations combined, Dutch only)

Informatiebrief [Focus groep/Evaluatie] Virtual Reality-Omgeving voor Jeukvermindering

Op de afdeling Gezondheids-, Medische- en Neuropsychologie van de Faculteit Sociale Wetenschappen van de Universiteit Leiden is in samenwerking met de afdeling dermatologie in het Amsterdam UMC een onderzoek gaande om in kaart te brengen welke concepten mensen met chronische jeuk in verband brengen met jeukverlichting. Uit eerder onderzoek is gebleken dat virtual reality (VR) in staat is tot het (tijdelijk) verminderen van jeuk perceptie en krab gedrag bij mensen met jeuk. Zelfs het kijken naar specifieke kleuren zou de ervaren jeuk intensiteit al kunnen verlichten. Voor jeukverlichting op de langere termijn door VR bestaat er nog weinig duidelijkheid.

Een techniek die hoop biedt in de strijd tegen chronische jeuk is hypnose, wat een toestand van ontspanning is. Een studie heeft laten zien dat hypnose in ieder geval voor enige maanden de jeuk zou kunnen verminderen. Een van de grootste uitdagingen in het toepassen van hypnose is echter dat niet iedereen even makkelijk te hypnotiseren is. Door hypnose te combineren met VR is het mogelijk dat hypnose breder toepasbaar kan worden gemaakt met een langer aanhoudend effect dan tot op heden gezien bij VR-behandelingen.

Als onderzoeksteam zijn wij daarom bezig een studie op te zetten naar het effect van virtual reality met hypnose tegen jeuk. Om dit toekomstige onderzoek te kunnen uitvoeren is met de huidige studie ons doel om [concepten te achterhalen die mensen in verband brengen met jeukverlichting om deze te kunnen verwerken in] een VR-omgeving met focus tegen jeuk [met u te toetsen en te verbeteren]. Met behulp van uw inzichten en feedback beogen wij de betrokkenheid van de gebruiker en de jeuk-verlichtende associaties van deze nieuwe behandeling te verbeteren.

Via deze brief willen wij u informeren over dit deel van het onderzoek en u uitnodigen voor deelname aan een [focus groep (brainstormsessie)/evaluatiesessie]. Lees deze informatie nauwkeurig door voordat u besluit of u wel of niet mee wilt doen. U kan ons altijd om meer informatie vragen mocht er iets onduidelijk zijn.

<u>Wat vragen wij van deelnemers in onze studie?</u>

Als u akkoord gaat met deelname aan deze studie zal u eenmalig deelnemen aan een [online focus groep (brainstormsessie)/evaluatiesessie] van [1-]1.5 uur [via (video)bellen].

[Gedurende de focus groep zal u tezamen met één andere deelnemer gevraagd worden naar uw associaties bij de onderwerpen jeuk en jeukverlichting. Een onderzoeker leidt de groep en noteert steekwoorden voor de deelnemers en het overzicht in een woordweb. Te allen tijde is er ruimte voor persoonlijke ideeën en opmerkingen.

De audio van de sessie zal worden opgenomen via videobellen (Zoom, MS Teams, …) en zal bij gereedheid van de VR-omgeving verwijderd worden. Bij het inloggen in de (video)belomgeving zal u gevraagd worden uw voornaam op te geven danwel een nick name, indien gewenst. Vanuit het oogpunt van de privacy vragen wij u niet uw volledige naam op te geven in de belomgeving.]

[De evaluatiesessie bestaat uit twee delen. Gedurende het eerste deel van de evaluatiesessie zal u 2 x 15 minuten een game ervaren en beoordelen met behulp van een vragenlijst.
In het tweede deel krijgt u enkele fragmenten te horen en suggesties te lezen, welke u tevens gevraagd worden te beoordelen. Binnen de vragenlijsten is er ruimte voor persoonlijke ideeën en opmerkingen. Wij verzoeken u om tijdens de evaluaties de vragenlijsten erbij te houden op uw mobiel of ander apparaat en vooral tussendoor aantekeningen te maken. Het computerscherm van de gamelaptop zal namelijk volledig aan de game opgaan. Zorg indien gewenst voor pen en papier om aantekeningen te maken. Wij verzoeken u aan het einde alle aantekeningen bij de onderzoeker in te leveren.]

Alle verzamelde informatie zal behandeld worden naar vertrouwelijkheid (zie *Vertrouwelijkheid*). Uiteraard mag u uw deelname aan deze studie op elk moment beëindigen. [U krijgt een vergoeding voor de tijd die u investeert (*zie Vergoeding).]*

Wie kan deelnemen?

- U bent minimaal 18 jaar oud;
- [U heeft op het moment van de studie last van chronische jeuk (ondanks eventuele behandeling);
- U bent met deze aandoening bij een arts geweest voor onderzoek naar mogelijke oorzaken en behandeling;]

- U heeft gedurende de studie toegang tot het internet en een smartphone, laptop en/of tablet met werkende [camera- en] geluidsvoorziening om [deel te nemen aan een (video)belconferentie/online vragenlijsten in te kunnen vullen];
- U spreekt Nederlands en kunt online vragenlijsten invullen.

[Vergoeding

Na volledige deelname van 1 sessie van 1,5 uur ontvangt u €15 als beloning voor de tijd die u geïnvesteerd heeft.

Wanneer blijkt dat u niet voldoet aan de criteria die voor deelname worden gesteld (zie *Wie kan deelnemen*), is het helaas niet mogelijk om mee te doen of een vergoeding te ontvangen.]

Mogelijke nadelen van deelname

Deze studie vraagt om enige tijdsinvestering. Er zijn geen verdere nadelige gevolgen van dit onderzoek.

Ethische toetsing

Dit onderzoek is goedgekeurd door de ethische commissie van het Instituut Psychologie, Universiteit Leiden.

Vertrouwelijkheid

[Ter bescherming van uw persoonlijke gegevens vragen wij u tijdens de (video)belmomenten om niet uw (volledige) eigen naam te gebruiken of op te geven in het belaccount.]

Er zal vertrouwelijk worden omgegaan met alle informatie en gegevens die worden verkregen tijdens deze studie. Na deelname aan deze studie zullen wij de onderzoeksgegevens analyseren op een gecodeerde manier. Dit betekent dat wij een nummer toekennen aan elke deelnemer. De onderzoeksgegevens die wij verzamelen in deze studie bestaan uit uw antwoorden op de vragenlijsten. Deze onderzoeksgegevens zullen minimaal 15 jaar worden bewaard. Deze onderzoeksgegevens zullen ook gepubliceerd worden in een online database, maar omdat deze gecodeerd zijn, kunnen anderen deze niet herleiden naar u. De uitkomsten van deze studie zullen mogelijk ook worden gebruikt voor wetenschappelijke publicaties maar zullen onder geen beding terug te leiden zijn naar de deelnemers.

Uw persoonlijke gegevens, zoals uw naam en contactgegevens, zijn alleen toegankelijk voor de betrokken onderzoekers gedurende de duur van deze studie. Deze persoonlijke gegevens zullen

worden verwijderd wanneer de resultaten van de studie gepubliceerd worden in een wetenschappelijke publicatie, met een maximale opslag van 2 jaar na afronden van de metingen van de laatste deelnemer. Tot die tijd zullen uw persoonlijke gegevens worden opgeslagen in een met wachtwoord beveiligd document. De toestemmingsverklaringen zullen online worden opgeslagen voor een minimum van 10 jaar na afronding van de metingen van de laatste deelnemer. Als u zich bedenkt en uw persoonlijke data eerder verwijderd wilt hebben, kunt u contact opnemen met onderzoeker Jard Mattens via een e-mail naar j.d.j.mattens@fsw.leidenuniv.nl.

Als u enige vragen heeft over privacy, kunt u het Privacy Service Punt contacteren, bestaande uit privacy advocaten en de functionarissen gegevensbescherming. U kunt uw vraag e-mailen naar privacy.bb@leidenuniv.nl.

Deelname is geheel vrijwillig

Wij zouden uw deelname aan het onderzoek zeer op prijs stellen, maar wij willen u er nadrukkelijk op wijzen dat deelname geheel vrijwillig is. Als u besluit om niet deel te nemen aan het onderzoek, heeft dit op geen enkele manier nadelige gevolgen voor u. Indien u tijdens het onderzoek om welke reden dan ook wenst te stoppen, kan dit op elk moment zonder opgaaf van redenen.

Deelname registratie

Als u geïnteresseerd bent in deelname aan deze studie, vragen wij u om een e-mail te sturen naar j.d.j.mattens@fsw.leidenuniv.nl.

Klachten

Indien u klachten hebt over dit onderzoek, kunt u deze bespreken met de onderzoeker (Jard Mattens, j.d.j.mattens@fsw.leidenuniv.nl, of de projectleider (Dr. Antoinette van Laarhoven, a.vanlaarhoven@fsw.leidenuniv.nl).

Nog vragen over het onderzoek?

Mocht u nog vragen of opmerkingen over het onderzoek hebben, dan kunt u een e-mail sturen naar j.d.j.mattens@fsw.leidenuniv.nl.

Met vriendelijke groet,
Het projectteam
Jard Mattens

Dr. Antoinette van Laarhoven

Toestemmingsverklaring focusgroep virtual reality-omgeving voor jeukvermindering (informed consent)

Welkom in deze toestemmingsverklaring voor deelname aan de focusgroep ten behoeve van de ontwikkeling van een virtual reality-omgeving voor jeukvermindering!

Eerder heeft u de informatiebrief "Focusgroep ten behoeve van de ontwikkeling van een virtual reality-omgeving voor jeukvermindering" ontvangen.

Door onder de volgende statements uw naam en de datum in te vullen geeft u uw toestemming om deel te nemen aan dit onderzoek. Klik tot slot op de knop met het pijltje om de toestemmingsverklaring in te sturen.

Ik ben voldoende geïnformeerd over het onderzoek. Ik heb schriftelijke informatie gekregen en ik ben in de gelegenheid gesteld om vragen over het onderzoek te stellen. Mijn vragen zijn adequaat beantwoord. Ik heb voldoende tijd gehad om te beslissen of ik wel of niet wil deelnemen.

Ik begrijp dat deelname aan het onderzoek geheel vrijwillig is en dat ik op ieder moment kan stoppen met het onderzoek zonder dat ik daarvoor een reden hoef op te geven. Ik ben geïnformeerd over de vergoeding die wordt gegeven wanneer ik het onderzoek niet voltooi.

Ik ben mij ervan bewust dat mijn persoonlijke en onderzoeksgegevens – de laatste gepseudonimiseerd - zullen worden opgeslagen tot de resultaten worden gepubliceerd in een wetenschappelijke publicatie. Ik geef toestemming om mijn gegevens te gebruiken voor de doeleinden vermeld in de informatiebrief. Ik begrijp dat voor studiedoeleinden sommigen individuen toegang hebben tot al mijn gegevens. Deze mensen staan vermeld in de informatiebrief. Ik geef toestemming voor toegang tot mijn gegevens door deze personen.

Door dit document in onderstaande tekstbalk te ondertekenen met volledige naam en datum, stem ik in met deelname aan het onderzoek: "Focusgroep ten behoeve van de ontwikkeling van een virtual reality-omgeving voor jeukvermindering".

_____

Geeft u toestemming om na dit onderzoek opnieuw te worden benaderd voor eventuele deelname aan een toekomstig onderzoek?

- ○ Ja, ik sta ervoor open om benaderd te worden voor toekomstig onderzoek
- ○ Nee, ik geef geen toestemming om voor toekomstig onderzoek benaderd te worden

Appendix B: Focus group questions and word webs (Dutch only)

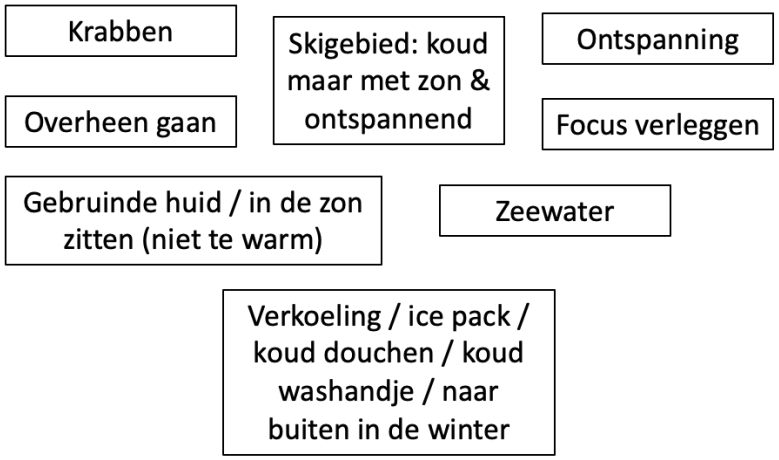
Ronde 1: ***Algemene associaties met jeuk***

Wat komt er het eerste bij u op als u denkt aan “jeuk”?

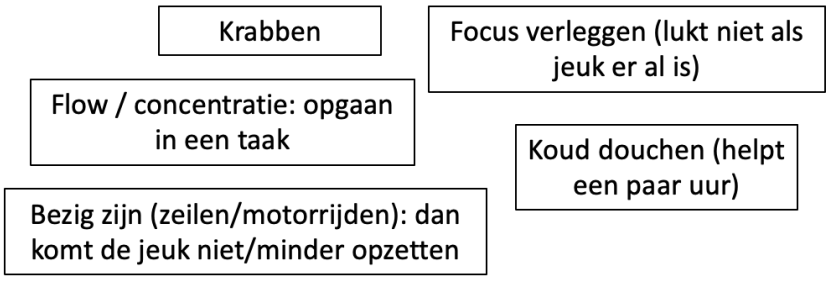
Welke factoren brengt u in verband met verergering van jeuk?

Ronde 2: ***Jeukverlichting en algemene concepten als kleur, objecten, situaties, etc.***

Wat komt er het eerste bij u op als u denkt aan “jeukverlichting”?



Wat helpt bij u het beste om jeuk te verlichten?



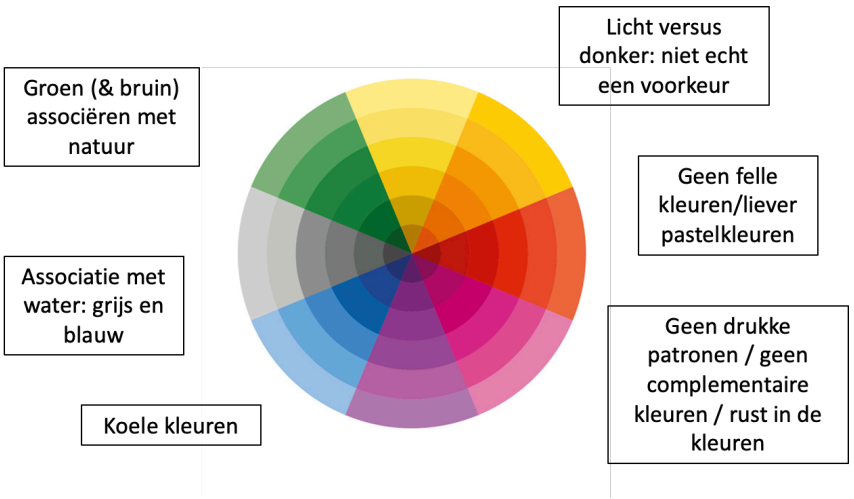
Wat is het gekste of meest creatieve dat u ooit gedaan heeft om uw jeuk te verlichten?

- Hypnose geprobeerd
- Meditatie / yoga
- Oppassen met voeding
- Katoenen medische handschoenen
- Op de huid kloppen/masseren/ prikkeldraad zelf geven
- Nieuwe producten (o.a. Glad skin)
- Afgeronde objecten om mee te krabben

Wat komt er het eerste bij u op als u denkt aan “objecten en jeukverlichting”?

- Ruggenkrabbertje
- Lange schoenlepel
- Pincet/ nagelschaartje (als de nagels te kort zijn om verlichting te geven)
- Hoek van de muur
- Verkoelingsmethoden zien werkt niet
- Boek lezen (mogelijk wel onbewust krabben)
- Kunst / foto’s / schilderijen
- Gitaar spelen/ tekenen
- Tv kijken

Wat komt er het eerste bij u op als u denkt aan “kleur en jeukverlichting”?



Wat komt er het eerste bij u op als u denkt aan “situaties/momenten en jeukverlichting”?

Saunabezoek: heet en hard afkoelen → ontspanning (/ desensibiliseren)	Samenzijn met anderen /persoonlijke affectie kan helpen voor de een
Zelfverzorging: Goed de tijd voor persoonlijke verzorging, incl. goed insmeren	Iets goed doen /afronden: beloningservaring

Pauze

Ronde 3: *Jeukverlichting en stem/geluid*

Wat komt er het eerste bij u op als u denkt aan “geluid en jeukverlichting”?

Natuurgeluiden (wind, ruisen, geluid van regen, stromend water, golfslag)	Muziek
	Jazz / koffiekamer-achtig
Constant ruisen voor korte duur (bijv. van een snelweg; NB tinnitus werkt niet)	Afhankelijk van de situatie: extreem traag of heftig

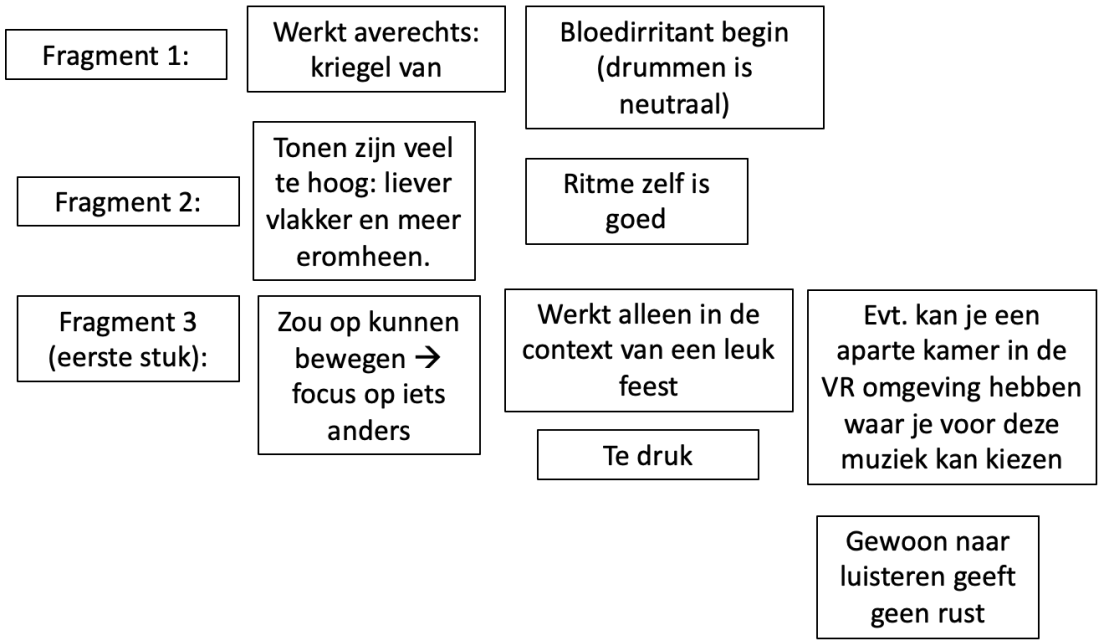
Hoe zou voor u een “jeukverlichtende” stem klinken?

ASMR: geluiden die rust geven o.a. een stem /ritselgeluiden
Vloeiende tongval / zuidelijke accenten
Accent: liefst passend bij wat ik gewend ben
Trance-inductie: trance-stem: **rustig**, laag

Wat doen de volgende fragmenten met uw jeuk (verlichten/verergeren/neutraal)?

Heeft u enig idee waar dit aan zou kunnen liggen?

Wat doen de volgende fragmenten met uw jeuk (verlichten/verergeren/neutraal)?
Heeft u enig idee waar dit aan zou kunnen liggen?



Ronde 4: *Jeukverlichting en beweging/acties*

Wat komt er het eerste bij u op als u denkt aan “beweging en jeukverlichting”?

Body movement language (Gaga, Israëlisch) = Bewustwording van je lijf → helemaal geen jeuk

Op de motor (circuit): heel bewust bewegen

Mountainbiken: focus en flow

Yoga (alleen in een relaxte pose kan het juist weer niet werken)

Ademhalingsoefeningen

Tijdens zingen: focus & ademhaling

Doelgerichte bewegingen, taakgestuurd, aandacht erbij en bewustwording

Appendix C: Conceptual design sketches

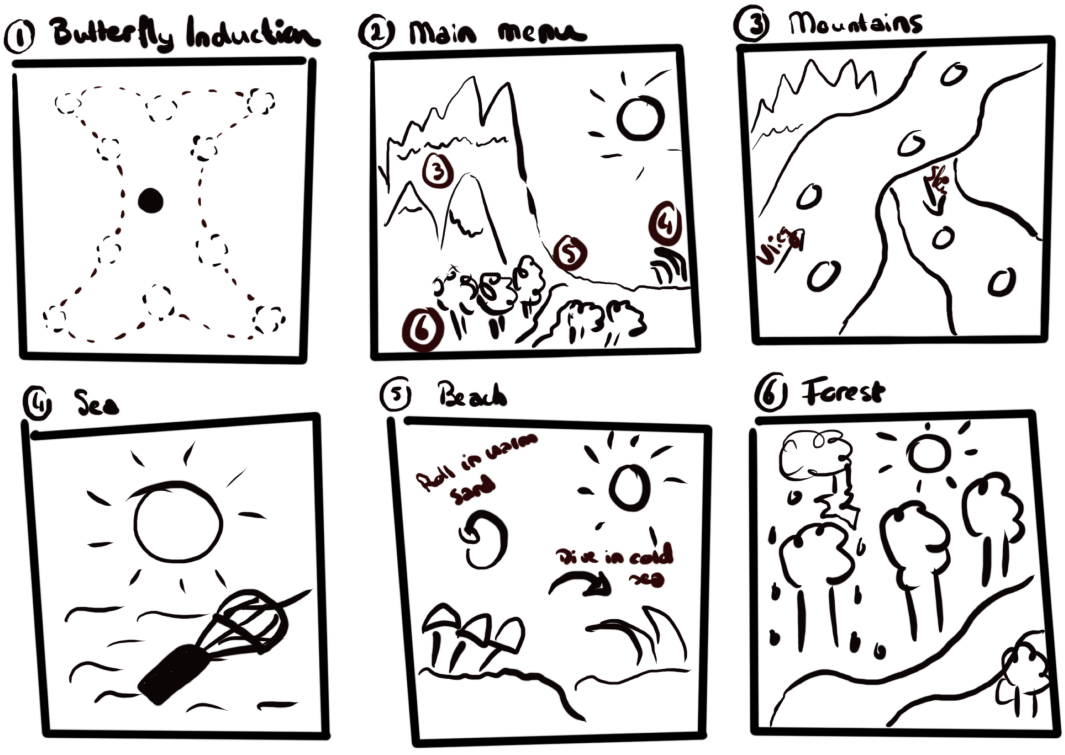


Figure C.1 VR concept design

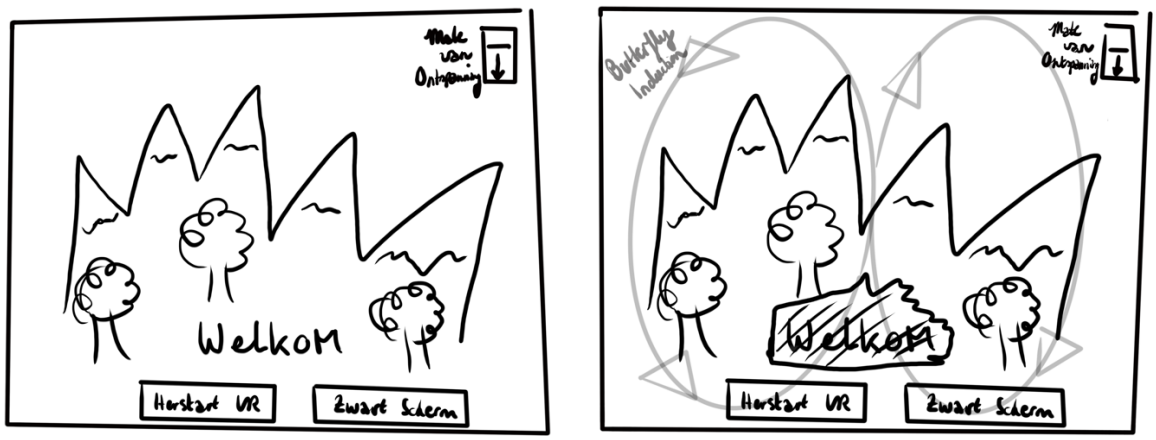


Figure C.2 VRH concept UI design

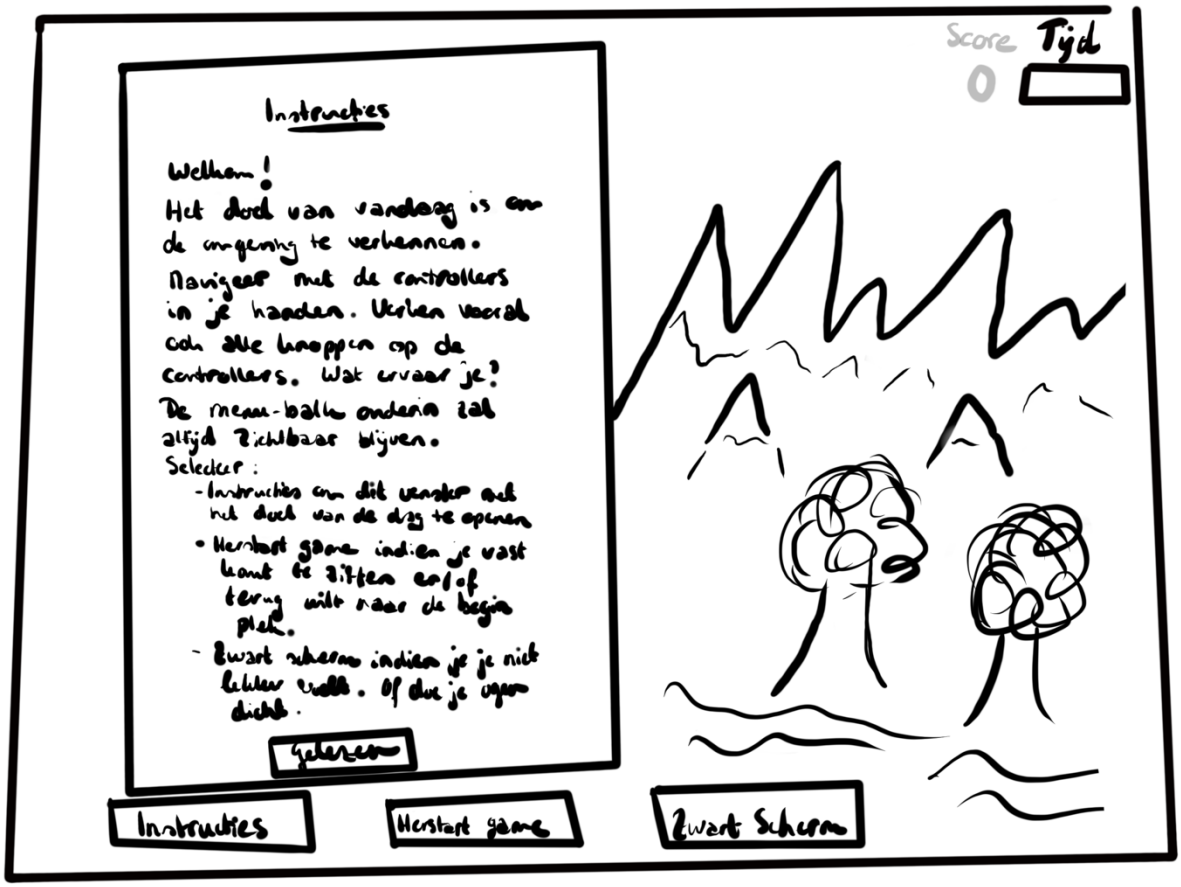


Figure C.3 VR concept UI design

Appendix D: Concept storyline VR control group

Week 1: The assignment is to explore the (virtual reality) environment.
Week 2: The assignment is to look for potential for the presence of other people in the environment.
Week 3: The assignment is to find cubes to build a shelter later (click until different colour).
Week 4: The assignment is to look for balls as good luck charms (click until different colour).
Week 5: The assignment is to arrange the cubes (previously found or not) by placing them around the reels up to the green side, so that they can be built more easily later.
Week 6: The assignment is to go mushroom hunting. In this environment, all possible mushrooms are edible. Try to find as many mushrooms as possible.
Week 7: The assignment is to find the thief of the cubes you have previously used to build with.
Week 8: The assignment is to rearrange the cubes after the theft by rolling them over until the green side is down. Then a shelter can be built.

Appendix E: Example VRH script (Dutch only)

Sessie 1: Een keer moet de eerste zijn

Inductie: Conversationeel/Elmann

Verdieping: Afdaling [+VR]

Post hypnotische suggesties: zachte huid, lichte koele aangename verzachtende rustgevende bries, strijken/ontspannen i.p.v. krabben, rustig, versterking met oefenen

Deductie: Aftellen

Inductie: Welkom! Ga maar lekker zitten en ontspan. Beweeg je schouders maar op en neer, en doe dat nog maar een keer, en laat ze maar ontspannen hangen. Heel goed. Terwijl je je schouders zo ontspannen laat hangen, adem je diep in, hou je dat vast en adem je uit. Goed zo! Het kan zijn dan je gedachten nog ergens anders zijn. Dat is ok, wanneer je dat merkt breng je je aandacht langzaam terug naar hoe je hier zit.

Je hoeft zelf niet meer te denken. Dat doet jouw onderbewustzijn wel voor je. En dat gaat helemaal vanzelf … Jouw onderbewustzijn weet precies wat goed voor jou is. Het onderbewustzijn regelt van alles voor je; je lichaamstemperatuur, je bloedsomloop, je hartslag … Dat gaat helemaal vanzelf, daar hoef jij niet bij na te denken, toch? Dus hoef je nu ook niet na te denken over wat je onderbewustzijn nu gaat ontdekken, ervaren en leren. Je gaat lekker helemaal ontspannen.

Terwijl je nu zo in- en uitademt, zal je ademhaling steeds rustiger worden en terwijl je ademhaling steeds rustiger wordt, raak jij dieper in ontspanning. Voel het maar gebeuren. Het gaat helemaal vanzelf. Langzaam stroomt bij iedere ademhaling de ontspanning via je longen je lichaam in, steeds een stukje verder, langzaam via je buik, langs je benen tot in je tenen, en … langs je schouders, je

nek tot in je hoofd. Adem in en adem uit, en adem in, houd dat vast 3,2,1, en adem uit, 5,4,3,2,1. En adem in, houd dat vast 3,2,1, en adem uit, 5,4,3,2,1. Heel goed.
Het is donker als je goed kijkt. Kijk maar eens van rechts naar links met je ogen, en van links naar rechts. Heel goed. Jij hebt te allen tijde de controle. Ga zo door. En terwijl je dit doet, ga je vanuit deze controle je ogen steeds langzamer bewegen tot je vanuit deze ontspanning voelt dat je ogen langzaam dichtvallen. Nu. Doe ze maar dicht. En merk maar hoe fijn het is om je ogen even dicht te hebben. En open je ogen maar, want dat kan je gewoon, jij hebt de controle. Heel goed. Terwijl je langzaam in- en uitademt, doe je je ogen dicht, nu, en ben je opnieuw 10 keer meer ontspannen, en doe je ogen maar weer open.

Je bent gearriveerd op een hele fijne plaats, doe je ogen nog maar even dicht, nu, je bent 10 keer meer ontspannen, goed zo, en open je ogen maar weer.
Verdieping: Kijk maar eens goed om je heen, naar wat je ziet. Noem het maar hardop, waar je bent. En merk dat je ook rond kan lopen met de joysticks in je handen. Ervaar maar eens hoe vrij je bent. Misschien kom je soms even vast te zitten, je kan altijd opnieuw beginnen, zoals je jezelf in het leven soms ook steeds weer nieuwe kansen moet geven. Als je merkt dat je je even niet lekker voelt, dan doe je gewoon je ogen dicht en zeg je het hardop. Dat kan op elk moment. Probeer je dan zelf een fijne omgeving voor te stellen, waar je ontspant. Je weet dat je elk moment met de ervaring kan stoppen, maar weet ook dat je dat nu nog niet wilt, want het is hier veel te fijn en ontspannen en vrij. En omdat je vrij bent, zoals je de komende tijd ook steeds meer in het dagelijks leven gaat ervaren, voel je je steeds beter. Zolang je je ogen open hebt, ervaar je de omgeving. Misschien probeer je wel te rennen, of te springen. Voel dat maar. Je weet dat er niets kan gebeuren, dat je beschermd bent, compleet veilig. Kijk maar eens rond wat je kunt ontdekken. Wat je voelt.

Misschien hoor je wel wat op verschillende plekken, ga maar daar, waar je het het fijnst vindt. Focus maar op wat je hoort en probeer het maar te volgen met je ogen, waar komt het vandaan, het geluid, en waar gaat het heen? Merk met elk stuk dat je aflegt dat je langzaam steeds ontspannener wordt. Tot je ogen misschien wel bijna dichtvallen en je er niet meer aan kan weerstaan om ze dicht te doen.

- Doe nu je ogen maar dicht, en word zo 10 keer meer ontspannen. Concentreer je maar op hoe je schouders zich steeds meer ontspannen. Misschien voel je jezelf wel wat lichter worden, voel maar wat er gebeurt. Misschien voel je het wel wat aangenaam koeler worden om je heen, voel dat maar eens. Misschien voel je wel een enorme zachtheid die je omarmt, voel het maar komen. Het is fijn. Misschien voel je het, misschien nu nog niet. Je zal de komende tijd ervaren dat jouw huid en hoofd steeds fijner en ontspannener gaan aanvoelen.

Suggesties: Je doet het erg goed. Je huid wordt zacht en rustig en zo ook de zenuwen van je huid tot in je hersenen, ontspannen, aangenaam. De aangename en nuttige gevoelens in jouw huid zullen meer en meer het gevoel in je huid gaan bepalen. Zachtheid, fijne koele rust, alsof er een aangenaam verzachtend, rustgevend briesje langs je heen gaat. Nu, en ook straks, zal je gevoel, in je hoofd en in je huid alleen maar aangenamer worden. Misschien dat het in het begin nog af en toe wegblijft. Je hoeft alleen maar goed voor jezelf te zorgen, te ontspannen, en daarin zal je rust vinden. Jij weet dat je elk moment dit gevoel van verzachtende koelte en rust kan oproepen door aan dit moment te denken. Dat je er maar aan hoeft te denken, een keer diep in hoeft te ademen en dat je in de rust een rustige aangename huid voelt. Elke keer dat je onder hypnose gaat wordt dit fijne gevoel sterker, blijft het langer bij je, en zo ga je steeds makkelijker onder hypnose, ontspan je je steeds sneller, hier, maar vooral thuis. Je zal merken dat je eigenlijk een natuurtalent bent in ontspannen. Misschien dat je het even vergeten was. Vanaf vandaag zal je uit gaan vinden dat ontspannen je heel natuurlijk afgaat, en terwijl je dat ontdekt ontspant je huid steeds makkelijker, voel jij je steeds fijner, en weet je dat fijne gevoel ook steeds makkelijker vast te houden, roep je het sneller op, geheel vanuit jezelf, want jij bent een natuurtalent en doet het erg goed.

Deductie: Zo meteen tel ik af van 5 tot 1 en bij 1, nu nog niet maar bij 1, doe je je ogen open en ben je weer helemaal wakker en alert en in het hier en nu, waarbij het aangenaam koelende zachte ontspannen gevoel op jouw huid blijft. 5… je voelt je al weer een beetje meer in het hier en nu, vol positiviteit, ontspanning en zachtheid die de komende tijd steeds sterker gaan worden en met elke oefening verder versterkt worden… 4… je bent je weer meer bewust dat je een bril op je hoofd voelt en ondertussen neem je de aangename koele zachtheid op je huid mee…3… misschien hoor je alweer wat op de achtergrond en je bent weer een stapje dichter bij het hier en nu…2…de zachte aangename koelte neem je mee op je huid en zal er de komende tijd steeds vaker zijn en ook steeds aangenamer worden, waardoor je je steeds beter gaat voelen. Wanneer je zo meteen bij 1 nu nog niet maar bij 1 je ogen opent, dan ben je weer helemaal wakker en alert en in het hier en nu en voel jij je ontspannen met je huid en geweldig …1… open je ogen maar en wanneer jij daar klaar voor bent mag je de bril afzetten. Goed gedaan vandaag, je verdient het om deze tijd voor jezelf te nemen en zo te werken aan herstel, ontspan, neem je tijd, drink misschien even wat en ga vooral door goed voor jezelf te zorgen. Goed bezig!

Appendix F: Example VRH and VR home exercises with instructions (Dutch only)

Instructies thuisoefeningen

Goede dag. Goed dat u aan de slag gaat met de thuisoefeningen! De volgende punten zijn belangrijk wanneer u de thuisoefeningen gaat doen:

- Neemt u plaats op een rustige plek waar u niet gestoord kan worden.
- Zorg dat u één of meerdere fijne kussens bij u heeft om met uw hoofd op te liggen, dan wel om in uw schoot te leggen.
- U kunt de oefeningen doen op *elk moment* van de dag, bijvoorbeeld na het opstaan of wanneer u moe bent, bijvoorbeeld voor het slapen gaan. Kies een moment dat u *het beste uitkomt*. Dit kan per dag verschillen. B*ij voorkeur is het een vast moment* op uw dag, zodat u het niet vergeet.
- De fragmenten duren tussen de 5 en 10 minuten, zodat u het luisteren ervan makkelijk in uw dagelijks leven kan inpassen.
- Mocht uw fragment eindigen met muziek, voel u vrij dit af te luisteren.
- Mocht er iets zijn waardoor u de oefeningen als lastig ervaart, neemt u dan direct contact op met onderzoeker Jard Mattens via j.d.j.mattens@fsw.leidenuniv.nl. Dan kunnen we samen kijken voor een oplossing.

Wij wensen u veel succes en ontspanning met het luisteren!

VRH Thuisoefening Dag 1

“Welkom bij deze oefening voor dag 1 van de week. Zorg dat je een fijn kussen bij je hebt en je op een plek bent waar je niet gestoord wordt.

Ga maar lekker ontspannen liggen met je hoofd op een kussen. Leg je benen naast elkaar en laat je armen maar ontspannen naast je lichaam liggen. Doe je ogen maar dicht. Voel je hoofd ondersteund door het kussen. Is het kussen zacht, of is het wat harder? Probeer maar met gesloten ogen de kleur van het kussen voor je te zien. En misschien heeft het kussen wel een geur, … , of een bepaald gevoel. Is het een groot kussen? Voel je hoofd er maar op liggen. Heel goed.

En adem diep in. Terwijl je inademt, tel met mij mee van 1 tot 3, houd dan je adem vast en adem uit terwijl we terugtellen van 5 tot 1: 1,2,3, hou dat vast, en je merkt langzaamaan dat je steeds ontspannener begint te voelen. En adem uit: 5,4,3,2,1. En adem in 1,2,3, hou dat vast en uit 5,4,3,2,1. En dit doen we nog twee keer. Adem in 1,2,3, hou dat vast en uit 5,4,3,2,1. En adem in 1,2,3, hou dat vast en uit 5,4,3,2,1. En adem maar rustig door, op een manier die voor jou fijn is. Want je bent goed zoals je bent. Voel de spieren in je nek maar ontspannen, en in je schouders, misschien voel je je billen wel ontspannen, en je tenen. Voel je tenen maar.

En terwijl je zo lekker ontspannen bent, stel je maar voor dat je op je favoriete plek bent. … Waar ben je? … Hoe voel je je? … Wat zie je? … Misschien hoor je wel iets? … Misschien ruik je wel iets? Misschien proef je wel iets? Ervaar het maar en voel maar goed hoe fijn het is om daar te zijn. Het kan zijn dat je af en toe even weg dwaalt met je gedachten, en dat is ok. Je komt vanzelf weer terug in dit moment, naar deze plek. Misschien ben je wel met iemand? Ervaar het allemaal maar. Ontspan maar. Hoe voelt dat? Je doet het heel goed.

Vanaf nu ervaar je stukje bij beetje bewust en onbewust een steeds prettiger gevoel vanuit je huid, een aangenaam gevoel, zo zal je merken dat je aandacht steeds makkelijker naar andere dingen uit kan gaan dan je huid en je je steeds fijner voelt, en terwijl je je steeds fijner voelt, ben je je steeds minder van je huid bewust en zo komt het ook dat je op een gegeven moment helemaal geen behoefte meer zal voelen om aan je huid te zitten, stukje bij beetje, en zo voel je je steeds aangenamer. Je ontspant en weet dat je huid zo het snelst fijn aanvoelt. Je ontspant, en je huid gaat fijner aanvoelen en zo word je steeds beter in ontspannen zodanig dat ook wanneer je een keer niet ontspannen bent, je huid nog steeds fijn aanvoelt. En terwijl je huid zo aangenaam aanvoelt, ontspan jij weer, en jij weet dat je dit op elk moment kan inzetten, ook als je even denkt dat het niet kan kom je er vanzelf achter dat jij eigenlijk heel goed bent in ontspannen en een fijn gevoel geven aan je huid en met deze

oefeningen word jij er de komende tijd alleen maar beter in. Je ontspant, en je huid voelt steeds fijner aan, en dat gaat steeds gemakkelijker de komende tijd en als je dat eenmaal geleerd hebt, verleer je het niet meer: jij hebt onbewust de controle over jouw huid. Goed zo!
Zo meteen tel ik van 10 tot 1 en bij 1 ben je weer helemaal wakker en alert en in het hier en nu. 10, 9, je voelt je hoofd weer in het kussen liggen, 8, je zal de komende dagen merken dat de huid steeds een beetje meer tot rust komt, 7, je zult voelen hoe je steeds minder met je huid bezig hoeft te zijn zodat je huid steeds meer en meer ontspant, en dat je het daarmee steeds makkelijker en fijner gaat vinden om deze zelfoefeningen te doen en onder hypnose te gaan, dat dat zo steeds beter gaat lukken ook, 6, je bent goed zoals je bent, 5, helemaal zacht en ontspannen, 4, kom je langzaam weer naar het hier en nu, 3, misschien hoor je alweer wat, 2, en niet nu maar zo meteen bij 1 ben je weer helemaal wakker, alert en in het hier en nu en voel je je totaal zacht en ontspannen, 1. Wanneer het moment daar is voor jou mag je je ogen openen. “

VR Thuisoefening Dag 1

“Welkom bij deze oefening voor dag 1 van de week. Zorg dat je een fijn kussen bij je hebt en je op een plek bent waar je niet gestoord wordt.
Ga maar lekker ontspannen liggen met je hoofd op een kussen. Leg je benen naast elkaar en laat je armen maar ontspannen naast je lichaam liggen. Doe je ogen maar dicht. Voel je hoofd ondersteund door het kussen. Is het kussen zacht, of is het wat harder? Probeer maar met gesloten ogen de kleur van het kussen voor je te zien. En misschien heeft het kussen wel een geur, …, of een bepaald gevoel. Is het een groot kussen? Voel je hoofd er maar op liggen. Heel goed. Misschien dwalen je gedachten af en toe af, naar belangrijke dingen, en dat is goed, die dingen zijn belangrijk, en wanneer je dat erkent, kan je ze voor nu even loslaten, en breng je je aandacht weer helemaal naar mijn stem, naar het hier en nu, waar je bent, en waar alleen dat er even toe doet. Goed zo.
En adem maar eens diep in. En terwijl je inademt, tel met mij mee van 1 tot 3, houd dan je adem vast en adem uit terwijl we terugtellen van 5 tot 1: 1,2,3, hou dat vast, en je merkt langzaamaan dat je steeds ontspannener begint te voelen. En adem uit: 5,4,3,2,1. En adem in 1,2,3, hou dat vast en uit 5,4,3,2,1. En dit doen we nog twee keer. Adem in 1,2,3, hou dat vast en uit 5,4,3,2,1. En adem in 1,2,3, hou dat vast en uit 5,4,3,2,1. En adem maar rustig door, op een manier die voor jou fijn is. Voel de spieren in je nek maar ontspannen, en in je schouders, misschien voel je je billen wel ontspannen, en je tenen. Voel je tenen maar.
En vanuit die focus op je tenen, voel je langzaam hoe je ligt. Hoe je met je hele lichaam, je hele aandacht hier bent terwijl je luistert naar mijn stem. Hoe je je ontspannen en fijn voelt in het moment. Misschien voel je de ontspanning wel door je lichaam stromen. Voel maar of het snel stroomt, of rustig

aan, of het je hele lichaam, je spieren, al heeft losgemaakt in ontspanning, of dat het bezig is dat te doen. Voel maar hoe dit gevoel, dit proces voor jou voelt, terwijl je helemaal ontspannen kan. Blijf hier maar even… Heel goed. Vanuit deze ontspanning mag jij wanneer je daar klaar voor bent zo meteen je ogen weer opendoen. Dan ben je weer helemaal wakker en alert. Doe even rustig aan, gun jezelf de tijd, rek en strek wat, en drink misschien wat, voordat je verder gaat. Goed gedaan vandaag!

Appendix G: Heuristic evaluation principles virtual reality

Sutcliffe et al. (2004) describe the following twelve principles for the evaluation of virtual reality applications, along with the following problem-modification matrix for the evaluation of the identified usability problems.

Feature	Problem description	Problem rating	Design modification
Graphics			
Presence			
Interaction			
Environmental features			
Controls			
Hardware			

Heuristic	
1.	Natural engagement
2.	Compatibility with the user's task
3.	Natural expression of action
4.	Close coordination
5.	Realistic feedback
6.	Faithful viewpoints
7.	Navigation and orientation support
8.	Clear entry and exit points
9.	Consistent departures
10.	Support for learning
11.	Clear turn-taking
12.	Sense of presence

Figure G.1. Overview of heuristics and problem-modification matrix for evaluations of VR applications by Sutcliffe et al. (2004).

Appendix H: Heuristic evaluation questions

The heuristic evaluations were performed using *Qualtrics* (2005). After signing informed consent in Qualtrics, participants would automatically be guided to the Qualtrics evaluation form. Below an overview is presented of the questionnaire set-up along with a few test frames of the heuristic evaluations. The full (Dutch) Qualtrics questionnaires can be accessed through:

Informed consent form: https://leidenuniv.eu.qualtrics.com/jfe/form/SV_cCjuA2MRmdeH8do

Direct access to questionnaire: https://leidenuniv.eu.qualtrics.com/jfe/form/SV_1Bz0AkAnP3KktIa

Baseline questions (Dutch only)

Wat is uw geslacht?

- ○ Man
- ○ Vrouw
- ○ Anders
- ○ Zeg ik liever niet

Wat is uw leeftijd (in jaren)?

_____

Wat is uw hoogst behaalde opleidingsniveau?

- ○ Basisschool
- ○ Middelbaar onderwijs (e.g., MBO, HAVO, VWO)
- ○ Hoger beroepsonderwijs (e.g., HBO, WO)
- ○ Anders, namelijk: _____

Heeft u last van jeuk? Zo ja, welk van onderstaande oorzaken past het best bij uw jeuk?

- ○ Ik heb geen last van jeuk
- ○ Huidaandoening zoals eczeem, psoriasis, droge huid, schurft, galbulten/urticaria
- ○ Systemische aandoening, zoals lever- of nierfalen, bloedziekte, gevolg van medicijnen
- ○ Neurologische aandoening, bijvoorbeeld door zenuwschade
- ○ Somatoforme jeuk of aanhoudende jeuk zonder andere diagnose
- ○ Anders, namelijk: _____

Hoeveel jeuk heeft u de afgelopen 4 weken ervaren?

0: Geen jeuk — 10: Ergst voorstelbare jeuk

0 1 2 3 4 5 6 7 8 9 10

Jeuk 

Hoeveel jeuk ervaart u op dit moment?

0: Geen jeuk — 10: Ergst voorstelbare jeuk

0 1 2 3 4 5 6 7 8 9 10

Jeuk 

Hoe handig schat u uzelf in in het gebruik van computers? N.B. Wij testen dit niet. Het gaat erom hoe u dit zelf ziet.

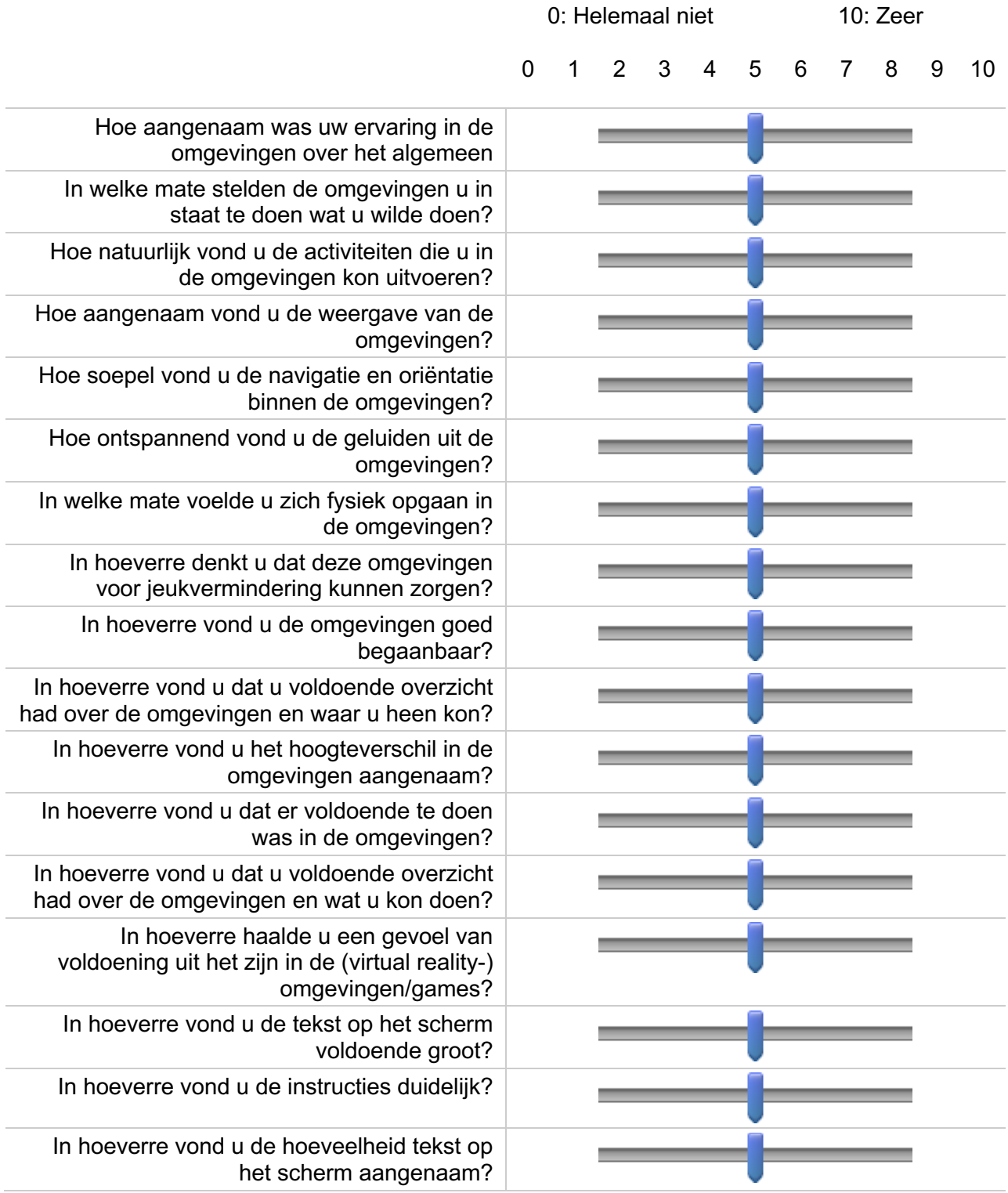
0: Heel erg onhandig (ik heb altijd hulp nodig) — 10: Heel erg handig

0 1 2 3 4 5 6 7 8 9 10

Computerhandigheid 

Evaluating VR-environments (Dutch only)

Beoordeelt u alstublieft de (virtual reality-)omgevingen/games met de volgende vragen op een schaal van 0-10.



Welke problemen en/of uitdagingen heeft u ervaren in de (virtual reality-) ervaringen/games?

_____

_____

Heeft u ideeën hoe deze problemen en/of uitdagingen (het beste) verholpen of verbeterd kunnen worden? Andere verbeterpunten zijn ook van harte welkom.

_____

_____

Kwam u op enig moment vast te zitten in de omgevingen? Zo ja, waar?

_____

_____

Heeft u nog ideeën wat u nog meer had kunnen of willen doen in de omgevingen/games?

_____

_____

Het is mogelijk op verschillende manieren door dit soort digitale omgevingen te navigeren. In deze omgevingen/games hebben we u laten wandelen met pijlknoppen, maar het is bijvoorbeeld ook mogelijk om stukken over te slaan. Zet de volgende opties op volgorde van uw voorkeur van meest naar minst aangenaam.

_____ Wandelen met pijlknoppen/joysticks
_____ Stukken overslaan (teleportatie) naar te selecteren vast plekken
_____ Stukken overslaan (teleportatie) naar plekken die u vrij kunt selecteren
_____ Geen voorkeur

Liep uw gezichtsveld ergens vast gedurende de ervaring? Zo ja, wanneer?

_____

_____

Zag u dingen die daar niet (zo) behoren? Zo ja, waar en wat?

_____

_____

Had u last van lichtflitsen of te fel licht? Zo ja, op welk moment?

_____

_____

Was er op enig moment sprake van te hard geluid? Zo ja, wanneer en waar?

_____

_____

Was er op enig moment sprake van te zacht geluid? Zo ja, wanneer en waar?

_____

_____

Heeft u nog suggesties voor jeukverminderende/ontspannende geluidsopnamen?
Wij laten u drie verschillende geluidsfragmenten horen ter inspiratie.
[Pixabay: Forest Wind & Birds, No Shame & Nature Walk]

_____

_____

Zitten er aspecten aan de (virtual reality-)omgevingen/games die bij u juist jeuk veroorzaakten of verergerden?

_____

_____

Heeft u nog ideeën voor elementen die wij kunnen veranderen of toevoegen om jeuk te verminderen? Denk bijvoorbeeld aan meer sneeuw en/of ijs, of andere veranderingen aan het ontwerp.

_____

_____

Heeft u verder nog opmerkingen en/of ideeën?

_____

_____

Hieronder ziet u een overzicht van de taken binnen de (virtual reality-) omgevingen/games per week van de behandeling. Onder aan het overzicht vindt u hier drie vragen over.

“De opdracht is om ...
Week 1: de (virtual reality-)omgeving te verkennen.
Week 2: te zoeken naar aanwijzingen voor de aanwezigheid van andere mensen in de omgeving.
Week 3: kubussen te vinden om later een beschutte plek mee te kunnen bouwen (aanklikken tot andere kleur).
Week 4: op zoek te gaan naar ballen als geluksbrengers (aanklikken tot andere kleur).
Week 5: de (al dan niet eerder gevonden) kubussen te ordenen door ze om te rollen tot de groene kant onder ligt, zodat er later makkelijker mee gebouwd kan worden. Er kan een begin gemaakt worden aan het bouwen van een beschutte plek met de kubussen (indien gewenst).
Week 6: voor het avondeten op zoek te gaan naar paddenstoelen. In deze omgeving zijn namelijk alle voorkomende paddenstoelen eetbaar.
Week 7: de dief te vinden die jouw kubussen gestolen heeft.
Week 8: de kubussen na de diefstal opnieuw te ordenen door ze om te rollen tot de groene kant onder ligt. Er kan ook een beschutte plek met de kubussen gebouwd worden (indien gewenst). ‘

In hoeverre denkt u dat de verhaallijn in de (virtual reality-)ervaringen/games interessant blijft?

0: Helemaal niet interessant 10: Zeer interessant

0 1 2 3 4 5 6 7 8 9 10

Heeft u nog ideeën/tips om de verhaallijn in de (virtual reality-) ervaringen/games interessant te houden?

_____

_____

Bovenstaande verhaallijn is gebaseerd op opdrachten. Een andere mogelijkheid is om geen opdracht te hebben, maar gewoon te concentreren op ontspanning. Waar gaat uw voorkeur naar uit?

- ○ Een vaste opdracht per week
- ○ Een optionele opdracht
- ○ Geen opdracht
- ○ Geen voorkeur

Evaluating hypnosis script and audio recordings (Dutch only)

A questionnaire was developed to propose factors that could be of influence on the effectiveness of hypnosis and relaxation recordings. Questions were designed in seven distinct categories with three additional general questions: (1) voice, (2) pace, (3) maintaining attention, (4) inducing relaxation, (5) suggestion content, (6) duration, (7) adherence and overcoming barriers. The following general questions were added to the evaluation: (8) importance of presence hypnotherapist, (9) importance of supplier entity, (10) other recommendations.

Deel 1: Audio fragmenten

Hoe aangenaam vond u het om naar de stem te luisteren?

0: Erg onaangenaam Erg aangenaam

0 1 2 3 4 5 6 7 8 9 10

Heeft u opmerkingen of aanbevelingen over hoe wij de luisterervaring met betrekking tot de stem, de intonatie, etc. ervan kunnen verbeteren?

_____

_____

Hoe prettig vond u het tempo van de ontspanningsoefeningen?

0: Helemaal niet prettig 10: Zeer prettig

0 1 2 3 4 5 6 7 8 9 10

In hoeverre dwaalden uw gedachten (op niet ontspannen manier) af tijdens het luisteren naar de ontspanningsoefeningen?

0: Helemaal niet 10: Heel erg

0 1 2 3 4 5 6 7 8 9 10

In hoeverre voelde u zich ontspannen door het luisteren naar de ontspanningsoefeningen?

0: Helemaal niet 10: Volledig

0 1 2 3 4 5 6 7 8 9 10

Wat hielp om u meer te ontspannen? Wat hielp hier niet bij?

_____

_____

Wat vindt u van de totale duur van de ontspanningsoefeningen?

0: Veel te kort 10: Veel te lang

0 1 2 3 4 5 6 7 8 9 10

Hoezeer zou u elke dag naar een dergelijke ontspanningsoefening luisteren als dit onderdeel uit zou maken van een medische behandeling?

0: Helemaal niet 10: Altijd

0 1 2 3 4 5 6 7 8 9 10

Wat zouden barrières kunnen zijn voor mensen om elke dag naar dergelijke ontspanningsoefeningen te luisteren? En heeft u suggesties om deze barrières te overwinnen?

_____

_____

Wat verwacht u dat u voor u beter zal werken om onder hypnose te gaan: een (fysiek aanwezige) hypnotherapeut of een door een hypnotherapeut opgenomen audiofragment?

Sleept u de volgende stellingen op volgorde van meest naar minst mee eens.

_____ Een audiofragment van een hypnotherapeut zal voor mij waarschijnlijk beter werken om onder hypnose te gaan dan een sessie met een (fysiek aanwezige) hypnotherapeut.
_____ Een sessie met een (fysiek aanwezige) hypnotherapeut zal voor mij waarschijnlijk beter werken om onder hypnose te gaan dan een audiofragment van een hypnotherapeut.
_____ Ik verwacht dat beide interventies op mij een gelijk effect zullen hebben.
_____ Ik heb geen idee.

Sleep de volgende stellingen op volgorde van meest naar minst mee eens.

_____ Luisteren naar oefeningen die ter beschikking worden gesteld vanuit de behandelaar is meer effectief in een medische behandeling gericht op ontspanning dan luisteren naar zelfgekozen oefeningen/muziek/podcasts van het internet.
_____ Luisteren naar zelfgekozen oefeningen/muziek/podcasts van het internet is meer effectief in een medische behandeling gericht op ontspanning dan luisteren naar oefeningen die ter beschikking worden gesteld vanuit de behandelaar.
_____ Beide interventies zijn mijns inziens gelijkwaardig.
_____ Ik heb geen idee.

Deel 2: Scripts

Hieronder leest u **twee** korte fragmenten met suggesties.

Fragment 1:
"Zachtheid, fijne koele rust, alsof er een aangenaam verzachtend, rustgevend briesje langs je heen gaat. Nu, en ook straks, zal je gevoel, in je hoofd en in je huid alleen maar aangenamer worden. Misschien dat het in het begin nog af en toe wegblijft. Je hoeft alleen maar goed voor jezelf te zorgen, te ontspannen, en daarin zal je rust vinden. Jij weet dat je elk moment dit gevoel van verzachtende koelte en rust kan oproepen door aan dit moment te denken."

Fragment 2:
"Nu, en ook straks, zal je gevoel alleen maar fijner worden. Ook straks kan je af en toe nog uit balans raken, dat hoort erbij. Maar jij hebt ondertussen al geleerd hoe jij de balans hervindt en behoudt, en je blijft daar continu steeds beter in worden, vanuit jouw natuurtalent. Een natuurtalent voor aangename stabiliteit. De komende tijd wordt een verdere ontdekkingsreis naar jezelf, waarom vind ik leuk wat ik leuk vind, waar heb ik behoefte aan, en je gaat de balans uitdagen, de controle opzoeken in de rust. Gedurende deze reis ontdek je dat je huid steeds makkelijker ontspant, voel jij je steeds fijner, en weet je dat fijne gevoel ook steeds makkelijker vast te houden, roep je het sneller op, geheel vanuit jezelf."

In hoeverre vindt u dat de inhoud van de suggesties in de fragmenten overeenkomt met het gewenste effect, namelijk om jeuk te verminderen en algemeen welbevinden te vergroten?

0: Helemaal niet 10: Volledig

0 1 2 3 4 5 6 7 8 9 10

Zou u andere suggesties hebben gegeven? Zo ja, welke suggesties zou u hebben gegeven?

_____

_____

Heeft u nog andere opmerkingen, tips of ideeën voor ons?

_____

_____

Screen impressions of the Qualtrics evaluations

Figure H.1. Overview of the Qualtrics evaluation surveys on screen

Appendix I: Computer specifications

The computer used for the heuristic evaluations had the following specs, confirming to the minimal specs as detailed by Meta (2023) and Vive (2023) respectively:

OMEN by HP Gaming Laptop 16-c0xxx

- Processor: AMD Ryzen 9 5900HX with Radeon Graphics, 3301 Mhz, 8 Core(s), 16 Logical Processor(s)
- Graphics card: NVIDIA® GeForce® RTX 3070 3,30 GHz
- Memory: 16,0 GB RAM
- Video out: DisplayPort 1.4
- USB ports: UCM-UCSI ACPI Device
- Operating system: Windows 11

Appendix J: Risk analysis and risk management plan for clinical trial

Benefit-Risk Analysis

The benefit of using the device is experimental but promising. Based on the previous studies regarding the use of either hypnosis or VR in people with chronic itch [e.g. Leibovici et al., 2009; Lopes et al, 2020; Baschong et al., 2021], it is expected that itch intensity will on average decrease as a result of the interventions [see also section 1 in protocol C1]. Given adequate management of the risks below as described, the overall benefit-risk ratio is therefore expected to be significantly favorable towards using the device.

Evaluation and control of known and foreseeable hazards of the device set-up

Below follow descriptions of the identified risks and the envisioned adopted control measures.

Risk of Injury During Use

Mechanical injury

To reduce the risk of injury during use due to imbalance or collision with objects or walls, participants are seated during the intervention. There are no sharp components on the devices. This makes the injury risk acceptable.

Electric/thermic effects (active device)

Leakage current (earth leakage, enclosure leakage), magnetic fields, static discharge, voltage and hyperthermic effects need furthermore to be taken into account when using active devices. Risks are acceptable given normal use conform the user manuals of the individual products along with the exclusion criteria and warnings in the information letter E1/E2 provided to the participants and checked with them (e.g. exclusion of people with active implantable devices). Every time before use, the status of the VR set up is checked according to the user manuals.

Contra-indications, participant exclusion and medical risk reduction

Contra-indications for participation in the study are mentioned in section 1.1c on page 7 in this document and in protocol C1 section 4.3 and the participant information letter E1/E2 as exclusion criteria. The contra-indications are checked verbally with each participant as well before enrollment in the study.

The exclusion criteria precautiously include any active implantable device (such as a defibrillator or pacemaker), or any other vital dependency on an electric device according to the warnings set by the VR device manufacturers (see e.g. the attachments "IMDD 2.a Meta Information Sheet" and "IMDD 2.a HTC Safety and Regulatory Guide incl. EU Declaration of Conformity"). In this way, risk associated with device interference and associated critical dysfunction is reduced to acceptable level.

Other exclusion criteria include a history of epilepsy, migraines, balance problems, susceptibility to motion sickness, (severe) psychiatric comorbidities and face, head, neck, or palmar hand injury. In this way, risks for epileptic responses and/or other light sensitive reactions [e.g. Kasteleijn-Nolst Trenité et al., 2010], for VR-related motion sickness and instability [e.g. Chattha et al., 2020], for panic attacks (reported in 0.4% of VR-user cases [Schaefert et al., 2014]), and for ergonomic challenges are reduced to acceptable level for the combination of the VR component and the hypnosis [e.g. Coe et al., 1979; Hammond, 2007].

Furthermore, if the participant does not want to undergo hypnosis, the treatment will not work and there will be no effects, nor side effects. The participant may at all times during the intervention close their eyes and/or take off the VR-glasses. A researcher is always present to (temporarily) halt the treatment in case this desire, or necessity may arise.

Contamination of device

Contamination of the device is a serious risk that needs to be taken into account given the vulnerable testing population. Therefore, the following standard operating procedure for disinfection and contamination prevention by Roberts et al. (2022) is followed.

The suggested standard operating procedure for the disinfection of virtual reality devices by Roberts et al. (2022) is used:

Before use

- *The device is not used in contact with lesional skin or in patients with active infections on the head or hands that cannot be covered. This is omitted by the clause facial, head or neck injury in the exclusion criteria.*

- *The participant and researchers perform hand hygiene.*
- *The devices are disinfected using alcohol and antibacterial wipes to make sure that all surfaces of the headset, the controllers, and the face cover are adequately cleaned. A wipe is used on one single device only.*
    - *The hair is covered using a surgical cap.*
    - *The VR glasses will be covered with a face cover to prevent the glasses from touching the patient's face.*

After use

- *The participant and researchers perform hand hygiene.*
- *The researchers wear nitrile gloves unless circumstances require other personal protective equipment.*
- *The VR glasses and controllers are taken from the participant and put on a clean disposable padding.*
- *The disposable face cover is discarded.*
- *Disposable wipes are used to clean visibly dirty areas on the VR glasses and controllers.*
- *Disinfection is redone as described in "Before use" above.*
- *The VR glasses and controllers are put to dry.*
- *The equipment is then stored in a dry place, separate from nondisinfected equipment.*
- *The participant and researchers perform hand hygiene again.*

In this way contamination risks are reduced to an acceptable level.

Allergic reactions

To materials of the equipment

Skin irritation/allergic reactions to the foam on the VR glasses touching the face have been reported in a very minor part of the user population. It is estimated that it concerns 0.01% of the user population, mostly mild cases resolving on their own [Meta, 22 December 2020]. For HTC Vive, some incidental reports of skin irritation after use can be found on internet fora [e.g. TheLoneTenno on Reddit, 2019]. HTC has not reported upon necessity to change materials.

To optimize safety, we decided to use the Meta Quest 2 silicone cover provided by Meta to minimize allergic reactions in this vulnerable research population to an acceptable risk. For the HTC glasses, it is chosen to use the glasses as they come.

For hygienic purposes the VR glasses are complemented with a disposable facial VR mask, e.g. ones made from spunlace (viscose and polyester mix). Such fabrics are widely used in clothing as well and are in themselves only very rarely a causative agent of allergic reactions [e.g. Svedman et al., 2019].

In case there may be any allergic reaction to the gloves provided, there may be decided for alternative gloves on individual basis dependent on which gloves are free from allergic reactions in that individual.

In this way, the materials constitute an acceptable risk.

To the disinfectant

The devices are disinfected using alcohol and antibacterial wipes. Being used as major disinfectant in hospitals all over the world, alcohol and antibacterial wipes have a comparably minimal risk for induction of allergic contact dermatitis. By furthermore letting the components dry adequately (minimum 3 min), by using e.g. the face masks and surgical caps, and given the limited time spend in contact over the whole treatment duration, the contact with the disinfectants is minimized. Therefore, the use of this disinfectant constitutes an acceptable risk.

Data

The device does not collect any patient data. Hence no risk is involved on that end for the device itself. Patient data that is collected for the study is treated according to described in the research protocol C1.

Delivery challenges: sound/light distortions, quantity, etc.

Risk for sound and/or light distortions in the VR environment are minimized through user evaluations according to the VR evaluation principles described by Sutcliffe et al. (2004), which also ensure an appropriate duration and content of the treatment.

For safety reasons, a researcher is always present during the interventions. The researcher can always see on a screen what the participant is seeing and can help the participant halt the treatment and/or restart the treatment if necessary. The participant is explicitly instructed beforehand and during the treatment again that they can always during the treatment approach the researcher by talking out loud. Audio volume is checked beforehand with the participant.

In this way any medical risks and risks on discomfort are taken care of and reduced to acceptable.

Functionality

Ergonomics and critical performance

The VR set up including headset, controllers and gaming laptop consists of products that are separately CE certified and readily available on the market. This ensures ergonomic functionality and critical performance. Still, a researcher is always present for evaluation and adaptation if necessary and risks are reduced to acceptable.

Device maintenance

VR set up components are stored, treated, and maintained according to the prescriptions by the manufacturers as detailed in amongst others their information sheets and user manuals as referred to in section 2 of this brochure to ensure optimal functioning with acceptable risks.

Inclusive instructions

The technical competencies and learning abilities of the participants may vary. There is always a researcher present, to take care of the full set up. Instructions may be repeated. Also, the most important instructions, e.g. what to do when you feel sick (close your eyes and talk out loud to the researcher) are repeated in the scripts within the VR also every time. As it is furthermore not the exact task in VR to achieve something other than to explore and use the VR for relaxation, technical competence is not a determining factor and no risks are expected.

Compatibility and technical problems

All products are individually compatible according to the manufacturer's requirements (see also section 1.1 L).

The full set up and its functionality are tested by the researcher before arrival of the participant. A back-up compatible game laptop and VR set are available within reasonable time frame. In case this may for any circumstance not provide a solution at the time, the participant is notified as soon as possible, reimbursed for travel costs and, if indicated, an appointment at a different date is arranged as part of the study.

Procedure technical problems

In case a problem arises before an intervention session, the set up will first be investigated and if necessary, restarted. If this does not provide a solution, it may be opted to replace the components. The VR glasses and their controllers may be replaced by other VR glasses of any of the types mentioned in section 1.1a of this brochure and the laptop may be replaced by another laptop that is compatible with the requirements set by the VR glass manufacturer as described in section 1.1 L of this brochure.

In case a problem arises during an intervention session, the software may be restarted and/or the hardware replaced similarly. On-site technical support is available. VR environments as designed in Unity can be halted and/or restarted by a simple click any time by the researcher and/or the participant in case this is desired or necessary. The VR glasses can be taken off any time and patients are instructed to do so, or to close their eyes and say so out loud for the attending researcher in case they experience any significant discomfort related to the intervention. In any case, the patient will be taken care of by the researcher with hypnosis qualification to ensure the patient is deduced from hypnosis adequately. In case it appears possible to solve the problem within reasonable time, the treatment session may be restarted from the beginning. Otherwise, the patient will be apologized, reimbursed and, if indicated, a different date will be set.

In these ways risks involved with technical malfunction are reduced to acceptable levels.

Instructions Intended Use

Before the start of the first intervention with the device, the VR environment is introduced shortly without hypnosis record, and with instructions from the researcher, where necessary, to ensure the participants knows about the functionality of the system. During the subsequent treatments, the researcher can also watch along with the participant in the environment on a screen. In this way, it can be checked whether the device is used correctly and risks for misuse are acceptable.

Communication residual risks

Residual risks, e.g. risk of fear and motion sickness, are included in the information letter provided to the participants. The participants are instructed to inform the researchers in case they experience any symptom new to them, or in case any symptom worsens during the intervention period. Together, it will then be individually evaluated whether the participant stays on the study and recommendations for help may be given.

In case of a serious incident

In case a serious incident happens during the intervention sessions with the device, the researcher takes care of reporting the incident to the manufacturer and the authorities in The Netherlands, i.e. the Medical Ethical Committee Leiden-The Hague-Delft and the Inspectorate, according to the legal protocol as amongst others delineated on https://english.igj.nl/medical-technology/market-supervision/vigilance-reporting-incidents-and-corrective-actions/report-incidents-and-field-safety-corrective-actions.

Appendix K: Short version research proposal clinical trial

OBJECTIVES

Primary objective

The primary objective in this study is:

- *To analyse whether virtual reality-assisted hypnosis (VRH) and virtual reality (VR) can lead to clinical itch relief at the end of treatment and at follow-up (6 weeks after the last treatment session) in adults suffering from chronic itch when compared to baseline. It is expected that VR/VRH (i.e. the combined group) leads to a significant reduction in clinical itch intensity.*

Secondary objectives

The secondary objectives are:

- *To assess whether VR/VRH is a useful technique [within group] (with clinically relevant effect) and (if data allows) more useful than VR [between group] [end of treatment and follow-up compared to baseline] in terms of*

(a) the impact of the itch and overall wellbeing (Impact of Skin Disease on Daily Life (ISDL) scales for skin status, physical symptoms, scratching, impact of illness, psychological functioning, and illness cognitions; and the Hospital Anxiety and Depression Scale (HADS))

VR/VRH is hypothesized to be an effective strategy in reducing (itch-related) psychological distress. VRH is furthermore hypothesized to be more effective than VR alone.

(b) medical treatment need (type of drug/treatment x quantification)

It is expected that VR/VRH leads to a significant reduction in itch treatment need. VRH is furthermore hypothesized to be more effective than VR alone

(c) itch sensitivity (upon application of cowhage)

It is expected that VR/VRH leads to a significant reduction in itch sensitivity. VRH is hypothesized to be a more effective strategy in reducing itch sensitivity than VR alone.

Exploratory objectives

Further exploratory objectives are:

- To investigate the influence of individuals' hypnotic susceptibility and the effect of the VR/VRH intervention on the effects on clinical itch intensity [at end of treatment and follow-up].

It is expected that both the VRH and the VR intervention do not depend in their effectiveness on an individual's hypnotic susceptibility.

- To investigate the influence of the participants' treatment confidence in VR/VRH and the effect of the VR/VRH intervention on the effects on clinical itch intensity [at end of treatment and follow-up].

Higher treatment confidence is expected to be a predictor of higher treatment success.

- To investigate the influence of the participants' perceived sense of presence in VR during the VR/VRH intervention on the effects on clinical itch intensity [at end of treatment and follow-up].

Higher sense of presence in VR/VRH is expected to be a predictor of higher treatment success.

STUDY DESIGN

Measure overview

The measures used to study the objectives described above are described below:

- Hypnotizability is measured by the Stanford Hypnotic Susceptibility Scale C [e.g. Näring et al., 2001; Weitzenhoffer & Hilgard, 1962] by an experienced hypnotherapist who will bring the participants in hypnosis and give the suggestions according to the scale to determine the extent to which the individual participants respond to the suggestions. The total score ranges from 0-12, where a higher score (full points only) characterizes more easily hypnotized participants. Low hypnotizable participants score 0-3, medium hypnotizable participants score 4-8, and highly hypnotizable individuals score 9-12.

<u>Questionnaires</u>:

- A Numerical Rating Scale (NRS) score 0-10 is used for quantification of the itch intensity (0 represents no itch at all and 10 represents worst imaginable itch) [e.g. Kimball et al., 2016].
- The impact of the itch on the participants' overall wellbeing is measured by the Impact of Skin Disease on Daily Life (ISDL) Questionnaire [Evers et al., 2008]. The following subscales are used: (1) skin status (items 7 t/m 10), (2) physical symptoms (items 11 to 16), (3) scratching (items 17 to 23), (4) impact of disease on daily life (items 24 and 26), (5) psychological functioning (items 27 and 28), and (6) illness cognitions (items 31 and 32).
- The hospital anxiety and depression scale (HADS) [Zigmond et al., 1983] is used to assess the development of anxiety and depressive symptoms over the course of the study.

- Treatment confidence is measured through an adapted General Attitude towards Medication Questionnaire (GAMQ) [Tekampe et al., 2019]. Instead of “medication”, in this scale of items rated on a 5-point Likert scale “VR/VRH treatment” may be read.
- A Numerical Rating Scale (NRS) score 0-10 is used for quantification of sense of presence in VR/VRH (0 on this scale represents no feeling of presence in the virtual environment at all and 10 represents a feeling of complete sense of presence in the virtual environment) [e.g. Witmer & Singer, 1998].

Overview general procedures

The study is set up in the first place, as a within group comparison for both conditions (VRH and VR) merged, comparing pre-intervention, post-intervention and follow-up, and the comparison between the two treatments in the second place. An overview of the study process is depicted in Figure K.1 below.

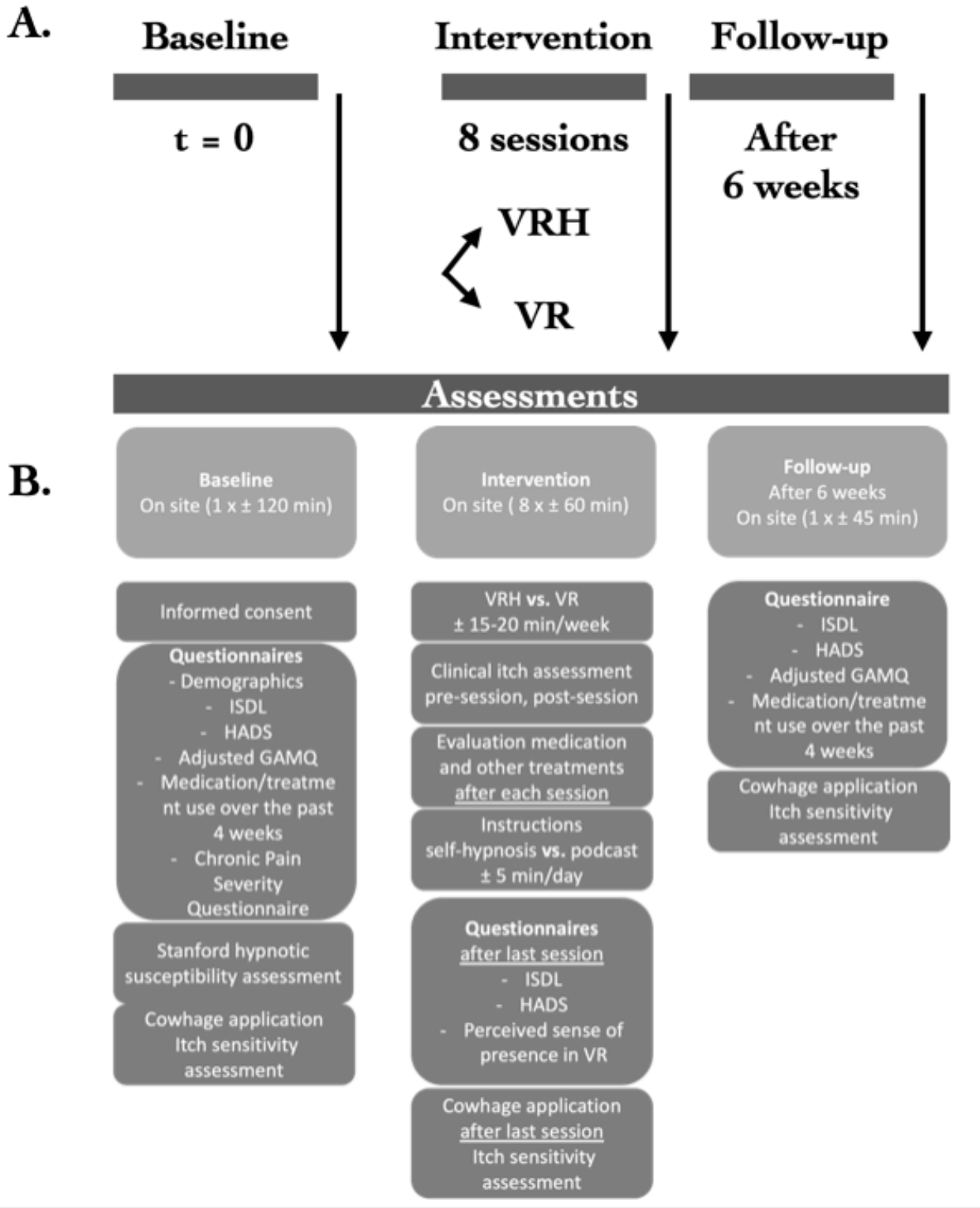


Figure K.1. Overview of the study process, with a timeline (A) and an overview of the assessments (B). ISDL= Impact of Skin Disease on Daily Life scale, HADS = Hospital Anxiety and Depression Scale, GAMQ = General Attitude towards Medication Questionnaire.

Baseline assessments

Upon showing interest, potential participants are at first contacted over phone and/or email to answer possible questions before participation and to affirm the criteria for participation are met. When the individual agrees on participating (via phone or email at any time after this first contact) an individual on-site 2-hour baseline session will be conducted. In *figure K.1B* an overview is given of the assessments during this session.

Firstly, written informed consent is requested and the participants are requested to sign that they do not meet any of the exclusion criteria. Secondly, the participants are asked to fill out the questionnaires as listed above in paragraph 3 under measure overview online via *Qualtrics* (2005). Furthermore, participants are asked for their medication usage and/or other itch-directed treatments (e.g. light therapy) they have had over the last 4 weeks. As next step, cowhage spicules (25 spicules) are rubbed on the participants' forearm (or at the closest non-lesional site) for 45 seconds and the participants are asked to rate the subsequent itch sensitivity on the 0-10 NRS for itch for in total up to 4 minutes [e.g. Blythe et al., 2021; Weng et al., 2022]. Hereafter, the spicules are removed with skin-friendly tape (3M), and water will be used to rinse the arm to definitely remove all spicules. Lastly, the participants' individual hypnotic susceptibility (Stanford Hypnotic Susceptibility Scale C [e.g. Näring et al., 2001]) is evaluated by an experienced hypnotherapist who will bring the participants in hypnosis and give the suggestions according to this scale.

After the baseline session, the participants are randomized over the two intervention conditions: VRH and VR. Before and after each intervention session, the participants are asked for their current itch intensity on a 0-10 NRS. Before each intervention session, the participants are also asked for an update on their medication use and/or other treatments they may have received.

After the last treatment session, an additional questionnaire is provided containing the questionnaires administered at baseline as well as some questions on the perceived sense of presence in VR/VRH during the treatment sessions on a 0-10 NRS (see *figure K.1B*). Also, cowhage is applied to the skin in a similar fashion as during the baseline session to assess itch sensitivity.

Intervention: VRH (± 15-20 min per session)

For the VRH condition, throughout the hypnotic induction, the participants will experience a VR environment designed based on input from individuals suffering from chronic itch. After the induction, assisted with the VR environment, the participants are instructed to close their eyes, while they will continue to listen to the recorded hypnotic script developed based on general hypnotic principles as

amongst others described by Yapko (2013). Direct antipruritic suggestions are used such as "*your skin will feel so soft, relaxed and cool, it is fully at ease*". After these standardized suggestions, the participants will be alerted again.

Control: VR (± 15-20 min per session)

For the VR condition, participants will experience the same VR environment while listening to an informative podcast without the hypnotic induction and suggestions.

Home exercises (± 5 min per day)

The participants on the VRH condition are provided with six different recorded guided self-hypnosis records with direct antipruritic suggestions (for each day of the week excluding the treatment day, for the duration of the intervention).

The participants on the VR condition are provided with six different informative records for a similar duration without (antipruritic) suggestions (see *figure K.1B*).

Follow-up

Six weeks after the last treatment session, a follow-up session of about 45 minutes is organized with a final questionnaire containing the same questionnaires as at baseline (see *figure K.1B*). Next, cowhage is applied to the skin of the participant and itch sensitivity is assessed again in a similar manner as during the baseline and final treatment sessions. Lastly, participants are given tips to continue applying the interventional techniques.

STUDY POPULATION

Population (base)

Twenty adults aged between 18-80 years and suffering from chronic itch for at least 1 year before entering the study will be eligible for inclusion in the study.

Inclusion criteria

Adults (aged 18-80 years) with chronic pruritus of any origin for at least 1 year prior to inclusion in this study, who have been seen by a physician for the itch. The itch leads to psychological and/or functional impairment despite standard medical treatment. Patients should speak and understand Dutch and be able to complete questionnaires.

Exclusion criteria

Exclusion criteria are severe psychiatric comorbidities irrelated to their itch condition such as psychosis or severe clinical depression or anxiety disorder (anxiety and depressive symptoms in itself are common in individuals with chronic symptoms and therefore no reason for exclusion); history of seizures; history of severe migraine; severe susceptibility to motion sickness; balance problems; face, head, or neck injury; visual or audiological impairment; pacemaker, defibrillator and/or other electronic (implantable) device of vital importance; pregnancy or when lactating; and participation in another interventional itch study.

Sample size calculation

In view of the effect sizes (Cohen's d) of VR, VRH or hypnosis when comparing baseline with post-intervention (within-group effect) itch or pain ratings in previous studies, ranging from 0.36 to 1.17 [Patterson et al., 2006, 2010; Leibovici et al., 2009], an estimated effect of 0.8 is used for the sample size calculation. Based on a two-tailed paired t-test, this results in a required sample size of 20 participants for the main effect pre/post intervention (within subjects), with an alpha of 0.05 and a study power of 90%. The study sample size is calculated using G*Power 3 [Faul et al., 2007]. See paragraph 8.5 for the participant replacement protocol.

METHODS

Main and secondary study parameters/endpoints

The main goal of study is to assess whether VR/VRH intervention is effective [primary objective, within-group], with VRH being more effective than VR alone [secondary objective, between-group], in itch mitigation on short (directly after the first session and after the set of 8 sessions) and longer term (up to 6 weeks post treatment), in terms of:

a) Itch intensity (0-10 NRS), comparing end of treatment (primary endpoint) and follow-up (secondary endpoint) with baseline.

b) Itch treatment need (type x quantification), comparing end of treatment and follow-up with baseline (secondary endpoint).

c) Itch-related psychological wellbeing as measured using the Impact of Skin Disease on Daily Life (ISDL) subscales for skin status, physical symptoms, scratching, impact of disease, psychological

functioning, and illness cognitions, comparing end of treatment and follow-up with baseline (secondary endpoint).

d) Psychological distress as measured using the Hospital Anxiety and Depression Scale (HADS), comparing end of treatment and follow-up with baseline (secondary end- point).

e) Itch sensitivity (0-10 NRS) (upon application of cowhage spicules), comparing end of treatment and follow-up with baseline (secondary endpoint).

Other study parameters

Explorative objectives are to investigate:

- whether participants' hypnotic susceptibility has an influence on the effect of the VR/VRH intervention on the difference in clinical itch intensity (at the end of treatment and for follow-up compared to baseline).
- whether the participants' treatment confidence in VR/VRH has an influence on the effect of the VR/VRH intervention on the difference in clinical itch intensity (at the end of treatment and for follow-up compared to baseline).
- whether the participants' perceived sense of presence in VR during the VR/VRH intervention has an influence on the difference in clinical itch intensity (at the end of treatment and for follow-up compared to baseline).

Randomization, blinding and treatment allocation

Patients are randomly assigned to one of two conditions (VRH/VR), while being stratified for initial worst clinical itch intensity over the previous 4 weeks (baseline) (low-moderate 0-5, high 6-10 on NRS 0-10) and hypnotic susceptibility (low 0-3, medium 4-8, high 9-12, on the Stanford Hypnotic Susceptibility Scale C [e.g. Näring et al., 2001] as described in the measures overview in section 3). After the baseline session, a participant is appointed to one of the six strata (see example below) after which simple randomization is used to determine the treatment the participant receives. An online random sequence generator [e.g. Urbaniak et al., 2013] is used to specify the treatment allocation order per stratum, with the aim to equally divide the participants over both conditions (using a block design).

<u>Example</u>:

Stratum # (hypnotic susceptibility L/M/H, itch intensity L/H): sequential allocation of participants over groups (1=VR, 2=VRH)

Stratum 1 (L,L): 1, 2, 1, 2 - 1, 1, 2, 2

Stratum 2 (M,L): 2, 1, 1, 2 - 1, 2, 2, 1

Stratum 3 (H,L): 1, 1, 2, 2 - 1, 1, 2, 2

Stratum 4 (L,H): 2, 1, 2, 1 - 2, 1, 1, 2

Stratum 5 (M,H): 1, 1, 2, 2 - 2, 1, 2, 1

Stratum 6 (H,H): 2, 1, 2, 1 - 1, 2, 1, 2

Study procedures

After inclusion in the study including given written informed consent, the participants will be invited for an on-site *baseline* session. After this session, the participants are randomized to either a VRH or VR intervention of 8 sessions, together spanning a total of 9-20 weeks, followed by six weeks till the follow-up session *(figure K.1).*

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.

Specific criteria for withdrawal

In case any doubt may arise concerning the fulfillment of the inclusion criteria, the participant may be expelled from the study by the researchers.

In case a participant scores very high on the Hospital Anxiety and Depression Scale (HADS) [Zigmond et al., 1983], or any other severe medical complaint may come up, the participant will be referred to the own general practitioner.

Replacement of individual subjects after withdrawal

In case less than 70% of a participant's data can be obtained (e.g. due to early withdrawal or technical issues) and/or less than half of the interventional sessions is attended, a replacement participant will be included in the respective intervention condition. Furthermore, an intention-to-treat analysis will be used.

Follow-up of subjects withdrawn from treatment

Subjects withdrawing from the study are approached once after withdrawal to ask whether they want to state their reasons for withdrawal - in order to know whether withdrawal is study-related - and they will be asked to indicate their current itch intensity.

Premature termination of the study

In the unlikely case that half through the study, in ³50% of the participants a considerable increase in itch is observed after the intervention, the study will be terminated prematurely.

STATISTICAL ANALYSIS

Primary and secondary parameters

The main goal of study is to assess whether a VR/VRH intervention is a useful technique [primary objective, within-group], and more useful than VR alone [secondary objective, between-group], in itch mitigation on short (directly after the first session and after the set of 8 sessions respectively) and longer term (up to 6 weeks post treatment), in terms of:

a. Itch intensity (continuous variable, 0-10 NRS), comparing end of treatment (primary end-point) and follow-up (secondary endpoint) with baseline.

For this assessment a repeated measures ANOVA with as within subjects factor "time" with three levels (baseline, end of treatment, follow-up), and as between subjects factor "group" (VRH vs. VR) is used. For the primary endpoint we will look at the main effect of time (disregarding the factor group). This analysis is applied similarly to the secondary endpoints in b-d below, where the interaction effect will be primarily looked at.

b. Itch treatment need (type x quantification), comparing end of treatment and follow-up with baseline (secondary endpoint).

c. ISDL subscales for skin status, physical symptoms, scratching, impact of disease, psychological functioning, and illness cognitions, comparing end of treatment and follow- up with baseline (secondary endpoint).

d. HADS for the quantification of anxiety and depression symptoms, comparing end of treatment and follow-up with baseline (secondary endpoint).

e. Itch sensitivity in response to cowhage application (continuous variable, 0-10 NRS), comparing end of treatment and follow-up with baseline (secondary endpoint).

Other study parameters

For the explorative objectives, regression analyses are planned with as dependent variable the difference in clinical itch intensity (0-10 NRS) at the end of treatment minus baseline and at follow-up minus baseline for the VR/VRH intervention and the following predictors:

- individuals' hypnotic susceptibility (categorical variable, 0-12 Stanford Hypnotic Susceptibility Scale C).
- the participants' treatment confidence in VR/VRH (categorical variable, GAMQ score)
- the participants' perceived sense of presence in VR during the VR/VRH intervention (continuous variable, 0-10 NRS).

Missing data on the primary objective will be compensated by inclusion of an additional participant. Furthermore, an intention-to-treat analysis is used. In the case that too much data is missing to perform the ANOVAs and regression analyses, multilevel analyses will be conducted with the data available.

Interim analysis

No *a priori* interim analyses are planned. However, in the unexpected case that itch seems to worsen in many patients, we will conduct analyses halfway data collection (See 8.7).

ETHICAL CONSIDERATIONS

Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Recruitment and consent

The participants will be recruited through convenience sampling. That means the participants may be recruited in diverse ways. The information folders may be spread through our research networks, patient societies, and social media, and they will be placed in the waiting rooms in the department of dermatology of the Amsterdam UMC and the Leiden University Treatment and Expertise Center (LUBEC), a center focused on the treatment of psychological consequences of somatic diseases. Here, medical doctors, psychotherapists, researchers etc. may make people aware of the research,

without any obligations. Furthermore, the information folders may be send to people who have previously indicated a wish to stay updated on our research concerning chronic itch.

Upon subsequent expression of interest, potential participants receive written information about the study (see Section E). Participants are informed about the study procedures, and they are informed that the study investigates the effectiveness of a hypnosis and virtual reality intervention against itch. After receiving the written information, potential participants can choose to fill out the screening questionnaires. When potential participants meet the inclusion criteria, they are invited to take part; the sessions are planned in consultation with the participant. At the beginning of the first session, participants will sign the informed consent form. After participation, participants will be debriefed.

The researchers involved in this research are responsible for obtaining the informed consent.