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Submitted to: JMIR Research Protocols
on: October 30, 2024

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Abstract

Background: Phantom limb pain (PLP) affects the majority of people living with lower limb amputations (LLAs). Nonpharmacological interventions, such as graded motor imagery (GMI), have demonstrated promise as PLP treatments. However, GMI access is limited by low patient buy-in and long public outpatient wait times. Considering PLP has been shown to be more prevalent and severe immediately following LLA, there is an urgent need to bypass barriers to allow for more prompt access to PLP interventions. In response to this need, the current multidisciplinary research team developed a virtual reality (VR) program that administers GMI treatment. This novel intervention may be completed independently and promptly within the postoperative acute care setting. Prior to a randomized controlled trial, the VR-GMI program must be validated and refined through a rigorous and multi-stage feasibility assessment.

Objective: The objective of the current protocol is to outline the development and feasibility of the VR-GMI prototype for treating people with LLAs in the postoperative acute care setting (i.e., inpatient and home settings) through an iterative, patient-centered, and descriptive approach.

Methods: Four phases of prototype development and assessment are conducted. In Phase 1 (completed), the VR-GMI prototype was developed in collaboration with engineers at the National Research Council (NRC) and in consultation with patient partners. In Phase 2 (completed), people with lived experience were recruited from local physiotherapy and prosthetic clinics to trial the VR-GMI program and provide feedback through semi-structured interviews and self-report measures. Phase 3 (completed) consisted of a descriptive case series of individuals who trialed the VR-GMI prototype immediately following their LLAs in hospital. Results from Phase 3 informed the development of a primary quantitative feasibility study. Phase 4 (underway) aims to evaluate the acceptability and pilot outcomes of the VR-GMI program in hospital and home, as well as improve study procedures for a future randomized controlled trial (Phase 4A). Iterative developments were made to the VR-GMI program between each phase to improve prototype fidelity. These iterative developments will also be reviewed in a series of focus groups to finalize the VR-GMI prototype (Phase 4B).

Results: Recruitment for Phases 1 and 2 were completed in September 2023. Phase 3 was completed in July 2024, and Phase 4A is currently underway.

Conclusions: The present intervention is the first VR PLP treatment implementing GMI and prioritizing an in-depth, patient-centered approach prior to assessing its efficacy. Doing so will improve the likelihood of successful clinical implementation. Moreover, very few PLP interventions have been assessed in the acute postoperative period when they may prevent PLP before its onset. Clinical Trial: Phase 4 has been registered on clinicaltrials.gov (#NCT06638918).

(JMIR Preprints 30/10/2024:68008)

DOI: <https://doi.org/10.2196/preprints.68008>

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Original Paper

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Background: Phantom limb pain (PLP) affects the majority of people living with lower limb amputations (LLAs). Nonpharmacological interventions, such as graded motor imagery (GMI), have demonstrated promise as PLP treatments. However, GMI access is limited by low patient buy-in and long public outpatient wait times. Considering PLP has been shown to be more prevalent and severe immediately following LLA, there is an urgent need to bypass barriers to allow for more prompt access to PLP interventions. In response to this need, the current multidisciplinary research team developed a virtual reality (VR) program that administers GMI treatment. This novel intervention may be completed independently and promptly within the postoperative acute care setting. Prior to a randomized controlled trial, the VR-GMI program must be validated and refined through a rigorous and multi-stage feasibility assessment.

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made to the VR-GMI program between each phase to improve prototype fidelity. These iterative developments will also be reviewed in a series of focus groups to finalize the VR-GMI prototype (Phase 4B).

Results: Recruitment for Phases 1 and 2 were completed in September 2023. Phase 3 was completed in July 2024, and Phase 4A is currently underway with 15 participants recruited as of March 2025.

Conclusions: The present intervention is the first VR PLP treatment implementing GMI and prioritizing an in-depth, patient-centered approach prior to assessing its efficacy. Doing so will improve the likelihood of successful clinical implementation. Moreover, very few PLP interventions have been assessed in the acute postoperative period when they may prevent PLP before its onset.

Trial Registration: Phase 4 has been registered on clinicaltrials.gov (#NCT06638918).

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Keywords: phantom limb pain; virtual reality; lower limb amputation; graded motor imagery; feasibility; postoperative; acute; patient-centered; preventative; pre-emptive

Introduction

Literature Review

More than 7000 lower limb amputations (LLAs) are performed in Canada each year due to (in order of decreasing prevalence) diabetic, vascular, traumatic, cancerous, and congenital indications [1]. Approximately 70% of these individuals will develop PLP [2,3], a type of neuropathic pain where one experiences uncomfortable kinesthetic and or somatosensory sensations in their missing limb following amputation [4]. PLP can be experienced for the first time within days following amputation (if not, within one year) and persists to variable degrees of intensity over a lifetime depending on the individual [5]. Research suggests that PLP is more likely to occur in people with more recent amputations compared to those sustained further in the past [2,3]. Additionally, those who have an amputation due to chronic conditions (e.g. vascular or diabetes mellitus) may have worse outcomes than those who sustain traumatic amputations because of preoperative factors (e.g. preamputation pain) [2]. While PLP may improve over time if untreated, lack of PLP treatment most often can significantly reduce quality of life, both psychologically and physically [6,7]. For example, research suggests PLP reduces mobility, which has adverse effects on independence (such as maintaining employment) and social role fulfillment [6,7]. PLP has also been implicated in a variety of other negative sequelae, including poorer sleep quality and increased depressive/anxious symptomatology [8-10]. The high prevalence of PLP among the growing number of LLAs, coupled with lack of outpatient support, reflects an urgent need to develop effective treatments tailored to address the gap in care between the inpatient and outpatient settings to mitigate these negative sequelae.

In response to this need, researchers have developed many pharmacological and nonpharmacological PLP treatments. Currently, pharmacological interventions are among the most prevalent in clinical practice to treat PLP [11,12]. However, recent studies suggest pharmacological interventions are both ineffective compared to placebo and considered unsatisfactory by patients with PLP [10-14]. Accordingly, researchers have turned their attention to nonpharmacological PLP treatments. One such treatment, graded motor imagery (GMI) [15], directly targets the central mechanisms implicated in PLP [16] and consists of three stages. The first stage of GMI is left/right discrimination (aka implicit motor imagery), which entails quickly sorting images of left and right

limbs. The patient then moves to the second stage, explicit motor imagery, which involves deliberate focus on phantom limb visualization. In the third stage, the patient undergoes mirror therapy, which involves visual feedback of the reflected intact limb (in a mirror box) to create the illusion of phantom limb movement. Despite the efficacy of GMI for PLP [15,17], it is often not clinically feasible due to its heavy reliance on physiotherapists with specialized training [18]. In Manitoba (where the current research is being conducted), it can take up to two years to visit a pain specialist from a public treatment center [19]—let alone a physiotherapist who specializes in GMI. To successfully implement GMI as a PLP treatment, barriers to its access need to be mitigated.

By eliminating GMI barriers, it may be possible to prevent or mitigate PLP onset through early intervention. While most treatments are administered well after PLP first occurs (i.e., > three months following amputation) [20], researchers have also successfully prevented PLP by administering both pharmacological and nonpharmacological interventions during the perioperative period of amputation [20-23]. For example, both epidural and systemic analgesia (i.e., morphine and ketamine) administered before, during, and after major limb amputation have been shown to reduce PLP incidence compared to a control group up to one year and six months following the procedure, respectively [21]. Similarly, surgical intervention geared toward neuroma prevention (such as targeted muscle reinnervation) employed at the same time as major limb amputation has demonstrated significant PLP reduction compared to a control group at three-month follow-up [22]. More recently, researchers have even begun to investigate the prophylactic effects of nonpharmacological PLP interventions, which have been shown to reduce PLP incidence and intensity with mirror therapy if administered less than two months following LLA [20,23]. Administering PLP treatment early may not only bypass barriers to access—it may also be more efficacious including preventing the onset of PLP, which could have significant implications for negative downstream health and social sequelae.

Purpose and Rationale

To address current barriers to PLP care, our multidisciplinary research team (consisting of clinical psychologists, physiotherapists, physiatrists, anesthesiologists, surgeons, and engineers) developed a novel virtual reality (VR) program that allows people with LLAs to self-administer GMI treatment. VR is a computer-generated three-dimensional simulated environment in which a user may be immersed with the use of a mounted headset. In recent years, it has been used to treat PLP by simulating mirror therapy or other gamified interventions [24]. The potential advantages of an integration between VR and GMI are threefold. First, research suggests VR is more motivating and usable than two-dimensional treatment administration modalities [25,26]. The novelty offered by VR will be invaluable to administer GMI psychoeducation and tasks in a gamified manner to increase patient buy-in, knowledge, and adherence [27]. Second, all GMI psychoeducation and treatment tasks are embedded on the device, removing the need to wait for and travel to a physiotherapist. In recent studies, VR PLP (without embedded GMI) treatment has already been self-administered by participants in their homes and produced promising pilot and feasibility outcomes [28,29]. Lastly, virtual visual feedback may be of particular benefit to people with LLAs. Research suggests lower limb movements are more natural when performed asymmetrically (such as pedaling or walking); therefore, VR (through its capacity for asymmetrical movement) may produce more favourable outcomes for people with LLA compared to traditional mirror therapy (which can only be used symmetrically) by generating a higher sense of agency and ownership (defined as perceived control over and possession of the virtual limb, respectively) [30-32]. By bypassing barriers to care through a novel VR-GMI program, PLP can be targeted in the perioperative setting before its onset, when PLP is suggested to be the most intense and receptive to intervention [3,20].

Study Aims

The current program of research aims to develop and assess the feasibility of a novel VR-GMI program for the treatment and prevention of PLP in persons with LLAs through four developmental and evaluative phases. The aim of Phase 1 (completed) was to develop the initial prototype of the VR program through a multidisciplinary and patient-oriented approach, in accordance with GMI literature and feedback from people with LLAs. In Phase 2 (completed), the perceptions of the VR prototype from people with LLAs living in the community were evaluated using a multi-method design. In Phase 3 (completed), the preliminary feasibility of the VR prototype was assessed in the acute postoperative setting using a case series design. In Phase 4A (in progress), a larger quantitative feasibility study is being conducted to evaluate the VR program in the acute postoperative period (including the hospital and transition to home) immediately following LLA. Phase 4B will conclude with a series of focus groups in which a subset of feasibility participants will discuss their experiences in the VR-GMI program and how it might be improved.

Each of the four phases were designed according to the Virtual Reality Clinical Outcomes Research Experts (VR-CORE) Model [33], which outlines expert recommendations on how to validate a medical VR program. VR1 studies are patient-centered and involve collecting feedback from the population the VR program is designed for (including both clinicians and patients) to ascertain attitudes and expectations regarding treatment. To ensure the VR-GMI program reflects the needs of people with LLA, Phases 1, 2, and 3 all meet the criteria for a VR1 study. Meanwhile, Phase 4A meets the criteria of a VR2 study, which focuses on establishing the acceptability, feasibility, tolerability, and preliminary efficacy of the VR program. Birkhead et al. also describe VR3 studies, which entail employing a randomized controlled trial to assess the efficacy of a VR program. The VR3 study of the VR-GMI program will be outlined in a separate future protocol. The VR-GMI program will be finalized through a focus group (a VR1 study) to ensure the prototype is of the highest fidelity before proceeding to VR3. See image below (Figure 1) for an overview of the four studies that will evaluate the feasibility of the initial VR-GMI prototype.

Figure 1: Visual overview of the four phases through which the feasibility of the VR-GMI program will be assessed.

Methods

Ethical Considerations

Phase 1 did not involve participants; therefore, ethical approval was not required. Consent forms relevant for each phase will be reviewed by a research assistant with participants to ensure informed consent. Any ethical amendments were immediately addressed, updated and communicated to participants. Data will be de-identified using a random computer generated 5-item alphanumeric code. All data will be stored in a locked cabinet in a locked office in a secure facility. All investigator communications are completed via password protected files and any paper notes (with no identifiers) will be destroyed immediately after use. Any photos taken during this study will receive additional consent from the participants. Ethical approvals for each phase were received. Phase 2 received ethical approval from the Research Ethics Board (Fort Garry) at the University of Manitoba (HE20220374); Phase 3 received approval from The Research Ethics Board (Bannatyne) from the University of Manitoba (B2022107); and phase 4 The Research Ethics Board (Bannatyne) from the University of Manitoba provided ethical approval for this study (B2022107). Honorariums of \$50 were provided to study partners in Phase 1 and \$25 gift cards will be provided to participants in all other phases.

Phase 1: Multidisciplinary and Patient-Centered Prototype Development (Completed)

Overview and Objective

In Phase 1, the initial VR prototype was developed collaboratively within a multidisciplinary team including a lead engineer (MS) affiliated with the National Research Council (NRC) of Canada and led by a clinical psychologist (RE) from the University of Manitoba. In addition, study partners (including people with LLAs and physiotherapists) and collaborators (anesthetists and physiatrists) were consulted to iteratively incorporate their feedback and lived experience during initial prototype development. The objective of Phase 1 was to develop a virtual GMI prototype through multidisciplinary and patient-centered feedback. No participants were involved in this component of the research, therefore ethical approval was not required.

Study Partners

The study partners consisted of five people with lived experience with amputations, including two physiotherapists (EH and PG) and three people with LLA. Both physiotherapists had experience working with people with LLA, using GMI (EH) or other forms of physiotherapy (PG). All three of the study partners (two males and one female) with LLAs had experienced disruptive PLP at some point following their surgeries, with the pain being reported to be the worst at its onset. Study partners who were people with LLA were given a \$50 honorarium for their participation.

Procedures

An initial multidisciplinary team meeting was held on January 2021 to formulate a plan for prototype development. Team members then aimed to recruit $n=5$ people with lived LLA experience. Study partners who were people with lived LLA experience were approached by team members in their respective clinics to ask about interest in participation in this program of research. If they expressed interest, the potential study partners directly contacted study personnel to receive further information. Interested partners ($n=3$) participated in an initial semi-structured interview in August 2021 with the PI (RE), research personnel, and lead engineer via Zoom (due to COVID-19). Interview questions inquired about amputation history (including current and past interventions accessed for PLP), initial thoughts relating to proposed VR prototype, and continued interest in involvement throughout development. Interviews were one hour in length. Partners were continually engaged in initial development via Zoom and e-mail to provide feedback on prototype development. Once a prototype was in place, multidisciplinary team members and study partners both viewed videos of the prototype and trialed it at the NRC to provide feedback. It should be noted that, due to delays in development, the explicit motor imagery task was not evaluated by study partners over video or in-person; however, the written scripts were reviewed and revised by partnered physiotherapists. Additionally, one of the study partners with a LLA stopped responding to research correspondence midway through development for unknown reasons. See images (Figure 2) of our research team and one of our partners (with respective consents provided) trialing the VR-GMI program.

Figure 2: Research team member trialing the hand control trackers attached to the legs via 3D-printed adapters (upper left). Study partner trialing the VR prototype (upper right). Larger image of limb simulation stage in program (lower).

The Initial VR-GMI Prototype

The VR-GMI program was developed using the Unity game engine and operates on the Oculus Quest 2, a commercially available VR hardware system with head-mounted display and hand

controllers. This stand-alone system is advantageous as it is not encumbered by wires connecting it to an external computer, allowing for ease of set-up and use. It also includes functionality for the clinician/research personnel to follow along with the participant by casting over wi-fi through the Oculus app (or by attaching a Link cable if wi-fi is unavailable) a mirror image of the virtual environment as experienced by the participant to a separate display device such as a smartphone or tablet. To increase feelings of embodiment for the participant by having their virtual leg movements follow their real-world leg movements, leg tracking was also incorporated in the system. Initial experimentation with third-party tracking devices utilizing ultrasound and inertial measurement units (IMUs) was promising but performance was inconsistent when tested in different environments. Prioritizing consistency to avoid breaking presence in VR, an alternate approach was adopted utilizing the Oculus Quest 2 hand controllers to track the participant's legs. Custom adapters for attaching the controllers to the user's legs were designed and 3D printed. When leg tracking is enabled in the program, the hand controllers are strapped to the participant's legs above the knee using the custom adapters (see Figure 2).

Following initial development of the base prototype, GMI elements were included with guidance from physiotherapist partners. The GMI stages—including left/right discrimination, explicit motor imagery, and mirror therapy—formed the basis of the VR program. Implementation was designed to take advantage of the unique affordances of VR. For example, the left/right discrimination task was implemented in a whimsical environment in which the user interacts with the images of feet using their controllers to increase engagement. The explicit motor imagery phase incorporated recorded audio of a body scan to enhance relaxation and focus on the phantom limb [34-36]. Meanwhile, the mirror therapy stage included asymmetrical exercises in the virtual visual feedback, a feature that is not feasible during traditional mirror therapy. Due to the capacity of VR to provide asymmetrical visual feedback, the mirror therapy stage was dubbed “limb simulation”.

Priorities for Future Development

Across both virtual and in-person meetings with study partners, common recommendations emerged that informed the optimization of the VR prototype. These developmental priorities included addressing technological barriers and improving leg tracking. The details of these recommendations can be reviewed in the Multimedia Appendix.

Phase 2: Attitudes and Impressions from People with Lived Experience (completed)

Overview

In Phase 2, developmental priorities for the finalized VR-GMI prototype were assessed by collecting feedback from people with LLAs to ascertain preliminary treatment attitudes and expectations. To accomplish this, twelve ($n = 12$) people with LLAs were recruited from community settings to trial the VR-GMI program and detail their experience through a combination of observations, self-report measures, and semi-structured interviews.

Study Design and Objectives

This study employed a multi-method design to elucidate participant perspectives on the VR-GMI prototype in a single, intensive VR session. The first, and primary, objective was to assess anticipated barriers and facilitators to using the VR-GMI program in the intended administration settings (including home and hospital settings immediately following LLA) through semi-structured interviews. A second objective was to evaluate how engaging and immersive the VR-GMI prototype was using self-report measures. Observations and informal discussions throughout the VR sessions provided context to the triangulated data to inform program development. On January 13, 2023, this study received ethical approval from the Research Ethics Board (Fort Garry) at the University of

Manitoba (HE20220374).

Recruitment and Inclusion Criteria

The research team planned to recruit 10-15 participants via purposive sampling through community partners, including physiotherapists, surgeons, and prosthetists. Such a sample size is akin to similar user-centered studies evaluating the development of novel interventions [37,38]. Recruitment posters were disseminated in-person, as well as through email and institutional social media accounts. Interested individuals contacted the researchers directly or were contacted over the phone if the participant provided verbal consent to a community partner. Potential participants were screened over the phone for the following eligibility criteria: must have a unilateral LLA proximal to the ankle; must be eighteen years of age or older; must not be experiencing any hearing or vision loss that would affect interaction with a VR headset; must have experienced phantom limb pain or sensation either in the past or present; and must agree to be audio recorded. Participants were also informed that they would be given a \$25 gift card to Tim Horton's to thank them for participating. The research team aimed to recruit 10-15 participants between March 2023 to September 2023. By the end of this recruitment period, $n = 12$ participants were recruited.

VR Intervention Procedure

Each participant tested the VR program in an intensive session (approximately 2.5 hours in duration) at the NRC building in Winnipeg, Canada. Appointments were booked via phone following eligibility screening. Gift cards were given promptly following completion of the informed consent form. Prior to using the VR program, each participant completed a semi-structured interview to collect baseline characteristics, including amputation etiology and pain history. The research assistant (MC) then verbally administered GMI psychoeducation and technical instructions regarding the VR hardware. Afterwards, the participant was instructed to vocalize all thoughts they had about each of the three VR GMI stages as they navigated them, including operational or instructional confusion, stylistic choices, etc. During program use, the research assistant recorded observations of the participant's behaviour on a laptop, as well as any vocalizations from the participant. Approximately half of the sessions included at least two research personnel, with an engineer at most of the sessions.

Following each of the three VR stages, the participant doffed the headset to discuss their experience in that particular task. The research assistant also clarified any observations made during that stage. Once the participant completed the entire VR program, the participant filled out a series of self-report measures to gauge the quality of their experience in the VR program, in the following order:

- The User Engagement Scale (UES) [39], a thirty-one item questionnaire that measures how rewarding a given user experience was. It was rated on a five-point Likert scale and validated in the head-mounted VR context [40].
- The Presence Questionnaire (PQ) [41], a validated twenty-item questionnaire that measures how immersive a virtual experience was. Each item was rated on a seven-point Likert scale.

Participation concluded with an exit interview discussing anticipated barriers and facilitators to using the VR program. The final exit interviews were audio recorded via Trint for later transcription and analysis.

Statistical Analysis

Given the small sample size and nature of this study, scores across various measures were descriptively analyzed using R software. Meanwhile, exit interview transcripts were coded line-by-line and examined using reflexive thematic analysis [42,43]. Following separate qualitative and quantitative analyses, the results were integrated, along with observations, for interpretation and extrapolation of developmental priorities for the VR-GMI program.

Phase 3: Inpatient Feasibility Case Series (completed)

Overview

In Phase 3, the VR-GMI prototype was implemented in the acute postoperative hospital setting immediately following LLA. Given the novelty of this methodological approach, the research aimed to understand participant experience and feedback on the intervention, as well as identify barriers encountered during recruitment and administration prior to the initiation of a larger feasibility trial. The information gathered directly impacted modification to the Phase 4 protocol to optimize feasibility. The Research Ethics Board (Bannatyne) from the University of Manitoba provided ethical approval for this study (B2022107).

Study Design and Objectives

Phase 3 was a prospective descriptive case series. Participants were recruited and administered the VR-GMI program at the Health Sciences Centre (HSC) in Winnipeg, Canada, a large academic tertiary hospital and level 1 trauma center. The VR-GMI program was administered daily immediately following LLA for a maximum of 10 sessions or until hospital discharge. Quantitative and qualitative self-reported data were gathered pertaining to patient experience and details about recruitment and retention were documented.

Phase 3 included two objectives. The primary objective was to evaluate preliminary recruitment and retention trends, as well as identify potential recruitment barriers for Phase 4. The secondary objective was to describe participant experience with the VR-GMI program in three domains, including immersion, tolerability, and overall helpfulness.

Recruitment

The research team aimed to recruit 5-10 participants by the end of the recruitment period (January 2024 to July 2024), resulting in a sample size of $n = 6$. Participants were required to meet the following inclusion criteria: underwent (postoperative) or were about to undergo (preoperative) a unilateral LLA (hip, below-knee, above-knee, or foot) of either elective or traumatic mechanisms within the last five days; currently receiving inpatient treatment at the Health Sciences Centre (HSC) in Winnipeg, Canada; and fluent in English (speak and read). Potential participants were not eligible if they met the following exclusion criteria: any visual, hearing, or motor impairment that would affect engaging with a head-mounted VR headset or hand controls; anyone with or about to undergo a bilateral leg amputation; and anyone younger than eighteen years old. Potential participants were screened from the following avenues: the preanesthetic clinic (which hosts presurgical visits between anesthesiologists and patients prior to LLA); and elective and emergency operating room slates (which contain the information of every patient about to undergo an LLA). Any LLAs that appeared eligible were recorded. Once potential participants were identified, healthcare professionals in their circle of care approached them to ascertain their interest in hearing more about the study from research personnel. If interested, research personnel approached the participant at the HSC to ensure they met eligibility criteria and administer the informed consent form. If a patient was ineligible or declined participation, the reason was recorded.

VR Intervention Procedure

Participants engaged in one VR session per day for approximately twenty minutes from their respective ward (orthopedic, vascular, or rehabilitation). At the beginning of the first VR session, after informed consent was obtained and the honorarium was given to the participant, the research assistant administered the sociodemographic and patient characteristics questionnaire (including age, amputation etiology, place of residence, etc.). The research assistant then gave a brief verbal introduction to the VR-GMI system and instructed the participant how to use the VR headset and

handheld controls. Following VR instruction and at the beginning of each subsequent VR session, the research assistant verbally administered Numerical Rating Scales (NRSs; eleven-point Likert scales) for PLP, residual limb pain (RLP; i.e., physical pain at the amputation site), and nausea prior to asking if they want to engage with the VR program that day. If they declined participation, their reason was recorded.

Participants were only permitted to engage in one stage per day. They could only move onto the next VR stage if their RLP, PLP, or nausea NRS scores did not increase by more than two points during or prior to their next session (given that treatment may exacerbate pain or nausea, and three points is considered a clinically significant increase) [44-47]. The participant was permitted to spend as much time as they preferred in each VR stage. If the participant chose to stop the session prior to the twenty-minute goal (a session length utilized in previous studies) [23,48], the research assistant asked for and recorded their reason(s) for discontinuation. Afterwards, the research assistant verbally readministered the NRSs for PLP, RLP, and nausea. Any impromptu feedback or observations made by research personnel were recorded as field notes.

Participants were asked to engage in up to 10 VR-GMI sessions or until hospital discharge, whichever came first. After the last VR-GMI session, prior to discharge, the iGroup Presence Questionnaire (IPQ, measuring VR immersion) [49] and Virtual Reality Impressions Scale (developed by the lab for the purposes of descriptive evaluation of a VR intervention; see Figure 3) [50] were administered.

Figure 3: The Virtual Reality (VR) Impressions Scale.

Data Analysis

For the first objective, eligibility and consent rates were calculated according to the number of patients screened. Reasons for refusals or ineligibility were recorded in pie charts. The secondary objective analyzed patient experience with the VR-GMI program by describing the qualitative and quantitative data of each participant individually to capture unique perspectives. Specifically, participant ratings on tolerability (measured by NRS for PLP, RLP, and nausea), immersion (measured by the iGroup Presence Questionnaire), and overall helpfulness (measured by the VR Impressions Scale) were described individually in conjunction with sociodemographic characteristics (such as age, length of hospital stay, etc.) to provide context for interpretation. The qualitative data, including participants' quotes and observations made by research personnel, were integrated to triangulate and increase the strength of the findings.

Phase 4A: Hospital and Home Feasibility Study (underway)

Overview

In Phase 4A, the research team will assess the feasibility and pilot outcomes of the VR-GMI program in the acute postoperative period immediately following LLA (including the hospital and home). We aim to recruit thirty participants ($n = 30$) who recently underwent a LLA through the HSC. A research assistant will visit participants daily to administer the VR-GMI program for approximately seventeen days. Participants will then be contacted again one month following their final VR session via phone call to assess postoperative PLP. Quantitative data will be collected to assess whether the VR-GMI program and study procedures are sufficient for a randomized controlled trial. Phase 4 is registered on clinicaltrials.gov (#NCT06638918). The Research Ethics Board (Bannatyne) from the University of Manitoba provided ethical approval for this study (B2022107).

Study Design and Objectives

Phase 4A will consist of a quantitative feasibility study using a one-group post-test only design in line with methodological recommendations [33,51]. The feasibility of the program will be evaluated

through self-report and administrative quantitative data. The objectives and affiliated hypotheses are as follows:

1. **Intervention Feasibility.** Participants will consider the VR-GMI program to be acceptable, tolerable, and engaging across administration settings (inpatient, outpatient, and home settings) and VR stages.
2. **Procedural Feasibility.** The employed recruitment strategies and study procedures will be appropriate for a randomized controlled trial, as indicated by comparing sample characteristics to administrative data (reflecting all people undergoing LLAs during the recruitment period) in addition to predetermined recruitment, retention, and attrition rate criteria [52].
3. **Pilot Outcomes.** Participants who spend a longer length of time in the VR-GMI program will report lower PLP incidence, as well as (for individuals who have already experienced PLP onset) intensity and interference. These predictions are in line with previous research investigating prophylactic PLP treatment through mirror therapy in the postoperative period [23].
4. **Exploratory Outcomes.** The research team will explore reasons for rejecting participation, as well as session/study withdrawal. The research team will also investigate whether acceptability, engagement, or PLP incidence/intensity varies according to baseline, sociodemographic, and exploratory variables (such as anxiety, depression, amputation indication, etc.).

Recruitment

The research team aims to recruit thirty participants ($n = 30$), five of which we expect for dropout ($n = 5$) and twenty-five to complete the program ($n = 25$). This sample size is in line with previous pilot studies for PLP treatments that precede randomized controlled trials [38] and suits the descriptive and exploratory aims of the study. This sample size also has 80% power to detect the desired recruitment criterion [53].

Potential participants will be approached according to the recruitment strategies and eligibility criteria outlined and recommended in Phase 3, with three exceptions to help mitigate recruitment barriers faced in the previous phase. First, clinical resource nurses on units where LLAs are treated at the HSC will be called each week to ascertain where eligible patients are to increase the recruitment rate. Second, individuals with bilateral amputations will also be eligible for recruitment, given preliminary data from Phase 3 suggesting this may be feasible. Third, patients will be eligible to participate for up to two months following their LLA, in line with literature to suggest such a timeframe is suitable for the administration of acute PLP intervention [20].

VR Intervention Procedures

Similar procedures to Phase 3 will be employed in Phase 4A, with three exceptions made in accordance with preliminary Phase 3 data. First, following baseline measure administration, the research assistant will administer a brief video via laptop that introduces the participant to the VR-GMI program, including how to operate the controls and put on the headset. The video (rather than verbal instruction) serves to standardize study expectations and technical knowledge across participants. Second, new measures have been introduced in addition to the measures employed in Phase 3. The first time a participant completes a stage, they will be administered the Theoretical Framework of Acceptability Questionnaire (TFAQ), which consists of seven items rated on a seven-point Likert scale inquiring about the acceptability of a behavioural intervention [54] (Figure 4). Additionally, following the limb simulation stage (both with and without leg tracking), each participant will be administered the Virtual Embodiment Questionnaire (VEQ), a validated measure for agency and ownership in a virtual experience involving avatar embodiment [55]. Lastly, the Brief Pain Inventory (BPI) and Patient Reported Outcomes Measurement Information System (PROMIS)

will be verbally administered over the phone one month following each participant's final VR session to measure PLP intensity and interference, respectively, through validated self-report measures [56-58].

The last and most significant amendment made between Phases 3 and 4A is the administration of the VR-GMI program in the home setting following hospital discharge. Data from Phase 3 suggests participants were discharged from the hospital before two weeks have passed, which prevents them from receiving the VR dose necessary to see a treatment effect [23]. Therefore, a research assistant will contact participants over the phone following their discharge to inquire about their interest in continuing participation for the remaining sessions in their home. If they wish to continue (and they live in Winnipeg), their participation will proceed with home visits. If they do not reside in Winnipeg, their participation will be discontinued by the researcher; however, their willingness to continue the program will be recorded. Participants will be allowed to continue the VR-GMI program for up to seventeen days to analyze long-term acceptability and dosage effects. Immediately following the completion of the feasibility trial, relevant modifications will be made to the prototype based on results.

Figure 4: Adapted Theoretical Framework of Acceptability Questionnaire (TFAQ).

Data Analysis

Objectives 1, 2, and 4 will be evaluated descriptively via bar graphs and means to compare each objective across administration setting and VR stage according to preset feasibility criteria. Preset feasibility criteria must be met to determine if the VR program is acceptable (mean TFAQ > 3, which indicates a more favourable acceptability rating than no opinion; Sekhon et al., 2022), tolerable (at least 70% of participants do not report any pre/post NRS increases ≥ 3 for PLP, RLP, or nausea), and engaging (mean session duration ≥ 20 minutes). Similar progression criteria [52] must be met to determine whether procedural feasibility is appropriate for a randomized controlled trial, including recruitment (at least 50% of the patients at the HSC who appear to meet the eligibility criteria will be screened through the established pathways), retention (at least 70% of participants who live in Winnipeg will continue to participate in the study for as long as they are able to), and attrition (at least 80% of participants will respond at the one-month follow-up period following their final session) rate criteria. The sample will also be compared to the population of all persons who underwent an LLA at the HSC during the recruitment period (from June 2024 to March 2025) via administrative chart review to evaluate whether the characteristics are relatively proportional to one another.

For objective 3, scatterplots will be generated to explore the association between length of program engagement and BPI/PROMIS Pain Interference. Mean or median difference in length of program engagement between participants who have and have not yet experienced PLP onset will also be calculated. If appropriate, exploratory regression models will be employed to examine the effect of VR dosage on PLP outcomes.

Phase 4B: Focus Groups

Phase 4B will conclude with a series of focus groups (2) consisting of a subset of interested participants ($n = 5-10$) from Phase 4A following the completion. Participants will meet in person to discuss their experiences with the VR GMI program in the hospital and home (if applicable) facilitated by members of the research team using a semi-structured interview. Immediately following the initial discussion, participants will be invited to trial the updated prototype (5 headsets will be circulated and snacks will be provided to those waiting their turns). Following the trial, another group discussion will occur to provide feedback on the new developments also using a semi-structured interview format. The focus group transcripts will then be analyzed through reflexive thematic analysis [42,43] and interpreted to inform final development of the VR GMI program.

Results

Initial funding for prototype development and Phase 1 was obtained through the NRC New Beginnings Fund awarded to El-Gabalawy and Smith as co-PI's in December 2020 (\$25,000 + 0.2FTE (or 390 hours) of engineering time for development). Delays occurred in the initial development of the program due to COVID-19 and parental leave (RE). Phase 1 of the current study was completed in January 2023, at which point recruitment for Phase 2 was conducted until September 2023. Additional funding was obtained through the Winnipeg Foundation Innovation Fund (\$100,000; PI: El-Gabalawy) in November 2023. Recruitment for Phase 3 began in January 2024 and was completed in July 2024. As indicated above, several methodological modifications were conducted to the study protocol prior to initiation of the final phase. Phase 4A commenced in August 2024 and is expected to be completed in April 2025. As of March 2025, we have screened 101 patients for eligibility and successfully recruited 15 participants. Regardless of ethical approval to initiate intervention prior to surgery, hospital logistics and communications has created challenges around recruiting participants preoperatively. Phase 4B will be conducted in June 2025 followed by the final refinements of the VR-GMI program. Should significant adjustments need to be made to the program, an additional feasibility trial will be conducted prior to the larger clinical trial.

Meanwhile, the research team will utilize preliminary data to inform iterative development of the VR-GMI program; between studies, these developments are deployed so that each phase evaluates a higher fidelity prototype than the last. For example, information from Phase 2 suggested that a video was embedded into the VR-GMI program to educate patients on the potential benefits of using this treatment. Moreover, VR controls have continuously been simplified to promote treatment utilization by individuals with lower technological self-efficacy (e.g., allowing them to use only one control to operate the VR GMI program). Most notably, results from Phase 2 indicated better immersion may be experienced in the VR-GMI program via utilization of hand controls as leg trackers. Leg trackers were then 3D printed to allow trial in Phase 3. Detailed results from all phases will be available in a future article to be published. See Figure 5 for an overview of the VR-GMI prototype in its current state, given preliminary data collection and analysis.

Figure 5: The five stages of the VR-GMI program (prior to entering Phase 4A).

Discussion

Comparison with Prior Work

The current protocol represents both a novel methodological approach and intervention through which to treat PLP in people with LLAs. Despite the success VR and GMI have each demonstrated as independent PLP treatments [17,24], they have never been combined. Beyond its potential to increase GMI efficacy, VR can be used to streamline all the GMI components into a convenient, commercially available VR program, improving patient access both economically and logistically. Previous interventions have also leveraged this unique advantage of VR to administer PLP treatment in the home, often employing gamification [28,29,59]. However, this is the first protocol to deliberately tailor a VR PLP program to the postoperative acute care setting. Moreover, while previous studies have demonstrated the prophylactic capacity of mirror therapy [20,23], no research has focused on how VR might enhance patient engagement and improve administration efficiency to reduce or prevent PLP onset. These novel contributions are noteworthy strengths that could create a conceptual foundation for further inquiry.

Strengths and Limitations

The most significant strength of the current protocol is its prioritization of feasibility through a user-centered approach prior to empirically assessing the efficacy of the VR-GMI intervention in a

clinical trial design. According to the VR-CORE framework [33], employing patient-centered design is essential to the iterative development of an effective VR healthcare intervention. Recently, there has been a movement to design VR interventions with explicit consideration of implementation outcomes (such as acceptability) from the beginning of development [60]. Despite this recommendation, very few studies have examined the feasibility of VR PLP interventions in ecologically valid settings. Many researchers instead develop VR PLP interventions solely to assess their capacity for short-term PLP reduction [61,62]. Such inadequate focus on the feasibility of VR PLP interventions in target settings may contribute to low treatment adherence, limiting and confounding their effectiveness [63]. The current four-phase protocol attempts to address this common issue in VR literature with a thorough consideration of feasibility prior to conducting a randomized controlled trial, serving as an example for the application of the VR-CORE framework.

However, each phase of the protocol also presents limitations. The feedback collected in Phase 1 was collected informally through open-ended questions; therefore, the resulting recommendations were the result of simple compilation, rather than systematic analysis. Furthermore, due to the COVID-19 pandemic, only two study partners with lived PLP experience were available to trial the VR prototype in-person (all were able to observe video developments). Further, although the initial goal was to recruit five diverse partners with lived PLP experience, only three were consulted. Meanwhile, Phase 2 recruitment was completed via convenience sampling and was limited to interested individuals able to attend at the NRC building. Thus, the results of Phase 2 likely do not capture the barriers encountered by the diverse population undergoing LLAs in Canada. Phases 3 and 4 will encounter similar bias. While a more representative sample may be recruited at the outset, data from Phase 3 suggests participants are discharged from hospital prior to completing the VR program for the recommended treatment period. Since only individuals who live in Winnipeg may logistically continue the program after discharge, people who live in rural or Northern communities are unlikely to receive the VR dosage necessary to demonstrate a treatment effect. This exclusion limits generalizability to Indigenous peoples living in Northern communities, who are disproportionately affected by diabetic LLA [64]. These limitations highlight that, while we can use the data of the current protocol to inform VR development, more representative recruitment will be necessary before the clinical feasibility of the program for the general population can be ascertained.

Future Directions

Beyond the current protocol, further development of the VR-GMI program will prioritize clarifying its feasibility and evaluating its efficacy in the postoperative acute period. Depending on the results of Phase 4A, additional feasibility studies on the VR-GMI program may be necessary. This may include a longitudinal study conducted in the homes of participants beyond the city limits of Winnipeg, including focus groups, to capture a more representative sample. Furthermore, a randomized controlled trial (RCT) will be conducted to assess the efficacy of the program. The first RCT will compare virtual GMI to a distractor control (i.e., a natural VR environment), while another RCT may compare the program to traditional GMI. The studies enhance development of an effective VR program to prepare for clinical implementation. Dates for these studies have not yet been determined as initiation depends upon the results of Phases 4A&B.

The research team also aims to promote visibility of the proposed intervention through brand awareness to spark interest in its use by healthcare professionals. In line with this aim, the VR-GMI program will henceforth be coined GMI-PLAY (Graded Motor Imagery for Phantom Limb pain Acutely using virtual reality). GMI-PLAY will be referenced in upcoming publications, which will detail the results of Phases 2, 3, and 4. While a name is ultimately a very small change, it is a step towards connecting with healthcare professionals that may assist with clinical implementation of GMI-PLAY following prototype development.

Conclusions

The current protocol represents a novel methodological approach to iteratively develop a patient-centered VR intervention. Moreover, it outlines the development of GMI-PLAY, which could increase the effectiveness and accessibility of PLP treatment through engaging and prompt self-administration of GMI. Following rigorous feasibility and efficacy evaluation, the clinical implementation of GMI-PLAY could improve the quality of life of millions of people with LLAs by reducing their PLP and its downstream negative sequelae.

Acknowledgements

Phases 1 and 2 were funded by the NRC New Beginnings grant (NBR3-666; PIs: El-Gabalawy and Smith), while Phases 3 and 4 are funded by the Winnipeg Foundation Innovation Fund (327146-340100-2000; PI: El-Gabalawy). These funding sources did not unduly influence the execution of the research in any stage from design to publishing.

The authors would also like to acknowledge the NRC, as well as Jennifer Newman, Jim Harris, and Chris Marshall for assisting with prototype development.

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Data Availability

Data from this study will not be publicly available due to ethics approval to maintain patient confidentiality. Regardless of de-identification of the information collected, it is reasonable to assume that confidentiality may be breached given small sample sizes and collection of qualitative data. Should appropriate avenues be navigated, reasonable requests for data access to the corresponding author may be considered.

Conflicts of Interest

None declared.

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Abbreviations

BPI: Brief Pain Inventory

GAD-7: Generalized Anxiety Disorder 7

GMI: Graded motor imagery

HSC: Health Sciences Centre

IPQ: iGroup Presence Questionnaire

LLA: Lower limb amputation

NRC: National Research Council

NRS: Numerical Rating Scale

PHQ-8: Patient Health Questionnaire 8

PLP: Phantom limb pain

PQ: Presence Questionnaire

PROMIS: Patient-Reported Outcomes Measurement Information System

RLP: Residual Limb Pain

RCT: Randomized controlled trial

TFAQ: Theoretical Framework of Acceptability Questionnaire

UES: User Engagement Scale

VEQ: Virtual Embodiment Questionnaire

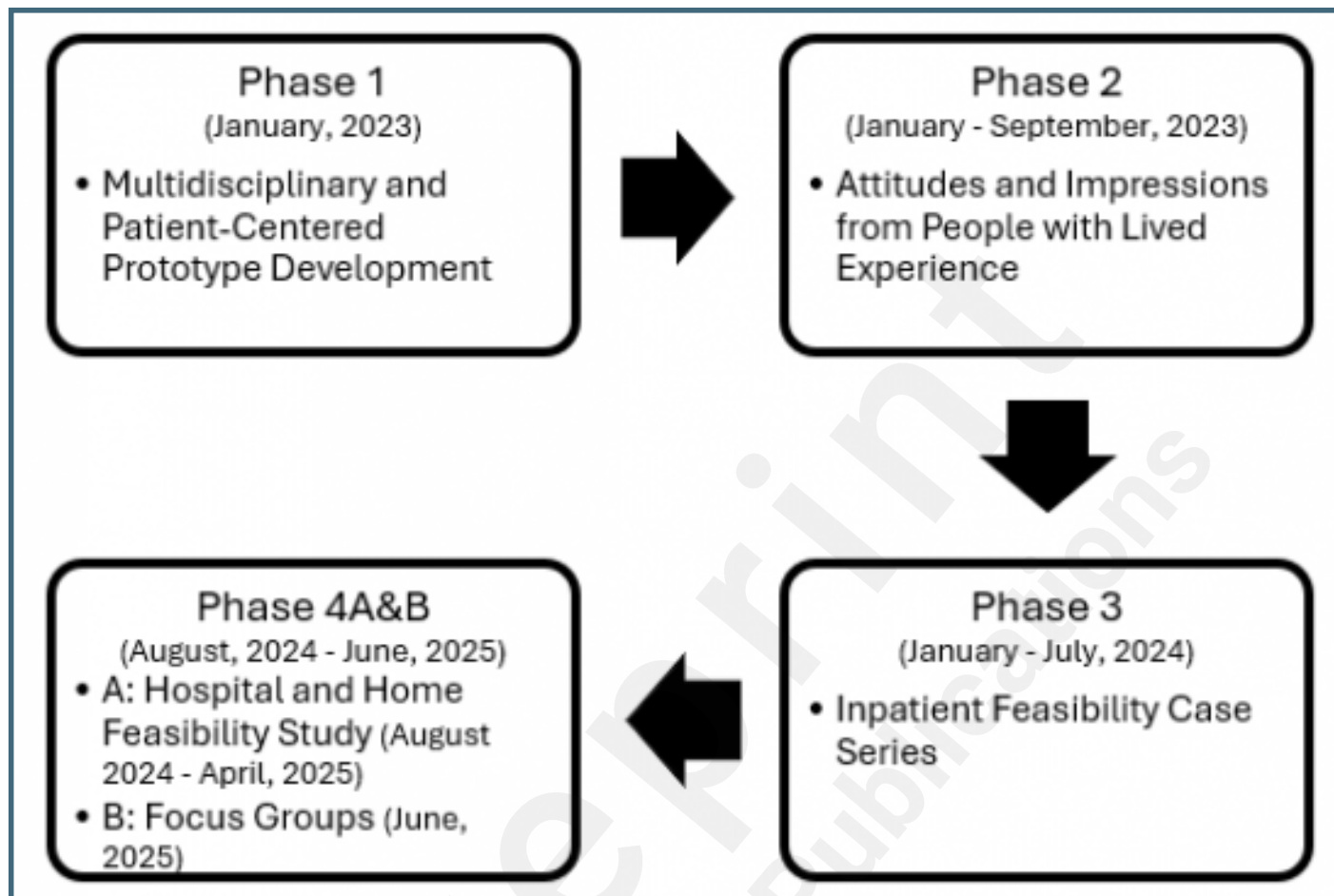
VR: Virtual reality

VR-CORE: Virtual Reality Clinical Outcomes Research Experts

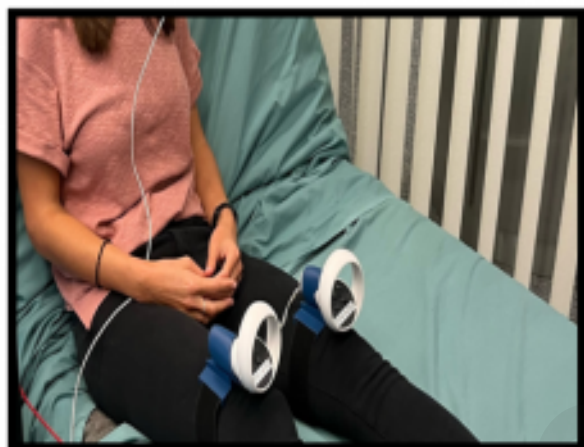
Supplementary Files

Figures

Visual overview of the four phases through which the feasibility of the VR-GMI program will be assessed.



Research team member trialing the hand control trackers attached to the legs via 3D-printed adapters (upper left). Study partner trialing the VR prototype (upper right). Larger image of limb simulation stage in program (lower).



The Virtual Reality (VR) Impressions Scale.

Virtual Reality Impressions Scale

Please rate the extent to which you agree with each statement related to your experience with the virtual reality (VR) intervention, ranging from 0% (completely disagree) to 100% (completely agree).

The way information was presented was clear and understandable _____ %

I enjoyed my session with the VR system _____ %

I could understand and act on the information provided by the system _____ %

The system had a very attractive presentation _____ %

I had to look for assistance when I used this system _____ %

The program froze or stopped unexpectedly _____ %

I found the VR system was helpful _____ %

Did you experience any motion sickness during the VR system>

☐	☐	☐	☐
0	1	2	3
None	Slight	Moderate	Severe

What did you like about the VR system? _____

What did you dislike about the VR system? _____

If you found it helpful: In what ways was the intervention helpful? _____

Was participating in the intervention worthwhile, considering the time commitment (for attending the VR session and completing measures)?

☐ Yes

☐ No

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Adapted Theoretical Framework of Acceptability Questionnaire (TFAQ).

Each TFAQ administration will be preceded with: "When you answer the following questions, think about your experience with this stage specifically in [the hospital/this clinic/your home]."

1. Did you like or dislike the [educational video/insert stage]?

Strongly dislike	Dislike	No opinion	Like	Strongly like
1	2	3	4	5

2. How much effort did it take to [access/engage with] the [educational video/stage]?

No effort at all	A little effort	No opinion	A lot of effort	Huge effort
1	2	3	4	5

3. How fair is it to expect people who recently had a leg amputation to [watch/engage with] the [educational video/stage]?

Very unfair	Unfair	No opinion	Fair	Very fair
1	2	3	4	5

4. It is clear to me how using the [VR program/stage] early on in my recovery will prevent/improve my phantom pain.

Strongly disagree	Disagree	No opinion	Agree	Strongly agree
1	2	3	4	5

5. How confident did you feel about [accessing/engaging with] the [educational video/stage]?

Very unconfident	Unconfident	No opinion	Confident	Very confident
1	2	3	4	5

6. [Watching/engaging with] the [educational video/stage] so soon after my amputation interfered with my other priorities.

Strongly disagree	Disagree	No opinion	Agree	Strongly agree
1	2	3	4	5

7. How acceptable was the [educational video/stage] to you?

Completely unacceptable	Unacceptable	No opinion	Acceptable	Completely acceptable
1	2	3	4	5

The five stages of the VR-GMI program (prior to entering Phase 4A).



Multimedia Appendixes

Development recommendations from study partners with lived experience.

URL: <http://asset.jmir.pub/assets/73d7a6f9c9df592ca14dbe88300e3869.docx>

