IRB Protocol Guidance

1- Background

After amputation, a patient commonly experiences the residual sensation of the limb creating the illusion that their missing limb is still intact. This residual sensation of the missing limb is often referred to as a phantom limb. Along with the phantom limb, patients commonly develop a painful sensation that is perceived as stemming from the missing limb (i.e., phantom limb pain). The Phantom Limb Pain (PLP) is a chronic pain which is considered as one of the most traumatic consequences of amputation. Research has shown that the phantom limb pain is a serious cause of severe distress and physical limitations in 85% of amputees. Restriction in normal activities and higher levels of depression often severely affects patient's social and work life. Although various surgical, psychological and pharmaceutical methods are employed to treat PLP, the effectiveness of these methods is often limited and short-term.

Phantom limb pain is considered to be closely related to neuroplastic changes in at least the primary somatosensory cortex. Based on neuroplasticity, Ramachandran et al. designed a classic method of mirror therapy for the relief of the phantom limb pain. In mirror therapy, a vertical mirror is placed inside a cardboard box with the top removed. The patient is asked to place his/her intact limb in the box such that its reflection in the mirror gets superimposed on the felt position of the phantom limb. Various studies have shown that the visual clue provided by the mirror therapy can induce the vivid sensation of the movement stemming from the muscles and joints of the patient's limb.

Blakemore et al. have aptly explained the fundamental principle of mirror box therapy in terms of the internal forward model of the central nervous system. Whenever any movements are performed, the forward model predicts the sensory consequences of motor commands. Hence, the experience of the limb movement is generally based on the predicted rather than the actual state. But when the limb is missing, motor commands are still issued, and the movement is predicted by the forward model simulating the experience of the movement of the phantom limb. However, as the limb is not actually moving, there is a discrepancy between the predicted movement and the visual feedback of the actual state. The mirror box therapy allows to complete this brain circuitry by providing the visual clue for the phantom limb movement and can restore the movement of the phantom limb voluntary.

Research studies done by Brodies et al. and MacLachlan et al. demonstrate that the mirror box therapy can successfully reduce phantom limb pain (PLP) in lower-limb amputees as well. MacLachlan et al. performed a detailed study with a patient experiencing a severe chronic phantom pain due to lower limb amputation. The study indicates that the phantom pain was reduced from 5-9 to 0 (on the scale of 0 -10, 0 = none and 10 = excruciating). Sherman et al. reported that the repeated attempt to move a phantom limb may result in an increase in control and a reduction in pain.

The user study conducted by Brodie et al. suggested that the addition of visual feedback of a moving virtual leg in conjunction with the attempted movement of the phantom leg significantly increases the ability of an amputee to move or control his/her phantom leg. Quantitatively, the visual feedback resulted in a threefold increase in the amount of movement control experienced by amputees. Next, Chan et al. conducted a study where 22 participants were randomly assigned to three groups: one that viewed the mirror image of their intact limb (mirror group) and another who

viewed the covered mirror (no reflection of the intact limb) and one that was trained in mental visualization. After 4 weeks of treatment, 100% of mirrored group reported a decrease in the phantom pain. In contrast, in the covered mirror group, only 17 % reported reduction in pain while 50% reported increase in the pain. In the mental visualization group 33% reported decrease in pain while 67% reported worsening pain.

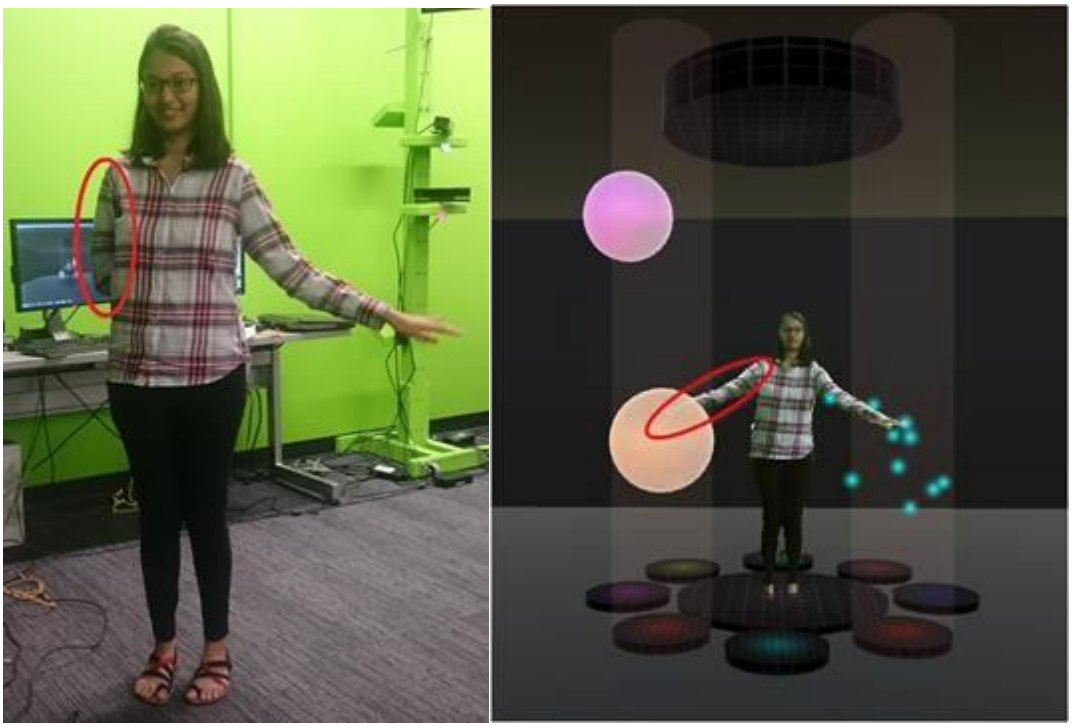
However, the mirror box therapy is highly constrained by the limited spatial movement, requirement of a patient to remain in the fixed posture. Furthermore, the illusion obtained is wavering in nature and requires the patient to pay continual attention only to the reflected image that can be tedious and stressful. To overcome the challenges presented by the mirror box therapy, various virtual reality-based methods are suggested in the literature. Most of these methods utilize a pre-built 3D model of the phantom limb generated using graphics tools. The movement of amputee's intact limb is captured using various body sensors and transposed to the 3D model of the phantom limb.

Virtual reality-based methods provide the similar illusion to the mirror box therapy while providing the higher flexibility in the movement and without the space constraints. However, these methods are highly susceptible to degraded immersive experience due to a mismatch in the skin color, clothes, artificial and rigid look and misalignment of the phantom limb. Furthermore, most of the virtual reality-based methods proposed in the literature rely on external devices or sensors to be worn by a person to capture the motion. Wearing such sensors can inhibit the natural user movement and can also cause skin irritations and discomfort. Due to the usage of such body sensors, these methods can be considered as invasive and present difficulties in employing them in pain relief sessions.

Our team is currently evaluating the application and utility of virtual reality and computer vision technologies in a novel tele-rehabilitation system for lower-limb amputation. The proposed pilot study would extend this work by designing, developing, and applying innovative technology to a lower limb amputee population. We have designed and developed a novel Mixed Reality based system for Managing Phantom Pain (Mr. MAPP). The proposed framework employs off-the-shelf RGB-D cameras such as Microsoft Kinect V2 to capture and generate a 3D model of the person in real-time.

An illusion of the virtual limb is crafted by mirroring the patient's symmetric anatomical limb in the captured data using various computer vision and graphics techniques. The major challenges in developing the Mr. MAPP framework are: a) capturing the live 3D models of the human, b) generating the 3D model for the phantom limb in the real-time, c) generating corresponding movement in the real-time, and d) rendering the 3D model of the person along with phantom limb for the immersive and interactive experience.

Also, to make the therapy sessions more engaging, fun and non-monotonous, it is also required to design an attractive virtual environment and game with the engaging task. Figure 1 shows the virtual environment developed for Mr. MAPP framework. The quantitative and qualitative evaluation of the Mr. MAPP framework is performed by a group of able-bodied participants and Subject-Matter Experts (SME). The results indicate the effectiveness and usefulness of the Mr. MAPP framework. Given the encouraging results of existing studies to determine the effectiveness of a classic mirror-box therapy, it also becomes crucial to evaluate the efficacy of virtual mirror box therapy using Mr. MAPP framework in a similar manner.



1-a 1-b

Figure 1-a: Real scene with healthy user keeping her right hand behind (to simulate amputation) Figure 1-b: Virtual scene with phantom limb.

2- Purpose

The primary goals of this pilot research project are a) to design and develop a mixed reality based system for managing phantom pain and b) to evaluate the feasibility and preliminary functional outcomes of this system in a sample of patients with lower limb amputation. Findings from this pilot study will serve as preliminary data to inform regarding a fully powered clinical trial to determine the effectiveness and practical implementation of these findings in real-world settings.

Aim1: Design and develop a feasible mixed reality-based system to manage phantom pain in patients with lower limb amputation qualifying for on-going mirror therapy.

Hypothesis 1: We hypothesize that our mixed reality-based system to manage phantom pain will be feasible and well received by a sample of patients with lower limb amputation needing mirror therapy.

Aim2: Evaluate functional outcomes in a sample of lower limb amputees (n=10), using this mixed reality-based system to manage phantom pain.

Hypothesis 2: Using this system, we hypothesize that patients who participate in our mixed reality-based system will show improvements in patient-reported outcome measures (PROs). We also hypothesize that this mixed reality-based system will help to alleviate the phantom pain based on Pain questionnaires and numerical rating scale (NRS).

3- Study Design

This is a pilot study is intended to yield preliminary data that will inform a fully powered trial to determine effectiveness of our novel Mixed Reality based system to manage phantom pain. A HIPAA waiver will be obtained to screen patients with lower limb amputation in the outpatient PM&R clinics. Eligible study candidates will be identified either during an initial visit as an outpatient during clinic visit with the physiatrist, or during review of prior visit with physiatrist. The eligible, pre-screened subjects will undergo a basic evaluation (by rehabilitation physician). After the evaluation, the patient will be asked to participate in the study or sent an invitation letter.

Once an eligible patient consents to enroll in the study with specific emphasis on safely performing the exercises independently at home, the research team will provide the laptop, camera and instruct the patient in its use at their home. The patient will then use the system and perform the personalized home exercises every day for a 1-month period (to evaluate sustainability of exercise behavior). At initial clinic visit, week 1 visit and 1-month visit, the patient will fill out pain questionnaires, functional questionnaire without any identifiable PHI. At the end of this period, the system will be returned by the patient at the final study visit. Research lab staff may retrieve the system may be retrieved from a patient's home if they are unable to bring it to the final visit. The images of the patients performing the exercises will be stored in the encrypted laptop and analyzed at UTD. All videos at UTD will be destroyed after 5 years, but a copy will be kept at the Dallas VA.

4- Functional Outcome Measures:

a- Numerical rating Scale (NRS)
b- Brief Pain Inventory (BPI)
c- McGill Pain Questionnaire
d- Patient Specific Functional Scale
e- Phantom Limp Pain Diary
f- Usability Survey g- Medication Use

At the end of the study, patients will have the option to leave feedback and suggestions for future use of this system.

5- Study Population

Patients 18 years of age and over with history of lower limb amputation and complaint of phantom limb pain. Phantom limb pain is a condition experienced commonly by patients with major limb amputations.

6- Criteria for Inclusion

Men and women, over the age of 18 with lower limb amputations (greater than 3 months post-surgery) with phantom limb pain.

7- Criteria for Exclusion

- Patients with lower limb amputations with open wounds or active infection in residual or contralateral limbs.
- Patients with history of seizures.
- Patients with visual (self-reported) or cognitive impairment (assessed by the mini-mental state examination) that interferes with ability to interact with, participate in, and adhere to a computerized rehabilitation system.
- Any patient with a cardiac event in the last 6 months.
- Any patient with an active medical issue to minimize risk of exacerbating their condition.
- Lives more than 60 miles away from the Dallas VA Medical Center.
- Any patient with the motion sickness induced by head mounted displays (HMDs) or immersive environment.
- Any patient experiencing the motion sickness induced by HMDs during the therapy session can also opt out of the study.

8- Number of participants

In this exploratory, pilot study, we will recruit a convenience sample of 10 patients. A sample of 10 subjects is adequate and consistent with other pilot behavioral intervention trials at the VA that have been completed and published.

To ensure meaningful statistical analysis of 10 sets of viable and complete data, one additional patient will be recruited to make up for each patient that withdraws from the study and whose date is not usable.

9- Study Procedures

The subject will be participating in a therapy session of 15 minutes per day for a duration of 4 weeks. Before starting a session, the subject will be provided with oral instructions about the overall system and the purpose of study. They will be asked to fill out questionnaires asking about the status of phantom pain, phantom limb movement, stress level etc.

After completing the questionnaire, they will be allowed to move in virtual world to get acquainted. Each session consists of three sub-sections where the subject is asked to play three different virtual games. These virtual games are designed specifically for lower limb amputees. Each game is targeting certain types of muscle movement.

We focused mainly on three types of movements: 1) knee flexion and extension, 2) ankle dorsiflexion and plantar flexion, and 3) tandem coordinated bilateral lower extremity movement. Each game will be played only for 5 minutes. After completing each sub-session, the subject is asked to fill out similar questionnaire to record the effect.

Figure 4: Lower Phantom Limb Illusion

Schedule of events:

		Visits		
		Baseline Visit	**1-Week Visit**	**1-Month Visit**
Study Procedures	**Informed Consent**	X		
	Past Medical History/Medication Use	X		X
	Numerical Rating Scale	X	X	X
	Brief Pain Inventory	X	X	X
	McGill Pain Questionnaire	X	X	X
	Patient-Specific Functional Scale	X	X	X
	System Setup, Instructions, Review	X	X	
	MrMAPP Usability Survey			X
	Return Phantom Limb Pain 4week daily diary			X
	Return System			X

10- System Overview

Our system consists of one Microsoft Kinect camera, Oculus Rift (a visualization device, see Figure 2) and a computer system with sufficient processing power. Microsoft Kinect is used to scan the person and to create corresponding 3D model. As shown in Figure 3, the 3D model for the phantom limb is obtained by mirroring the 3D model of the intact limb. So, the subject will be able to perceive both limbs in the virtual world. Our system provides a mixed reality-based implementation of mirror therapy for managing phantom pain.

Major features of this system include:

- Unconstrained movement: As patient will be performing exercise in virtual environment, the movement is not restricted by limited space as in case of traditional mirror box therapy where user can only move in the limits of box dimension.
- Realistic illusion of phantom limb: As the Mr. MAPP framework is using RGB-D camera to capture the movement of patients intact limb and mirror it to create the illusion of the phantom limb, the illusion obtained is very realistic instead of using pre-built 3D model of a limb (See Figure 4).
- Patient Encouragement: Use of an immersive gaming environment motivates and keeps the patient engaging while performing exercise. With the help of virtual reality, various engaging game can be developed that helps to remove monotonousness in therapy sessions.
- Feedback with positive Reinforcement: As each game is designed to encourage a patient to perform certain type of exercise, the points earned in the game motivates the patient to perform better.
- Adherence and compliance monitoring: by recording and annotating the therapy sessions, the coaching software will monitor parameters such as number of repetitions, dates and times of exercises, as well as correctness of performing the exercises. This will serve as a real-time diary which is considered more reliable than self-report diaries that rely on patient recall of activity.

Figure 2: Visualization using HMD (Oculus Rift)

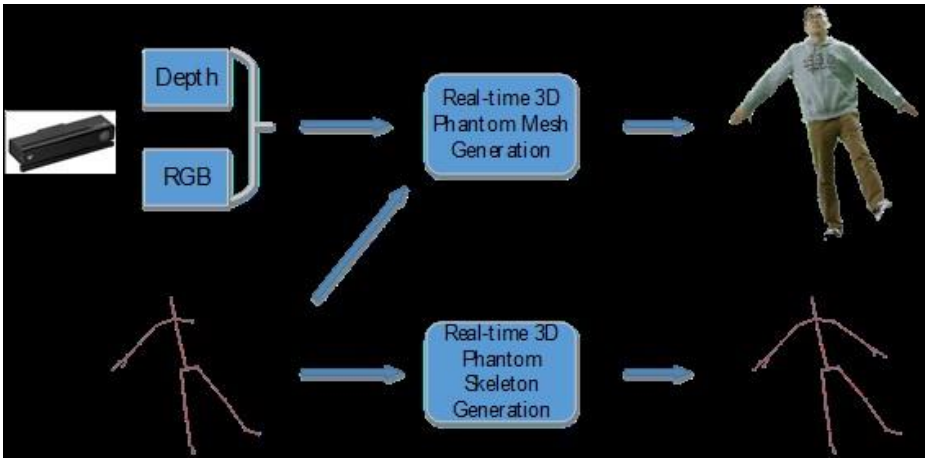


Figure 3: System Overview

11- Statistical Data Analysis

We will use descriptive methods to characterize our sample population. Pre-post t-tests or equivalent will be used to compare outcomes at one week and 1 month. Given the pilot nature of this proposed study, inferential statistics (and reporting of statistical significance) will not be used.

Feasibility outcomes will be descriptive, including calculating the percent of individuals enrolled in the study versus those eligible and the percent of individuals who remain in the study at month 1.

Aims 1 and 2 will help establish intervention acceptability and feasibility. The images of the patients will be stored in the encrypted laptop and analyzed at UTD. Participants' videos will be destroyed at UTD after 5 years, however, a copy will be kept at the Dallas VA.

12- Reporting Adverse Events

Using weekly telephone support and online ad-hoc support features of the proposed system, we will obtain adverse event data and intervene as needed for any safety issues that may arise during this pilot study.

13- Potential Risks

Anticipated adverse events include those that might reasonably be expected to occur in association with the patient's disease state. The following is a list of anticipated adverse events and reactions that may occur.

These may include, but may not be limited to:

- Increased baseline pain during rehabilitation
- Swelling

The overall risk classification for this research is minimal.

14- Data Safety Monitoring

This study does not require a Data Safety Monitoring Plan (DSMP) or a Data Safety Monitoring Board (DSMB). A Data and Safety Monitoring Board (DSMB) is required for Phase III studies. For phase I and II trials, the DSMB may be required if the study has multiple clinical sites, is blinded or employs high risk interventions or vulnerable populations.

15- Confidentiality and Protecting the Subject's Privacy

Results of this research study will continue to be securely maintained in accordance with VHA Record Control Schedule upon completion of the study. The records will be kept in a locked file cabinet or locked room with limited access. If the PI leaves the VA facility, the original research records will be retained by the institution All records of this research study will continue to be securely maintained in accordance with VHA Record Control Schedule upon completion of the study. The records will be kept in a locked file cabinet or locked room with limited access. If the PI leaves the VA facility, the original research records will be retained by the institution.

16- Documentation of Informed Consent

The PI, co-PIs and research coordinator will have the responsibility of approaching the patient. These individuals will enter the appropriate research enrollment accept note in CPRS. Research enrollment notes will be entered into CPRS following the structure in Chapter 8 of the PPHRS.

17- Payment to Subjects for Their Participation

Participants will receive a onetime $50 stipend for their time and inconvenience related to participating in this study. The payment voucher will be submitted and process after the patient returns to the VA for the last study visit and returns study equipment. If for any reason patients do not complete the study and withdraw prior to completion, they will not be eligible for the one-time stipend. Payments will be issued in the form of a mailed check or ClinCard. Participants' name and social security number must be disclosed to Dallas VA Research Corporation employees in order to process any payments.

18- Provisions for Data Storage and Confidentiality

In accordance with HIPAA, the HIPAA Authorization form describes to the subject what protected health information (PHI) will be obtained and/or stored and for what purpose, as well as a list of who may have access to this data, including outside agencies. For the data collected at the VA, the records will be kept in a locked file cabinet or locked room with limited access or stored at a VA-approved storage facility. Electronic data will be maintained in a password protected file on the VANTHCS server within the firewall. If the PI leaves the VA facility, the research records will be retained by the institution. For the data collected on the laptop, the laptop is encrypted, and the patients will be provided with their own username and password. If the laptop is lost/stolen, the encryption should prevent theft of any data. When the laptops are not in use, they will be kept in a secure location at UTD for data analysis for a limited time.

19- Dissemination of Research Results

This is a pilot study intended to yield preliminary data that will inform a fully powered trial. The data results may be presented at a national conference and/or submitted to a peer reviewed journal for publication. The results may be used in a proposal for funding.

Amendments

Amendment	Summary of Changes	Date
1	Substitute VAS for NRS, add BPI short form, include collection of medication use. Study personnel changes; schedule of visits. Recruit additional 6 patients.	22 Oct 2020
2	Include payment of $50 stipend for completing the study	23 August 2021