PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH
A Global Journal of Clinical Research

Enhancing Dissemination and Understanding in Clinical Research Protocols: Optimizing Visual Communication in a Phantom Limb Pain Clinical Trial

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Introduction

Clinical research offers the opportunity to observe tangible benefits coming from a laboratory- derived intervention. It is a critical step in the potential integration of the therapeutic into healthcare. Critically, unlike traditional laboratory research, clinical research deals closely with human patients, adding a layer of difficulty in how the study is communicated to both specialist and lay audiences. However, conveying the intricacies of research protocols can be challenging, often relying heavily on dense textual descriptions. This issue is compounded by the trend of increasing clinical trial complexity, especially in terms of protocol execution (Getz et al., 2017).

Trials with complex methodologies may place high burdens on research staff and patients alike, reducing the quality and quantity of collected data (Getz et al., 2017). In fact, complexity of trial protocol is a highly cited obstacle for patient recruitment and retention (Kadam et al., 2016). The impacts of complicated protocols are potentially more significant in pragmatic clinical trials (PCTs), wherein the protocol is designed to mimic real world data and thus may involve staff not used to clinical research protocols such as non-research physicians, nurses, or patients themselves–all individuals who did not take part in designing or writing the protocols and may not have a research background. Not only may these protocols prevent proper training of subjects involved in the study, but recruitment and drop-out rates that disproportionately affect different populations may introduce selection bias (Haff et al., 2018). For instance, complex protocols may be more of a deterrence against participation for subjects with lower health literacy or under-resourced clinics.

It is thus of great importance to consider the perspective of those taking part in the study and develop methods for simplifying complex protocols. Notably, visual communication is a highly effective but rather underutilized tool for facilitating this goal in clinical trials. They are important not only to depict results but to provide detailed information on the study design, significance, and outcomes. In essence, visuals provide an avenue for more patient-centric trial design while democratizing trial recruitment and adherence. Clear, compelling visuals can overcome language and literacy barriers to attract a larger and more diverse pool of participants. By utilizing visuals in protocol design, researchers can create more understandable materials for participants, leading to higher levels of adherence and engagement. These effects may improve the reliability and generalizability of trial results. In this editorial, the importance of visual communication in clinical research protocols will be emphasized using a pragmatic trial on phantom limb pain as an illustrative example.

Methods of Visual Communication

The incorporation of visuals into clinical research protocols, while seemingly simple, requires ample consideration. If designed correctly, visual aids in the forms of photographs, graphs, flowcharts, and diagrams can improve protocol clarity by making it more inclusive and accessible for a variety of populations. Thus, visual communication has been heavily adopted in prominent journals such as Nature and JAMA to enhance comprehension for non-specialist

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Received: February 23, 2024 **Accepted:** March 7, 2024
Published: May 23, 2024
Editor: Alma Sanchez Jimenez
Keywords: phantom limb pain, clinical research
DOI: http://dx.doi.org/10.21801/ppcrj.2024.101.8

researchers and lay audiences (Krause, 2017). Various types of visual communication exist, and their suitability hinges on the specific context in which they are used. For instance, concepts involving sequential or conditional processes may benefit from being visualized using flowcharts to facilitate a better understanding of the trial's structure and methodology. Results of a study are better conveyed using charts and graphs, which in itself contains a multitude of different options to best represent the data. Science illustrations and infographics combine powerful visuals with simple captions and are very versatile in their use. Videos and animations may be the most effective way to communicate concepts to the general public, but they require a greater investment of time and resources. In creating these visuals, traditional methods of sketching with a paper and pencil may not be ideal for clear communication of scientific illustration. There are several software packages that can help with digital visual illustration creation, with the Adobe Creative Cloud being the industry standard. Of the programs in this suite, Adobe Illustrator is most suitable for creating clear, precise linework for vector-based visualizations that can be easily scaled and distributed.

Two important considerations in creating the graphic are (Brunelli et al., 2015) the story the visual should convey and (Fregni, 2022) the intended audience receiving this message. Throughout the design process, it is crucial that clarity is not sacrificed for aesthetics; while the schematic should ideally be visually appealing, the top priority is to maintain a cohesive format that minimizes ambiguity for the audience–something that can be achieved by establishing a clear visual hierarchy and consistency in fonts, colors, themes, etc. (Kadam et al., 2016; Krause, 2017; Midway, 2020). As an example, different colors carry different connotations, i.e. red is usually associated with pain, so putting special thought into choosing colors will bolster the message being conveyed through the visual.

Visuals should also be made in a way that promotes inclusivity and accessibility. One way this can be achieved by using silhouettes so as to not profile race or gender unless it is a part of the message being conveyed. Additionally, fonts and colors (in addition to their value and transparency) should be carefully chosen to ensure readability in people with visual impairments such as color blindness. In clinical trial protocols, each figure created should be adjusted according to the target study population.

An Example of Using Visual Communication to Explain the Design of a Pragmatic Trial of Phantom Limb Pain Therapy

The PLP-EVEREST (PLP-EffectiVEness pRagmatic Stimulation Trial) (Fregni, 2022) aims to evaluate the effectiveness of remote transcranial direct current stimulation (tDCS) and somatosensory training on alleviating phantom limb pain (PLP). PLP affects 60-85% of amputees and can lead to permanent disability in over 40% of patients (Hanyu-Deutmeyer et al., 2023). However, there is no all-encompassing approach to treating PLP, with physical rehabilitation-based treatment methods exhibiting a wide range of efficacy–potentially attributable to factors such as patient nonadherence and lack of personalization to the unique clinical characteristics of each patient.

The premise of our trial involves transforming a previously validated PLP combination therapy into a home-based rehabilitation approach to increase patient adherence and treatment outcomes (Brunelli et al., 2015; Fregni, 2022). As PLP is believed to be caused by maladaptive neuroplasticity–i.e. the reorganization of cortical sensorimotor networks that erroneously leads to the perception of pain in a limb that no longer exists–neuromodulatory treatment approaches involving tDCS have been widely explored in clinical research (Morales-Quezada, 2017). Anodal tDCS in the M1 region of the brain influences the likelihood of neuronal firing in the primary motor cortex, whereas phantom limb exercises stimulate activity within somatosensory pathways affected by limb amputation. A combination of both therapies links the M1 and phantom sensorimotor stimulation to enhance the treatment effects of tDCS (Figure 1).

Central to our study was the home-based format of the PLP interventions (Figure 2). From the patient's perspective, remote tDCS presents as a more time and cost-effective alternative to that conducted in a traditional lab setting. However, confusion may arise regarding the proper execution of the trial's protocol without the presence of trained scientists. While these home-based pragmatic trials are more likely to be an accurate reflection of treatment effects in the real world outside of the tightly controlled environment of traditional clinical trials, the quality of the collected data depends on how accurately and precisely patients are able to carry out the protocol (Morales-Quezada, 2017). Thus, it is in both the patient and researchers' best interests to simplify protocols to obtain the most accurate results on the effectiveness of an intervention.

To ensure patients are equipped with the necessary training to proceed with remote tDCS, the PLP-

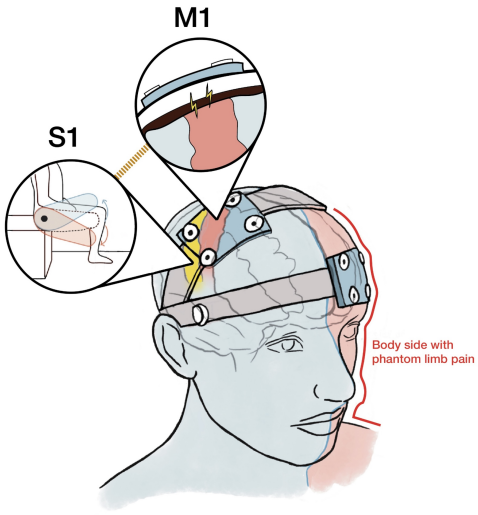

Figure 1: *Mechanism of action of the combination remote tDCS and somatosensory training, which is proposed to link electrical stimulation of the primary motor cortex (M1) to activation through PLP exercises in the primary somatosensory cortex (S1).*

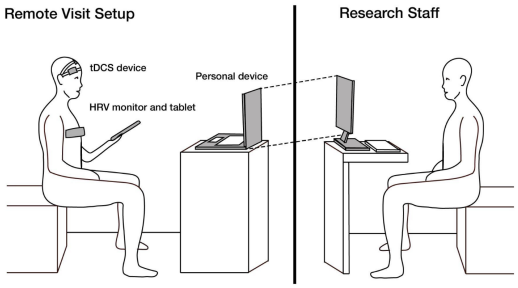

Figure 2: *Home-based visit setup for the PLP-EVEREST trial. For each visit, participants will wear an HRV chest sensor and collect this data on a tablet while being remotely monitored by the research staff.*

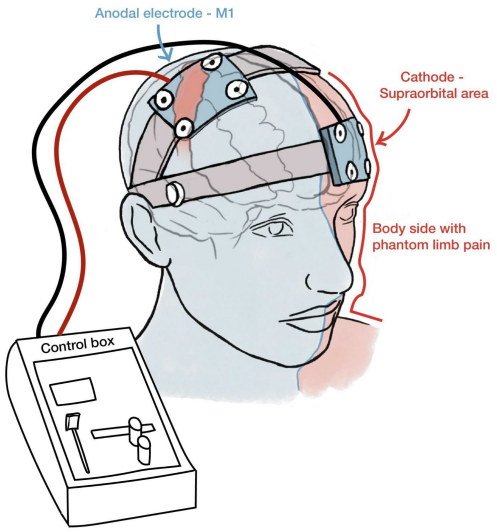

Figure 3: *Placement of the tDCS electrodes, with the body side with phantom limb pain shown in red and the contralateral side shown in blue.*

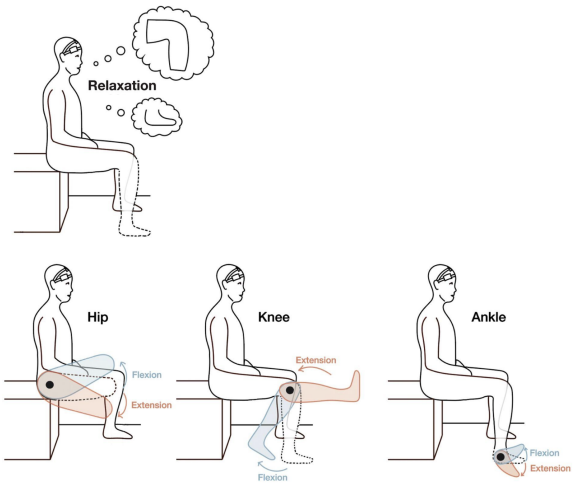

Figure 4: *Somatosensory training, with Relaxation stage (top) and phantom exercises (bottom).*

EVEREST study will provide each participant with a diagrammed exercise instruction booklet that will guide them through each home-based session. As shown in Figure 3, tDCS will be carried out by placing the anodal electrode over the M1 region contralateral to the side of the body with PLP pain whereas the cathode will be placed over the contralateral supraorbital area (forehead). The visualization of the anatomy of the cranium as well as the specific region of the target M1 region facilitates the accurate placement of the electrodes. Using both thick and thin outlines establishes contrast between components significant to the study protocol–such as the tDCS contraption–and elements that are to be used as guiding tools–such as the outline of the brain. Certain color choices, such as the use of red to represent the side of phantom limb pain, also aid the patients' understanding.

Figure 4 depicts the somatosensory training to be carried out by the patient during self-administration of tDCS. Figures were deracialized and degenderized to ensure a sense of inclusivity regardless of who views the pamphlet. The first part involves relaxation, in which subjects use the body scan technique to mentally establish a connection with each body part from head to toe. This is depicted in the figure through the top-down ordering of the thought bubbles. Next, patients will place their intact and phantom limb in the same position and perform imaginary movements with their phantom limb–specifically, 15 repetitions each of hip flexion/extension, knee flexion/extension, and ankle flexion/extension. Flexion and extension movements are distinguished by color as well as arrows, with the original position of the phantom limb shown in dotted lines as a reference point.

Figures were created first as sketches, validated for technical and protocol-relevant accuracy, and then finalized using Adobe Photoshop/Illustrator software. In this way, we visually delineated the procedures involved in the intervention and highlighted key elements such as electrode placement. While relatively straightforward, the significance of creating these illustrations should not be overlooked, as they can drastically enhance understanding and implementation of the study protocol in a remote setting. The PLP-EVEREST study aims to compare patients randomized to combination rehabilitation therapy vs. usual care alone (Figure 5). For those receiving the rehabilitation therapy, a home-based intervention kit will be mailed to them, which includes a laptop, tDCS device, and heart rate monitor. Therefore, if the subject is randomized to the tDCS, it will be mailed to their homes. The effectiveness of these two treatment approaches will be evaluated through autonomic responses. Higher heart rate variability (HRV) and reduced sympathetic activation will be regarded as signs of improved pain outcomes and, thus, reduced PLP (Fregni, 2022).

Furthermore, machine learning techniques will be used to identify clinical and neurophysiological predictors of the response to the combined interventions, providing insights for future treatments and personalized PLP care. Our trial incorporates innovative approaches to pain management, leveraging emerging technologies and therapeutic modalities. Especially given that this optimized remote therapy will make treatment options more accessible to populations such as those living in rural areas or with cognitive decline, incorporating visual communication aids in the study design may improve study adherence and satisfaction. Ultimately, our trial holds implications for the management of phantom limb pain, offering potential avenues for improving the

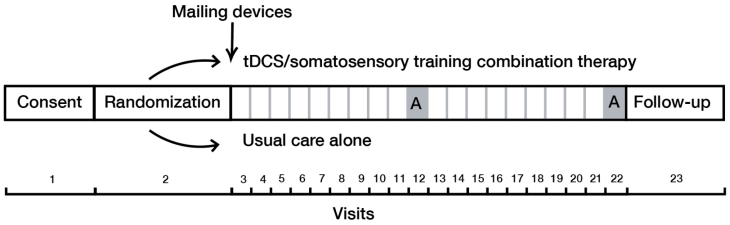

Figure 5: *Timeline view of the PLP-EVEREST study, which contains a total of 23 visits. After a consent meeting, participants will be randomized to either the tDCS/somatosensory training combination therapy or usual care alone. For the combination therapy, devices will be mailed to the participants' homes. Following this, 20 intervention sessions will be carried out, of which 2 sessions will involve assessments (A).*

quality of life for individuals living with this debilitating condition.

Conclusion

Clinical research is a culminating step in translating therapeutic interventions from a lab bench discovery into a real-world treatment–which underscores the importance of ensuring comprehension and transparency. As illustrated by our pragmatic trial on a combination PLP intervention, visual communication serves as a powerful tool for improving protocol clarity in the realm of clinical research. This graphical instruction approach should be expanded to pragmatic trials, including those involving physicians acting as facilitators of the study for each patient.

Visual communication can be effectively used in both traditional and pragmatic clinical research, whether it is through bare-bones flowcharts or intricate illustrations. Regardless of one's artistic ability, we envision that investing some time into thoughtfully creating visual aids would play a vital role in elucidating the complexities of clinical research protocols. In this way, researchers can convey essential information pertaining to study design, interventions, outcomes, innovation, and significance, thereby enhancing understanding during the trial as well as facilitating broader dissemination of research findings.

Funding

FF is supported by NIH grant (5R01HD082302-08). KPB is supported by the Spaulding Research Institute (Spaulding Research Accelerator Program).

Conflicts of Interest

The authors declare no conflict of interest.

References

- Brunelli, S., Morone, G., Iosa, M., Ciotti, C., De Giorgi, R., Foti, C., & Traballesi, M. (2015). Efficacy of progressive muscle relaxation, mental imagery, and phantom exercise training on phantom limb: A randomized controlled trial. Archives of Physical Medicine and Rehabilitation, 96(2), 181–187. https://doi.org/10.1016/j.apmr.2014.09.035
- Fregni, F. (2022). Pragmatic trial of remote tDCS and somatosensory training for phantom limb pain with machine learning to predict treatment response (PLP-EVEREST) [Identification No. NCT05188183]. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05188183
- Getz, K., & Campo, R. (2017). Trends in clinical trial design complexity. Nature Reviews Drug Discovery, 16, 307. https://doi.org/10.1038/nrd.2017.65
- Haff, N., & Choudhry, N. K. (2018). The promise and pitfalls of pragmatic clinical trials for improving health care quality. JAMA Network Open. https://doi.org/10.1001/jamanetworkopen.2018.3376
- Hanyu-Deutmeyer, A. A., Cascella, M., & Varacallo, M. (2023). Phantom limb pain. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK448188/
- Kadam, R. A., Borde, S. U., Madas, S. A., Salvi, S. S., & Limaye, S. S. (2016). Challenges in recruitment and retention of clinical trial subjects. Perspectives in Clinical Research, 7(3), 137–143. https://doi.org/10.4103/2229-3485.184820
- Krause, K. (2017). A framework for visual communication at Nature. Public Understanding of Science, 26(1), 15-24. https://doi.org/10.1177/0963662516640966

- Midway, S. R. (2020). Principles of effective data visualization. Patterns, 1(9), 100141. https://doi.org/10.1016/j.patter.2020.100141
- Morales-Quezada, L. (2017). Noninvasive brain stimulation, maladaptive plasticity, and Bayesian analysis in phantom limb pain. Medical Acupuncture, 29(4), 220–228. https://doi.org/10.1089/acu.2017.1240