PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A study protocol for a randomized controlled trial of virtual reality-based distraction for intravenous insertion-related distress in children
AUTHORS	Ali, Samina; Rajagopal, Manasi; Stinson, Jennifer; Ma, Keon; Vandermeer, Ben; Felkar, Bailey; Schreiner, Kurt; Proctor, Amanda; Plume, Jennifer; Hartling, Lisa

VERSION 1 – REVIEW

REVIEWER	Tighiouart, Mourad Cedars-Sinai Medical Center
REVIEW RETURNED	28-Oct-2021

GENERAL COMMENTS	A randomized controlled trial of virtual reality-based distraction for venipuncture-related distress in children This protocol describes a randomized controlled trial to investigate the effectiveness of the use of virtual reality using VR goggles and appropriate software in children undergoing IV insertion in reducing distress, pain, and fear, relative to standard of care strategies. The protocol is well written, contains all relevant literature and rationale for the study. The trial endpoints including primary and secondary objectives are clearly outlined and well justified using established metrics of quantifying measures of distress, pain, fear, safety, and satisfaction. Extensive details were included for measuring all outcome variables by trained research assistants are provided. The plan is to accrue 80 patients randomized to VR intervention vs. standard of care on a 1:1 ratio, accounting for 10 to 15% attrition rate. The trial is powered (80% power) to detect a practically significant effect size of 0.6 for distress at the two-sided 0.05 level of significance. The statistical analysis plan is clearly described, comprehensive, and is appropriate for testing all relevant hypotheses. My only comment is the lack of stratification variable(s) unless I missed it. Specifically, stratification by age (younger children vs, older children) since they use different software may be desirable although the trial has been open to accrual for over a year now.

REVIEWER	Foxen-Craft, Emily University of Michigan
REVIEW RETURNED	19-Nov-2021

GENERAL COMMENTS	Thank you for the opportunity to review this study protocol. This study aims to assess the clinical utility of using virtual reality to help manage distress among children undergoing intravenous insertions in the emergency room. The protocol addresses an important clinical need, is clearly written, and thoughtfully included a parent stakeholder perspective in the design. Addressing the following concerns would strengthen the manuscript for publication: Introduction 1) The authors could improve clarity by using more consistent or precise terminology between intravenous insertions, venipuncture, and needle insertion. 2) Here and in future publications, the authors should elaborate on how this study adds to the literature, highlighting the unique aspects of the ER settings. 3) The authors should consider citing research of VR in experimental pediatric pain research, and as well as research on VR in different settings, such as: a. Zeroth, J. A., Dahlquist, L. M., & Foxen-Craft, E. C. (2019). The effects of auditory background noise and virtual reality technology on video game distraction analgesia. Scandinavian journal of pain, 19(1), 207-217. b. Dahlquist, L. M., McKenna, K. D., Jones, K. K., Dillinger, L., Weiss, K. E., & Ackerman, C. S. (2007). Active and passive distraction using a head-mounted display helmet: effects on cold pressor pain in children. Health Psychology, 26(6), 794. c. Gold, J. I., Kim, S. H., Kant, A. J., Joseph, M. H., & Rizzo, A. S. (2006). Effectiveness of virtual reality for pediatric pain distraction during iv placement. CyberPsychology & Behavior, 9(2), 207-212. Methodology 4) The authors should consider tracking which games are used with the VR program, as there is likely variability in engagement (i.e. active vs passive) and the sensory stimuli used (in fact, the authors note that not all games incorporate the hand held controllers). 5) It is not clear how the portion of standard of care that includes child life services and nursing support can co-occur with VR administration. It may be difficult for readers to imagine, for instance, how a child life specialist may guide a child to engage in deep breathing when they have headphones on and their vision is occluded. The authors might consider elaborating on this, or reframe the study as a comparison rather than superiority trial. If the trial is a comparison of topical anesthetic and other standard nonpharmacological care vs topical anesthetic and VR, that should be articulated more clearly in the title, aims, and throughout the manuscript. 6) The authors should also discuss how the OSBD will be modified to accommodate the children in the VR condition who's faces will be covered by the goggles, and how that will be implemented consistently across the two study arms. For instance, crying may not be apparent if the child's eyes are covered by the Oculus headset. If this is not possible, the authors should consider a different primary outcome.

VERSION 1 – AUTHOR RESPONSE

Reviewer	Section	Comment	Response
1		This protocol describes a randomized controlled trial to investigate the effectiveness of the use of virtual reality using VR goggles and appropriate software in children undergoing IV insertion in reducing distress, pain, and fear, relative to standard of care strategies. The protocol is well written, contains all relevant literature and rationale for the study. The trial endpoints including primary and secondary objectives are clearly outlined and well justified using established metrics of quantifying measures of distress, pain, fear, safety, and satisfaction. Extensive details were included for measuring all outcome variables by trained research assistants.	Thank you for the kind comments.
		The plan is to accrue 80 patients randomized to VR intervention vs. standard of care on a 1:1 ratio, accounting for 10 to 15% attrition rate. The trial is powered (80% power) to detect a practically significant effect size of 0.6 for distress at the two-sided 0.05 level of significance. The statistical analysis plan is clearly described, comprehensive, and is appropriate for testing all relevant hypotheses. My only comment is the lack of stratification variable(s) unless I missed it. Specifically, stratification by	Thank you for this excellent suggestion. We will consider this for the planning of future trials, as we have been recruiting for nearly 18 months and are close to study completion. Stratification by age will most certainly be included in our team's future, planned multi-centre trials. Of note, we have planned for additional model-based analyses (multiple linear regression), as needed, with behavioural distress as the response variable, pre-procedure behavioral distress and group indicators as the explanatory variables along with some possible effect modifiers such as age, sex, and parental/caregiver anxiety levels. As such, we are taking age into

		age (younger children vs, older children) since they use different software may be desirable although the trial has been open to accrual for over a year now.	account in our planned analyses.
2	General	Thank you for the opportunity to review this study protocol. This study aims to assess the clinical utility of using virtual reality to help manage distress among children undergoing intravenous insertions in the emergency room. The protocol addresses an important clinical need, is clearly written, and thoughtfully included a parent stakeholder perspective in the design.	Thank you for your time.
	Introduction	The authors could improve clarity by using more consistent or precise terminology between intravenous insertions, venipuncture, and needle insertion.	Apologies for any confusion this created. We are now using the term 'intravenous insertion' throughout the paper, as well as in the title.
		Here and in future publications, the authors should elaborate on how this study adds to the literature, highlighting the unique aspects of the ER settings.	We have added the italicized sentence below to the paragraph that discusses the unique aspects of the ED setting: "The ED presents unique challenges when attempting to distract a child during a painful medical procedure. Due to the chaotic, noisy and unpredictable environment, it is an ideal place to 'stress-test' the ability of VR technology to immerse a child into a distracting and 'safe' space. Rapid advances in VR technology over the last few years, and improved cost-effectiveness, offers a unique opportunity to explore its use in the ED setting. A few recently published studies from the pediatric ED setting suggest that VR has a positive impact

			on IV insertion-related pain and satisfaction, [10, 12, 37-40] although outcomes such as distress and adverse effects remain poorly studied. [38] Recent systematic reviews, which have mostly focused on non-ED and in-patient settings, have shown that the current evidence is inconclusive and have called for further research in larger study groups. [41-42] Furthermore many previous trials utilize proprietary software designed specifically for medical use which may limit widespread accessibility to all centers. This study will evaluate an "off-the-shelf" device with a range of widely accessible software."
		The authors should consider citing research of VR in experimental pediatric pain research, and as well as research on VR in different settings, such as: a. Zeroth, J. A., Dahlquist, L. M., & Foxen-Craft, E. C. (2019). The effects of auditory background noise and virtual reality technology on video game distraction analgesia. Scandinavian journal of pain, 19(1), 207-217. b. Dahlquist, L. M., McKenna, K. D., Jones, K. K., Dillinger, L., Weiss, K. E., & Ackerman, C. S. (2007). Active and passive distraction using a head-mounted display helmet: effects on cold pressor pain in children. Health Psychology, 26(6), 794.	Thank you, we have reviewed the three suggested studies. Respectfully we have decided not to include them for the following reasons: Zeroth 2019 conducted their study in young adults, thus we chose not to include it as we are studying the pediatric population only. Dahlquist 2007 conducted their study with an experimental model and we are focusing on the ED and/or other clinical settings. While the Gold 2006 study took place in a pediatric clinical setting, given the word count limitations, we chose to focus on the following systematic review: Lambert V, Boylan P, Boran L, et al. Virtual reality distraction for acute pain in children, The Cochrane database of systematic reviews 2020;10 doi:10.1002/14651858.CD010686.pub2, which is more current and comprehensive.

		c. Gold, J. I., Kim, S. H., Kant, A. J., Joseph, M. H., & Rizzo, A. S. (2006). Effectiveness of virtual reality for pediatric pain distraction during iv placement. CyberPsychology & Behavior, 9(2), 207-212.	However, your important comment prompted us to update our literature review. We have now included the following new, relevant references: 1. Czech O, Wrzeciono A, Rutkowska A, Guzik A, Kiper P, Rutkowski S. Virtual reality interventions for needle-related procedural pain, fear and anxiety—A systematic review and meta-analysis. Journal of clinical medicine. 2021 Jan;10(15):3248. 2. Litwin SP, Nguyen C, Hundert A, Stuart S, Liu D, Maguire B, Matava C, Stinson J. Virtual reality to reduce procedural pain during IV insertion in the pediatric emergency department: a pilot randomized controlled trial. The Clinical Journal of Pain. 2021 Feb 1;37(2):94-101. 3. Goldman RD, Behboudi A. Virtual reality for intravenous placement in the emergency department—a randomized controlled trial. European Journal of Pediatrics. 2021 Mar;180(3):725-31. 4. Chen YJ, Cheng SF, Lee PC, Lai CH, Hou IC, Chen CW. Distraction using virtual reality for children during intravenous injections in an emergency department: A randomised trial. Journal of clinical nursing. 2020 Feb;29(3-4):503-10. 5. Osmanlliu E, Trottier ED, Bailey B, Lagacé M, Certain M, Khadra C, Sanchez M, Thériault C, Paquin D, Côtes-Turpin C, Le May S. Distraction in the Emergency department using Virtual reality for INtravenous procedures in Children to Improve comfort (DEVINCI): a pilot pragmatic randomized controlled trial. Canadian Journal of Emergency Medicine. 2021 Jan;23(1):94-102.
	Methodology	The authors should consider tracking which games are used with the VR program, as there is likely variability in	Thank you, we are tracking which games and applications the children are using in our data collection form. We have added the following line to the

		engagement (i.e. active vs passive) and the sensory stimuli used (in fact, the authors note that not all games incorporate the hand held controllers).	methods section to reflect this: "The game/application selected by the child will be recorded on the case report form."
		It is not clear how the portion of standard of care that includes child life services and nursing support can co-occur with VR administration. It may be difficult for readers to imagine, for instance, how a child life specialist may guide a child to engage in deep breathing when they have headphones on and their vision is occluded. The authors might consider elaborating on this, or reframe the study as a comparison rather than superiority trial. If the trial is a comparison of topical anesthetic and other standard nonpharmacological care vs topical anesthetic and VR, that should be articulated more clearly in the title, aims, and throughout the manuscript.	Despite the child having the VR goggles on, child life specialists are able to provide support prior to the procedure by educating children about the emergency department and their upcoming procedure as well as planning and rehearsing coping strategies. Following the procedure, they may provide support by using techniques such as distraction, relaxation and play. In many cases, children who use the VR goggles do not use the headphones thus they may be able to hear others in the room, including their parents and the child life specialist (if present). We have added the following to the manuscript for clarification: "Child life services include pre-procedural education, distraction and coaching, intra-procedural presence, and post-procedural support and prizes."
		The authors should also discuss how the OSBD will be modified to accommodate the children in the VR condition whose faces will be covered by the goggles, and how that will be implemented consistently across the two study arms. For instance, crying may not be apparent if the child's eyes are covered by the Oculus headset. If this is not possible, the authors should consider a different primary outcome.	The goggles only cover the eyes, and you are correct that this may limit the ability to see tears. Our RAs have noted that if a child is that upset, they usually end up removing the goggles, at which point we are able to see their full face. Otherwise, all other aspects of the OSBD-R (information seeking, screaming, restraint, verbal resistance, emotional support, verbal pain, and flailing) can be coded without seeing the patient's eyes. We will be sure to note this as a limitation when the results are published. Based on our team's previous experience coding many videos using the OSBD-R, we believe that vocalizations (i.e., crying sounds)

			with a combination of other visual prompts can successfully be used to determine crying. Given that this study has been recruiting for nearly 18 months now, changing the primary outcome is not feasible for us at this point.

VERSION 2 – REVIEW

REVIEWER	Foxen-Craft, Emily University of Michigan
REVIEW RETURNED	02-Mar-2022

GENERAL COMMENTS	Thank you for incorporation of most suggestions.