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Integrating Audiovisual Immersion Into Pediatric Radiation Therapy Across Multiple Centers: Methodology, Timeliness, and Cost of the Audiovisual-Assisted Therapeutic Ambience in Radiation Therapy Prospective Multi-Institutional Trial

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Purpose: The Audiovisual-Assisted Therapeutic Ambience in Radiotherapy (AVATAR) trial was a prospective multicenter study (NCT03991156) examining the combination of video immersion with radiation therapy and was successfully conducted through the collaboration of pediatric radiation oncology teams at 10 institutions independent of any pre-existing consortium. We sought to analyze and report the methodology of trial conception and development, process map, and cost.

Methods and Materials: The study enrolled patients aged 3 to 10 years preparing to undergo radiation therapy, integrated the combination of AVATAR-based video immersion with radiation therapy at each institution, and offered AVATAR use as an alternative to anesthesia, with rates of anesthesia use and outcomes of serial standardized anxiety and quality-of-life assessments assessed among the 81 children enrolled. A process map was created based on the trial timeline with the following components: study development time (time from conception of the trial to the accrual of the first patient, including design phase, agreement and approval phase, and site preparation phase), and accrual duration time (time from the first to last accrual). Costs and institutional success rates were calculated.

Results: Time from inception of study to last accrual was 3.6 years (1313 days). The study development time was 417 days (31.7%), and accrual duration time was 896 days (68.3%), with the final 50% of accrual occurring in <6 months. Equipment cost was approximately $550 per institution and was covered by funding from the lead study institution. All 10 centers were successful with AVATAR implementation, defined as ≥50% of patients able to avoid anesthesia with the use of AVATAR, including centers with both photon and proton therapy.

Conclusions: This report elaborates on the methodology and timeline of trial conception and development using data from a previously published supportive care study combining video immersion with radiation therapy among 10 cooperating pediatric oncology institutions. It highlights the potential for multicenter collaborations on prospective trials integrating supportive care therapies with radiation therapy.

Introduction

Prospective trials in pediatric oncology are important in promoting effective therapies that improve outcomes and ensure consistency of practice among institutions. These studies are often conducted in formal cooperative group settings, allowing for enrollment of the largest number of patients and providing the highest level of evidence, particularly critical for therapeutic questions. Although such studies have been a major driver of improvement in pediatric oncology outcomes, they can be very costly and complex.[1,2] In addition, the COVID-19 pandemic demonstrated the difficulty of operating large, complicated trials when unanticipated issues arise.[3] In some situations, more circumscribed research questions can be effectively studied in a smaller multi-institutional cooperative setting with teams motivated to collaborate and complete the trial.

Particularly in the setting of combining supportive care interventions with radiation therapy (RT), pediatric radiation oncology teams have a long history of interinstitutional sharing of techniques and technologies that have helped our patients.[4,5] Interventions ranging from allowing a child to decorate the immobilization mask, to visit a treasure chest to choose a prize after weekly treatment checks, and to drive a miniature car into the treatment vault have all been reported as tools to help children feel more comfortable when used in combination with the RT experience.[4,5] Recent interest has developed in video-based immersion in combination with RT with the goal of improving treatment tolerance and enabling more children to undergo anesthesia-free RT. The Audiovisual-Assisted Therapeutic Ambience in Radiotherapy (AVATAR) system is a radiation-compatible audiovisual system using a radiolucent screen, pico projector, and streaming video, developed in 2015 at Stanford University (Fig. 1).[6]

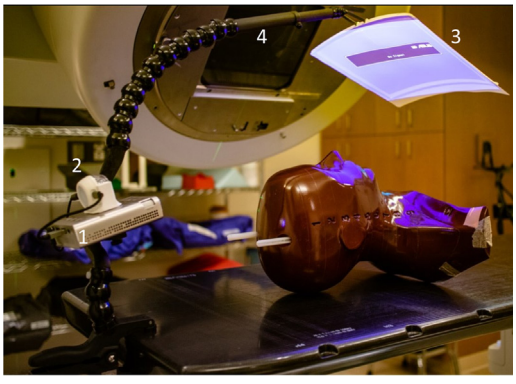

Figure 1 AVATAR system, shown with (1) pico projector, (2) speaker, (3) curved radiolucent screen, and (4) telescopic mount.

Abbreviation: AVATAR = Audiovisual-Assisted Therapeutic Ambience in Radiotherapy.

Initial institutional analyses showed significantly decreased use of anesthesia among children aged 3 to 12 years who were offered the use of AVATAR in combination with daily RT, along with decreased treatment time and reduced costs.[7] With the goal of sharing this institutionally successful technique with other pediatric radiation oncology teams and to assess the feasibility of AVATAR implementation at multiple centers and its effect on anesthesia use, anxiety, and quality of life, we opened the AVATAR multicenter trial with 10 cooperating institutions, independent of any pre-existing consortium. The recently reported results of the trial, which enrolled 81 patients aged 3 to 10 years, demonstrated that 78% avoided anesthesia with utilization of AVATAR, compared with 49% of age-matched historical controls.[7] All 10 institutions were successful with the implementation of AVATAR (defined as ≥50% of patients who were able to avoid anesthesia), including with both photon and proton therapy.[7] Using data from a previously published study, here, we elaborate on the methodology of trial conception and development, process map, and the cost of the AVATAR trial in studying the combination of video-based immersion with RT at 10 cooperating institutions.

Materials and Methods

The general parameters and results of the AVATAR trial (NCT03991156) have been recently described.[7] Centers were approached for potential participation in the multicenter trial after expressing interest in the AVATAR system following publication of the institutional analyses. After discussion regarding the study protocol between each participating institution and the lead study institution, Stanford University, ethics approval was obtained from the institutional review board of each center and of the lead study institution. Data use agreements defining the use and protection of data were created between each institution and the lead study institution. Each participating center was provided an AVATAR system manufactured as previously described and instructions on use, as well as access to additional materials as needed.[7] Each institution provided a study coordinator for institutional data collection and management. Virtual site initiation visits (SIVs) were conducted with the study coordinator, research team, and principal investigator from each institution and from the lead study institution. During the SIV, specifics of the study were discussed, and detailed instructions for AVATAR use were reviewed and demonstrated. Once the SIV was completed and the study was officially opened at a center, pediatric patients aged 3 to 10 years, preparing to undergo RT, were approached for enrollment in the study. After enrollment, patients were offered the use of AVATAR-based video immersion instead of anesthesia. Rates of anesthesia use were recorded, and serial anxiety metrics and quality-of-life surveys were performed at three prespecified timepoints.[7] Any issues or questions that arose regarding the AVATAR system at a given center were discussed with the lead study institution chief physicist, with modifications to the system parts made as appropriate for that center. A central RedCap database was used for the collection of clinical data and to electronically administer the surveys using an anonymized participant number. Through a secure link, patients enrolled at each institution were able to complete the designated survey. Each institution had a separate set of links for data management purposes.

Costs of the trial were reviewed. A process map was created based on the trial timeline with the following components: study development time (time from conception of the trial to accrual of first patient) and the accrual duration time (time from the first to last accrual).[8] The study development component included the design phase, agreement and approval phase, and the site preparation phase.[9,10]

Results

Eighty-one patients with a median age of 7.0 years were enrolled. Time from inception of study to last accrual was 3.6 years (1313 days). Study development time was 417 days (31.7%), and the accrual duration time was 896 days (68.3%) (Fig. 2A).

Within the study development phase, the length of subphases was as follows: design phase (52 days), approval and agreement phase (866 days), and site preparation phase (898 days). The trial was formally suspended for 4 months because of COVID, but after reopening completed accrual within 558 days (1.5 years), with the final 50% of patient accrual occurring in <6 months.

The cost of the equipment was approximately $550 per institution (Fig. 2B), covered by the lead institution, and no additional nominal funding was required for the trial. The source of funding for equipment was a research grant from the lead institution. Each institution was responsible for providing its own clinical research infrastructure and support for trial procedures and data collection. There was no industry sponsorship.

Discussion

The results from the AVATAR trial have been previously published.[6,7] In this additional report, we elaborate on the methodology and timeline of study development, demonstrating that for some research questions, independent prospective multi-institutional studies outside of a formal cooperative group or industry-sponsored setting may be feasible. Previous cooperative group studies have emphasized the importance of reducing study development time and potential delays because of the redundancy

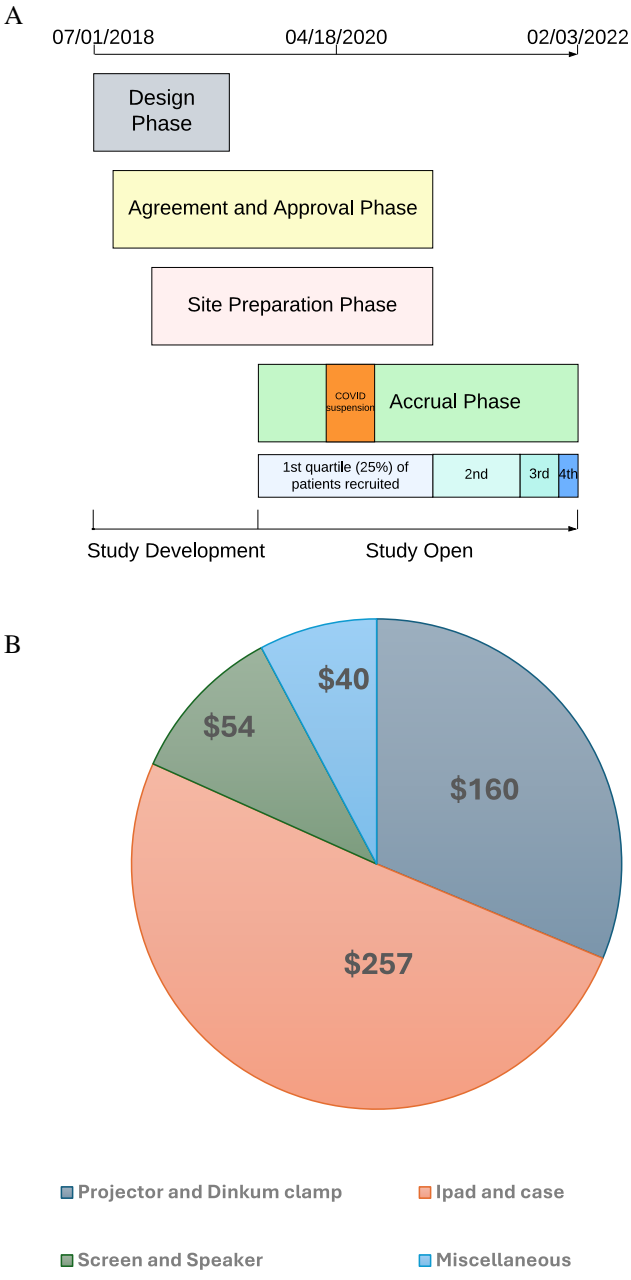

Figure 2 (A) Process map of trial design and accrual. (B) Cost of an AVATAR system in US dollars.
Abbreviation: AVATAR = Audiovisual-Assisted Therapeutic Ambience in Radiotherapy.

of steps in the development phase.[2,] For instance, Dilts et al[8] reported that historical phase 2 Eastern Cooperative Oncology Group trial development and open times were similar at 562 (44%) and 717 (56%) days, respectively, and noted that there were many redundant extraneous and institutional reviews of the scientific design of the study conducted as part of the industry or formal cooperative sponsorship. In comparison, study development time for AVATAR was shorter at 416 days (31.7%), although open time was longer at 896 days (68.3%), in part related to the COVID pandemic. The increased efficiency is attributable to the elimination of redundant extraneous reviews of the scientific design and focused ethics review by each participating institution. The process map demonstrates a significant overlap of the agreement and approval phase and the site preparation phase, suggesting that there may be lower barriers to development with independent trials, as institutions can initiate different phases simultaneously.

In the setting of unforeseen circumstances, independent trials may have increased flexibility to maneuver and adapt. A recent report suggests that because of the

COVID pandemic, 35% of US oncology trials were suspended longer than 4 months or withdrawn/terminated by March 2021.[3] Even after 4 months of formal suspension, the AVATAR trial was subsequently able to complete accrual within 1.5 years. Notably, the last 50% of accrual occurred in <6 months, suggesting that without the disruption by COVID, the trial may have had a significantly shorter study open time in comparison to historical phase 2 trials.

Limited funding has also been cited as a barrier to trial enrollment, particularly for RT trials.[11,12] In addition, industry sponsorship can be associated with the introduction of bias and conflict of interest.[2,13,14] The nominal cost of the AVATAR trial was the cost of the equipment for each institution. There was no additional study cost associated with site preparation, administration, and personnel, because these costs were accommodated by the research infrastructure of the respective institution. The participating institutions were eager and motivated to participate, likely related to potential benefits they saw for their patients, and this may have influenced their willingness to accommodate institutional costs associated with the study such as study coordinator time. This may also represent a limitation of the independent multi-institutional prospective study in that it requires and relies on the respective participating institution's established research infrastructure rather than extraneous funding sources for new research personnel and equipment. The opportunity costs of the study have not been accounted for, but because the nominal cost of equipment for the trial was small, monetary cost was covered by a single institutional research grant.

We note that studies involving pharmacologic interventions or prospective randomized trials requiring a large sample size to detect meaningful differences in efficacy are likely to require robust and systemic funding, personnel, and stringent protocol regulations that are best provided by an established large network of clinical sites to provide the highest level of evidence. Given the rising costs of running a prospective trial and potential bias related to industry sponsorship, this type of independent multicenter study among cooperating and motivated teams as demonstrated in the AVATAR trial may provide a pathway to answering some clinical questions, particularly regarding feasibility and generalizability of supportive care interventions in combination with RT.

In conclusion, this report demonstrates that for some research questions, multi-institutional prospective trials outside of industry sponsorship or established cooperative groups may be feasible, efficient, and cost effective.

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Disclosures

None.

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