Research Proposal Version 2
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Application of behavioral economic strategies to enhance recruitment into a pediatric randomized clinical trial

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The current document reflects the full pre-specified Statistical Analysis Plan that was used for the study.

PROTOCOL SUMMARY

Title	Application of behavioral economic strategies to enhance recruitment into a pediatric randomized clinical trial
Principal investigator	Vanessa A. Olbrecht, MD, MBA
Co-investigator(s)	Jack Stevens, PhD
Statistician	Archie Tram, PhD
Coordinator	TBD
Study staff (e.g., Research associates, fellow, resident, medical student)	Anitra Karthic (medical student)
Primary objective	To determine the impact of the application of behavioral economic strategies on recruitment of pediatric patients into a randomized clinical trial assessing the impact of technology-based interventions on postoperative pain management
Design (prospective, retrospective, database, QI, determination of human subjects)	Prospective, randomized, double-blind clinical trial
Hypothesis	We hypothesize that the use of behavioral economic strategies will increase the enrollment of pediatric patients into a randomized clinical trial versus a standard, biological approach
Primary outcomes	Patient enrollment
Secondary outcomes	Intention to adhere to treatment; acceptability of therapy; opinion of treatment burden; perception of efficacy of treatment; perception of risk
Interventions	Recruitment video using behavioral economics strategies versus biological strategies for both intervention and control arm
Estimated number of subjects (power analysis if applicable)	Phase 1*: 400 patients (behavioral economic vs biological approach for virtual reality intervention) Phase 2: 400 patients (behavioral economic vs biological approach for control intervention)

Phase 1 will be done as the MDSR project

Introduction

One of the largest challenges faced in clinical trials is patient recruitment. It is often associated with one of the largest costs of the trial and inability to enroll in a clinical trial can ultimately result in under-enrollment and failure of the trial to yield results.[1] According to data from the Institute of Medicine, more than 40% of National Cancer Institute-sponsored clinical trials do not reach the minimal accrual of patients when enrollment closes due to challenges with recruitment.[2] Underpowering studies because of enrollment difficulties will result in clinical trials that are not appropriately powered to answer the initial hypothesis, often resulting in participants being exposed to the risks associated with a clinical trial without any actual benefit.[3] Furthermore, challenges with recruitment may result in a very homogeneous study population, resulting in difficulty in applying results of a study to a larger, broader

population.[1] Over time, many strategies have been attempted to help enhance clinical trial enrollment, including offering financial incentives.[4] Financial incentives, however, may not be the best way to enhance enrollment as high financial incentives are often perceived to be associated with high risk and there are ethical concerns about payments made to subjects.[5]

Despite plaguing clinical trials, there are not many strategies that have effectively been shown to increase recruitment and enrollment into clinical trials.[6] A recent meta-analysis attempted to identify strategies to improve recruitment into trials. Of the 72 strategies assessed in the literature, only two showed some benefit: Using open trials rather than blinded, placebo trials; and using telephone reminders to people who do not respond to a mailed invitation.[6] The first is obviously contrary to the goal of a study and may influence its results and the second showed a very modest improvement of only 6% (95% CI 3% to 9%). As such, no clear strategies currently exist.

Behavioral economics (BE), a method of economic analysis that applies psychological insights into human behavior to explain economic decision-making, has broad applicability and its techniques offer a novel way that may be applied to try to help enhance study recruitment and enrollment. While many often assume that BE relates to how to optimize use of financial incentives and penalties, BE strategies can also provide insight into messaging and presentation of information, such as recruitment for clinical trials. Few studies have assessed the use of BE techniques for clinical trial recruitment and enrollment, including "nudges" and framing, to help enhance patient enrollment.[1,7,8] To our knowledge, this type of study has never been done in a pediatric population, which increases the complexity of enrollment as patients themselves are often not the ones consenting to participate and not only do the participants need to be convinced to participate but also their parent(s).[6] We are applying BE-based messaging and presentation strategies to patient recruitment and determining whether these strategies may enhance patient recruitment into a pediatric randomized clinical trial. We are looking at recruitment into both the intervention (VR-BF) as well as control (Manage My Pain) arm because in order for a trial to be successful, you must be able to successfully recruit not only into the intervention arm, but also into the control arm.

The goal of this study is to determine the impact of using a BE-informed recruitment video versus a similar recruitment video using a standard biological approach on teenagers' decision to enroll in a clinical study assessing the use of technology-based interventions to improve postoperative pain management into both the intervention as well as control arm. We will also assess the impact of the BE-informed script on the intention to adhere to the treatment, acceptability of the intervention, and perception of treatment burden, risk, and perceived efficacy assessed via patient survey. We hypothesize that using the BE-informed approach will enhance enrollment as well as the intention to adhere to treatment, acceptability of the intervention, and perceived efficacy while decreasing the perception of treatment burden and risk.

Methods

This is a single center, prospective, randomized, double-blinded clinical trial that will be conducted in two stages. Phase 1 will focus on patients that would be enrolled into a biofeedback-based virtual reality (VR-BF) arm and Phase 2 will focus on patients that would be enrolled into the control arm of a clinical trial with a control intervention, Manage My Pain application. Prior to beginning recruitment in Phase 1, we will create a script and film the videos associated with those scripts. Information learned in Phase 1 may result in slight modifications of the script and videos.

Patients will be identified prior to surgery by assessing the operating room schedule after being booked for surgery. In Phase 1, for the VR-BF intervention, patients and parents will be approached and asked if they would like to hear about an upcoming study with a technology that is under development but not yet available but that we would like to obtain their feedback as the study will involve patients having surgery similar to the one that he/she is undergoing. Although the literature suggests that patients should not be told that this is a hypothetical study to avoid bias ("self-prophecy") associated with telling them they do not have the opportunity to participate in the study,[1,7] it would be unethical in this situation to tell a family about a study that would potentially be of interest and then tell them that the patient is not eligible as the study does not exist, particularly in the stressful setting they are. However, to minimize social desirability bias, they will be explicitly be informed that the survey is one-time and anonymous and that answers/opinions will not impact clinical care in any capacity. In addition, the survey will be done on paper and placed by the patient into a collection box with other papers/surveys, emphasizing the anonymity of results and avoiding things like time stamps on electronic records that may make anonymity less believable to the patient and family. Patients in Phase 1 will be randomized to 1 of 2 groups: VR-BF recruitment video using a BE-based script and one using a standard biological approach. A total of 400 patients, 200 per group, will be recruited in this phase. Following agreement to participate and consent, subjects will be shown 1 of the 2 recruitment videos based upon randomization and then given a standardized survey assessing the decision to enroll and other components of acceptability.

The process for Phase 2 will be the same as Phase 1 with the exception of how the families are approached. Because Manage My Pain is commercially available and free on the app store (iOS and Android platforms), patients and families will be asked if they would like to hear about an upcoming study being offered to patients having surgery similar to the one that their child is undergoing. They will not explicitly be told that this is a hypothetical study to avoid the "self-prophecy" bias[1,7] but, in order to avoid disappointment and the ethical concerns, they will be informed that they are free to download the application and use it if they so desire at the conclusion of the study visit.

The surveys will not collect any data that may identify the patient to remain anonymous.

Study population and data source:

Inclusion criteria:

- Patients between the ages of 12 and 18 years of age
- Patients able to read, understand, and speak English
- Patients undergoing surgery requiring postoperative admission
- Patients undergoing surgery that usually requires narcotic administration

Exclusion criteria:

- Patients outside of the age range
- Patients with history of developmental delay, uncontrolled psychiatric conditions, or neurological conditions (i.e., epilepsy, motion sickness, nausea/vomiting)
- History of severe vertigo or dizziness
- History of chronic pain
- Patients that use opioids or benzodiazepines chronically
- Patients with conditions that would preclude placement of a VR headset, including craniofacial abnormalities or undergoing surgeries of the head and neck

List of variables/covariates:

- Age
- Sex
- Race
- Ethnicity
- Planned surgery
- Underlying co-morbidities
- Previous use of pain management techniques/medication
- Medications
- Postoperative pain management by the Acute Pain Service (yes/no)
- Survey (which will be developed separately) and include the following information: decision to enroll in the study, acceptability of therapy, opinion of treatment burden, perception of efficacy, perception of risk, intention to adhere to therapy

Outcome Measures:

Primary Outcome: Decision to enroll in the study → Percent of patients willing to enroll in each group

Secondary Outcomes: Intention to adhere to treatment; acceptability of therapy; opinion of treatment burden; perception of efficacy, treatment burden, and risk of the proposed therapy → Obtained through using a numerical scale in the survey given following viewing of the recruitment video

Statistical analysis:

Parametric continuous data will be presented as means and standard deviations. Non-parametric data will be presented as medians and interquartile ranges. Categorical variables will be presented as frequencies and percentages. Sample size calculation suggested that 400 patients (200 patients in each group) are required to have an 80% chance of detecting, with significance at the 5% level, an increase in the primary outcome measure from 80% in the control group to 90% in the BE group for the intervention with the same calculation in the control group. Although no study has been done like this before, the 10% difference is estimated from the BE literature.[7,9] A Chi-square test or Fisher Exact Test will evaluate the primary outcome (decision to enroll in the study). Two sample t-test or Wilcoxon rank-sum test, where appropriate, will be used to test effect differences for the secondary outcomes and other continuous clinical variables such as age, weight, etc. between the two groups. Type I error will be controlled at α=0.05 for single comparisons and with adjustment for multiple comparisons. A p-value of 0.05 will be considered statistically significant. Subgroup analysis will be done looking at these outcomes in patients followed by the Acute Pain Service to assist with obtaining pilot data for future grant applications.

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