

Patient navigation and clinical trial participation: A randomized controlled trial design

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ABSTRACT

Background: To our knowledge, no published studies utilizing a randomized controlled design have examined the efficacy of patient navigation for improving clinical trial enrollment.

Methods: This patient navigation and clinical trial participation study is a randomized controlled trial to assess the effect of a patient navigator on enrollment into therapeutic cancer clinical trials. Participants are randomly assigned to high intensity, patient navigator-delivered patient educational materials (PEM) and needs assessment vs. low intensity patient navigation (patient navigator-delivered patient educational materials [PEM] alone). **Discussion:** Effective enrollment strategies may include utilization of patient navigators as away to meet individual needs, barriers, and concerns of participants enrolled in clinical trials.

1. Introduction

Cancer is the second leading cause of death in the United States and accounts for one in every four deaths [1]. Clinical trials offer cancer patients access to cutting-edge treatments while offering an opportunity to improve treatment options for cancer patients in the future [2]. Clinical trials provide scientific evidence to inform the practices and policies of a health care system and participation in trials is essential to improving the overall care and well-being of cancer patients, yet few adults with cancer choose this option. Despite clinical importance [3,4], trial participation among adults with cancer remains as low as 3–5%, with minority groups continuing to be underrepresented [4,5]. The participation of ethnic minorities and medically underserved populations in clinical trials is critical to achieving progress in cancer control [6]. However, the literature on clinical trial participation cites numerous barriers that could impede patient awareness of clinical trials or the patients' opportunity to participate, particularly for minority populations [7].

Current efforts have addressed some clinical trial barriers; however, additional barriers, such as cost, family commitments, time, lack of

social support, and transportation may preclude some individuals from trial participation [7,8]. Addressing these remaining barriers may improve the number of individuals enrolled in clinical trials, which is an important aspect of care, particularly at National Cancer Institute (NCI)-designated cancer centers, where funding is dependent upon assurances that clinical trials are available and include women, minorities, and children. One proven approach to reducing barriers and increasing clinical trial participation is the use of patient navigators to provide patient navigation [9,10]. Patient navigation—the process of providing enhanced educational and facilitative services to the patient—provides a comprehensive range of healthcare services and support, and represents a potentially powerful tool to target health disparities and facilitate access to the healthcare system for underserved populations by connecting them to resources tailored to individual needs [6,11,12].

General enrollment rates of patients into clinical trials after receiving patient navigation is as high as 95% [13]. In studies exploring the impact of patient navigation on enrollment of minorities into clinical trials, strategies such as the following have been shown to achieve up to 86% enrollment of African Americans: improving communication

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about the purpose and risks and benefits of clinical trial participation, financial feasibility, timing of when trial information is provided, and who provides trial information. These strategies may also help reduce decision regret among trial participants [14–17]. Despite the positive results achieved through patient navigation and the call for use of a randomized controlled trial (RCT) design in exploring the impact of patient navigation [13], to our knowledge, no published studies have examined the efficacy of patient navigation for improving clinical trial enrollment. Our patient navigation and clinical trial participation study is an RCT designed to test the hypothesis of whether patients who receive high intensity patient navigation provided by a lay navigator are more likely to enroll in a therapeutic clinical trial than those who receive low intensity navigation. This study could help address patient concerns or needs that are unique to potential trial participants, including underrepresented populations [14].

2. Methods

2.1. Study design, population and setting

Our patient navigation study is an ongoing RCT design being implemented at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins to assess the efficacy of high intensity patient navigation delivered by a lay navigator (patient navigator-delivered patient educational materials [PEM] and needs assessment activities) vs. low intensity clinical trial navigation (patient navigator-delivered PEM alone (see Fig. 1). Participants are randomly assigned to the high or low intensity clinical trial navigation. The study population consists of patients 18 years and older with a primary solid tumor (initial focus: breast, multiple myeloma, colon, lung, pancreas, prostate, head/neck) diagnosis being seen at the SKCCC outpatient oncology clinic at Johns Hopkins. Other inclusion criteria for the study include: the availability of a therapeutic trial for the patient determined through pre-screening/medical record review, and resident of Maryland. Exclusion criteria include primary residence outside of Maryland, which is the catchment area for SKCCC and geographical region for which SKCCC is charged with reducing cancer burden, and no available therapeutic clinical trial as determined through medical record review.

2.2. Recruitment

Participant recruitment began in March 2016. Convenience sampling is utilized and a HIPAA waiver allows review of electronic records for trial eligibility. Potential study patients are identified from medical oncology clinic schedules one week in advance of the scheduled visit.

New SKCCC patients who are residents of the state of Maryland are pre-screened for available disease-specific therapeutic trials. To ensure efficiency in identifying available trials, query decision trees containing all active therapeutic trials were created for each cancer type using basic inclusion and exclusion criteria such as stage of disease, prior therapies, required biomarkers, and comorbid conditions. The patient navigator contacts patients for whom an available trial is identified by phone prior to the scheduled medical oncology clinic visit.

The goal of this call is to introduce the navigation study and determine patient interest in participating. If the patient expresses interest, the patient navigator meets with the patient on the day of their clinic visit, prior to their appointment with their medical oncologist to obtain informed consent and provide clinical trial educational material.

Patients who meet study inclusion criteria are randomized to the Low Intensity Navigation (control group) or High Intensity Navigation (intervention group) after consenting. Participants are enrolled in the patient navigation and clinical trial study for 3–7 months, depending on whether they enroll in a therapeutic trial offered during their visit with the medical oncologist. The patient navigator verifies trial offerings through the patient medical record (EPIC) and by following up with clinic providers, research staff, and study participants. Patients who

enroll in a therapeutic trial are in the study for 7 months. Patients who are not offered or decline enrollment in an available trial are in the navigation study for 3 months.

2.3. Interventions

2.3.1. Printed educational materials (PEM)

Participants randomized to both the Low and High Intensity Clinical Trial Navigation groups receive printed educational material (PEM) on clinical trials/clinical trial participation, cancer center support services, and community resources and services available to all SKCCC patients. These materials are predominantly developed by NCI and ACS. The patient navigator reviews the PEM with the patient prior to their clinic visit with the medical oncologist. Features of the PEM include an educational brochure that provides a definition of clinical trials, a description of commonly used words and phrases related to clinical trials, such as randomization, control group, informed consent, and placebo. The patient navigator also provides the participants a list of questions they may consider asking their oncologist related to clinical trials. Such questions may be related to the purpose of the clinical trial, start date and study duration, types of tests and treatments that will be involved, how much time they may have to decide about joining a clinical trial, possible risks and benefits associated with enrolling in a clinical trial, options to withdraw, and how to contact their oncologist or members of the research team with additional concerns and questions.

2.3.2. Low intensity clinical trial navigation

Participants randomized to low intensity patient navigation (control arm) receive the PEM only. Participants offered a clinical trial by their medical oncologist are contacted monthly by the patient navigator. During the monthly calls, if unmet needs are identified, the patient navigator communicates these needs or patient concerns to the patient's medical oncology clinical/research team so the team can initiate a referral to available cancer center services (e.g., Social work, Patient and Family Services, or Clinical Trials Recruitment Specialist).

2.3.3. High Intensity Clinical Trial Navigation

Participants randomized to high intensity patient navigation (intervention arm) receive the PEM plus active patient navigation services to identify needs, which, if unmet, could pose barriers to clinical trial participation. If the participant is offered a therapeutic clinical trial by their medical oncologist, high intensity navigation begins. Within one week of the clinical trial offer, the patient navigator arranges to meet with the patient (in person or by phone) to complete a needs assessment, to identify patient needs related to clinical trial participation and devise a plan for helping to meet those needs. The patient navigator follows up with the patient at least biweekly for up to four months to review and resolve identified needs. High intensity patient navigation is stopped if the patient decides not to participate in the therapeutic trial offered, is deemed ineligible for enrollment, or ends participation in the therapeutic study for reasons, such as disease progression, Principal Investigator discretion, patient withdraws consent for therapeutic trial or navigation, or death.

2.4. Follow-up data collection and study measures

All study participants complete an exit questionnaire by phone, to assess navigation services and satisfaction with clinical trial decision making. Those who enroll in a therapeutic clinical trial complete the exit questionnaire three months following completion of patient navigation (or seven months after enrollment), regardless of whether they are in the Low Intensity (control) or High Intensity (intervention) arm. In addition, individuals who do not complete high intensity navigation for any reason are contacted within two weeks of discontinuation to ensure all referrals to resources for identified needs have been completed. Participants randomized to either study arm who are not offered

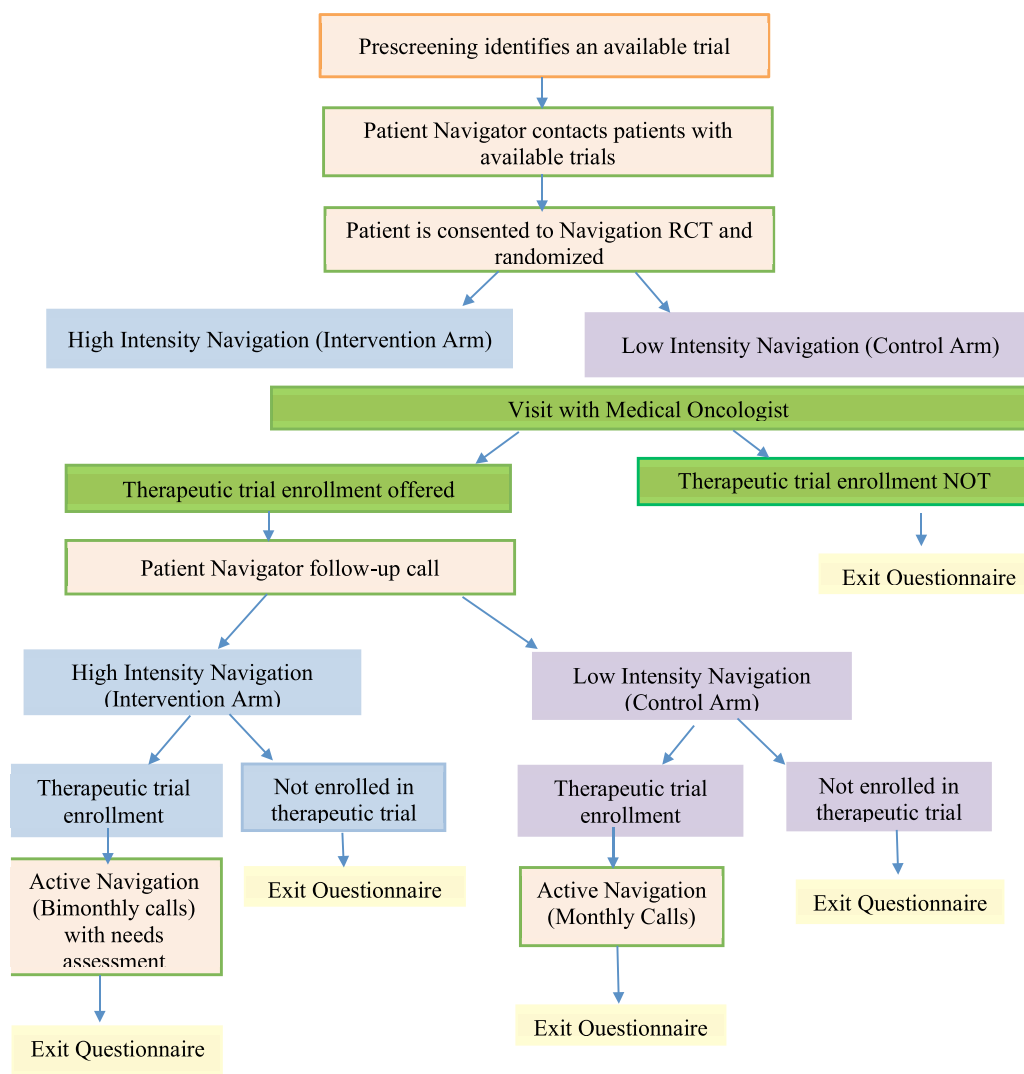


Fig. 1. Patient navigation schema.

or declined participation in a therapeutic clinical trial are contacted three months after navigation study enrollment to complete the exit questionnaire.

2.5. Outcome variables

The primary research question to be addressed by this study is whether high intensity patient navigation results in increased clinical trial enrollment as measured by a higher proportion of patients enrolled in the high intensity patient navigation group compared to the proportion enrolled in the low intensity patient navigation group. All analyses will be carried out according to intention to treat (ITT). Differences between groups will be assessed using the 2-sided Pearson's Chi-Square test at a 0.05 significance level.

As a supportive analysis (given sufficient numbers), we will attempt to stratify the analysis by cancer type. Only participants who are offered a therapeutic clinical trial will be included in the primary outcome analysis; participants who are not offered a therapeutic trial will be excluded. Participants who are lost to follow-up will be censored at their last visit in the study (e.g., on the date consent is withdrawn). The outcome variable will be obtained at time of exit from the study (at study completion or withdrawal). Access to participants' medical records allows the team to obtain outcome data even for individuals who are lost to follow up; therefore, we expect attrition rates for the

purposes of the main outcome to be minimal.

Using the chi-square test, we will compare the two study groups on certain demographics, cancer type, and other factors to assess the integrity of the randomization and determine the potential factors by which to stratify our analysis (with the understanding that stratification may not be feasible due to small numbers). The distribution of missing data will also be assessed by comparing demographic characteristics and other baseline factors between participants who complete the study and those lost to follow-up for each intervention arm. As part of our primary outcome analysis, we will also assess the feasibility of conducting the study using process outcome measures, including the following: ease of enrolling participants into a patient navigation RCT (our ability to streamline the enrollment process working with clinical trial screeners and the patients' medical team), effectiveness of properly delineating the patient navigation role in the process of clinical trial recruitment (vs. the role of a research nurse), and ability to effectively link patients to Hopkins and community resources in a timely manner.

Secondary analyses—including between group differences in clinical trial knowledge, preparation for decision making around clinical trial enrollment and satisfaction with navigation services—will be assessed using chi-square analysis. These secondary outcome variables will be collected during the time of exit from the study (or study withdrawal, if participants are willing to complete the exit questionnaire). Additionally, we will examine differences in the mode of

needs assessment administration using qualitative and quantitative data, as our sample allows.

2.6. Power calculation

This study will determine the feasibility of using a patient navigation intervention to improve participation among patients for whom therapeutic clinical trials are available. There are limited data on which to base a formal power calculation; however, based on the 2016 Johns Hopkins Cancer Registry (the most recent available data), over the course of 12 months, SKCCC saw: 1293 Maryland residents with a cancer type (i.e. breast, prostate, multiple myeloma, or head/neck) defined by study inclusion criteria. Because cancer type is not the only determinant of participant eligibility, we conservatively plan to enroll 110 participants. Given our sample size of 110 and current clinical trial enrollment among clinical trial eligible patients of 50%, we would be able to detect a 25% minimum difference in enrollment rates between the two groups at 80% power and $\alpha = 0.05$, two-sided significance level. Using a more conservative 15% difference between arms to plan sample size requirements, we would need a sample size of 364. Our plan is to use this study to provide preliminary data (i.e. effect size) to compute the sample size for a larger randomized controlled trial.

3. Ethics

This patient navigation study was approved by the Johns Hopkins School of Medicine's Institutional Review Board (NA_00072282) via an expedited review process. Informed consent is required for participation; study consents indicate that study participation is voluntary and can be discontinued at any time. Declining study participation does not impact a potential participant's healthcare provision. Any protocol modifications, adverse event reporting, or continuing review reports will be conveyed to the Institutional Review Board for processing and monitoring. Every effort is made to keep study information confidential and study data are only shared among the research team members, who have undergone human subjects protection and data security training. Data management procedures and databases are HIPAA compliant.

4. Discussion

Patient navigation has been studied and implemented as standard practice throughout the continuum of cancer care to improve access, quality of care, and patient satisfaction. It has also been used specifically to improve participation in clinical trials. However, to our knowledge, its influence on clinical trial decision making or improving cancer clinical trial participation has not been studied in a randomized controlled trial study design. Thus, this protocol is a unique and important contribution to the literature.

Our approach reduces the effect of two well-documented barriers to minority participation-clinical trial knowledge/awareness and patient barriers related to unmet social support needs. Because these barriers are not exclusive to minority populations, addressing them in conjunction with clinical trial education material delivery and tangible resources to facilitate trial participation early on may reduce existing racial disparities while improving overall participation in cancer clinical trials among other underrepresented populations and cancer patients at large.

Further, although this study is focused on cancer clinical trial participation, it will provide insight into lingering questions related to the delivery of navigation as our study uses a lay navigator as well as a comparison of the intensity of navigation. In this manner we hope to better understand and address concerns regarding how patients receive navigation as well as document the expense and outcomes of implementing a patient navigator program focused on clinical trial enrollment.

Abbreviations

ACS	American Cancer Society
HIPAA	Health Insurance Portability and Accountability Act
ITT	Intention to treat
NCI	National Cancer Institute
PEM	Patient educational materials
RCT	Randomized Controlled Trial
SKCCC	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Ethics approval and consent to participate

This research study was approved by the Johns Hopkins Medicine Institutional Review Board (NA_00072282).

Consent to publish

Not applicable; no data are being published at this time.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were analyzed during the current study.

Conflicts of interest

The authors declare that they have no competing interests.

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Authors' contributions

Study concept and design: D.L. and J.W.; Drafting of the manuscript: M.K.U.; Critical revision of the manuscript for important intellectual content: D.L., O.M., T.G., L.S., J.W.; Statistical Analysis: N/A; Obtained funding: D.L. and J.W.; Administrative, technical, or material support: M.K.U; All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2018.09.003>.

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