Predictors of Research Subject retention - Repetitive non-adherence or socioeconomic factors: Insights from a urological clinical trial

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Abstract

Background:

To investigate various patient level variables, specifically socioeconomic status, as risk factors for withdrawal in a recently completed clinical study. We specifically investigate a recent study in men on adherence to an observational prostate cancer imaging and biomarkers study.

Methods:

We performed a retrospective study to investigate risk factors for withdrawal in a prostate cancer imaging study that enrolled men on active surveillance from January 2016 to June 2019. For each subject, we assessed their retention status and collected demographic data. We compared values between the two retention groups using T-test, Chi-Squared, and logistic regression.

Results:

Out of 273 men screened, 123 men were enrolled and included in the results of this study. Of those, 106 (86%) were retained in the study and 17 (14%) were withdrawn. While we found no significant relationship between low socioeconomic status and retention, we did find that the number of non-adherences was a significant factor in withdrawal from the study (OR 2.5, 95% CI 3.5–40.5, $p < 0.001$).

Conclusions:

Expanding diverse inclusion and limiting withdrawal with real-time non-adherence monitoring will lead to more efficient clinical research and greater generalizability of results.

1. Background

Clinical research studies lead to discovery and improvements in the prevention, diagnosis, and treatment of disease.¹ As of December 10, 2021, ClinicalTrials.gov lists 397,984 studies across a total of 220 countries, with 78% being interventional trials and 22% being observational human research studies.² Unfortunately, marginalized groups are underrepresented in clinical research even though they face a greater disease burden.^{3,4} Traditional enrollment strategies target affluent patients thought to be more engaged and less likely to withdrawal from research studies.⁴ Frequently, research teams have emphasized strategies to overcome enrollment barriers, while we focus on the substantial issue regarding patient retainment and study completion.^{5,6,7}

Two of the most critical components for completing clinical research are the retention and protocol adherence of research subjects. Unfortunately, retaining subjects and ensuring adherence to the protocol are major challenges for clinical researchers.^{8,9,10} The retention and adherence of subjects is necessary for the credibility, accuracy, and validity of research studies as low retention and adherence can reduce statistical power, lead to selection bias, and influence the significance of a study's findings^{8,9,11,12} Additionally, a high number of withdrawn subjects and non-adherences can lead to a waste of resources and funds, create excess burden on research coordinators, and ultimately lengthen the duration of studies causing delays in advancing medical knowledge and providing better care to patients.¹¹

While subject retention and protocol adherence are essential for successful research studies, little is known about the specific factors that influence subjects to complete a study and adhere to the protocol. We investigate various patient level variables as risk factors for withdrawal in a recently completed prostate imaging study in men to specifically explore socioeconomic factors as potential barriers.

2. Material And Methods

2.1 Population and Setting: We enrolled men into a prostate cancer study exploring novel imaging to predict cancer outcomes from January 2016 to June 2019 under IRB HCS20150160H. An IRB exempt determination was obtained, HSC20200572E, to perform a retrospective chart review study to investigate risk factors for withdrawal. The prostate imaging study enrolled 123 prostate cancer subjects on active surveillance and consisted of a baseline visit, which included blood and urine collection and questionnaire completion, a research imaging MRI, and a standard of care MRI-guided prostate biopsy procedure.

2.2 Primary Outcome: For each subject, we assessed whether they were retained [defined as the proportion of patients that remained in the study to completion] on the study or were withdrawn [defined as the proportion of patients that did not complete the study] and the reason for withdrawal if applicable.

2.3 Primary predictor: Our primary predictor of interest we investigated was low socioeconomic status (SES). For each subject, their zip code was entered into the Economic Innovation Group Distressed Community Index (DCI) which ranks communities across seven measures: no high school diploma, housing vacancy rate, adults not working, poverty rate, median income ratio, change in employment, and change in establishments.¹³ (Supplemental Table 1) These rankings are "averaged and weighted equally" and "then normalized into a final score that ranges from approaching 0 (most prosperous) to 100 (most distressed). Zip code areas are further classified into five even distress tiers: prosperous, comfortable, mid-tier, at risk, or distressed.¹³ We further defined low SES as those with a DCI Distress tier of at risk or distressed.

2.4 Secondary predictors: In addition, we collected data on age, race, ethnicity, body mass index (BMI), smoking history, comorbidities using the Charlson Comorbidity Index, and time from prostate cancer diagnosis to enrollment in the prostate cancer imaging study. For each subject regardless of retention

outcome, we identified instances of non-adherence, defined as any incomplete study procedure or issues with scheduling visits. The reason for each non-adherence was documented.

2.5 Statistical analysis: We used the Student's T test for continuous variables and Chi-Squared tests for categorical variables. We used logistic regression for multivariable analysis. Additionally, we created bar graphs to display data regarding to predictive variables of withdrawals from the research study. We utilized SPSS v.25 for the statistical analysis.

3. Results

3.1 Demographics: We screened 273 men and enrolled 123 subjects for a participation rate of 45%. Out of the 123 subjects, we identified two comparison groups, the 106 (86%) who were retained and completed the study compared to the 17 (14%) who were withdrawn (Fig. 1). We enrolled a minority majority in that over 50% of our cohort was of minority race or ethnicity. We enrolled 24% (n = 30) African Americans and 32% (n = 39) Hispanic men.

3.2 Socioeconomic Stress and Clinical Study Retention

The mean DCI score was 39.15 with a standard deviation of 31.19, with 48 (39%) subjects falling in the prosperous tier, 21 (17%) in the comfortable tier, 16 (13%) in the mid-tier, 20 (16%) in the at risk tier, and 18 (15%) in the distressed tier.

We found no significant effect of the DCI Score (Table 1). The distribution of DCI Scores was skewed to the left (Supplemental Fig. 1), but we did have a substantial distribution of DCI scores. For one subject we utilized the county level DCI score rather than the zip code level DCI score due to this zip code not meeting the population, employment, and/or establishment data threshold for the DCI. We then grouped the DCI into distress tiers (Fig. 3) and low SES again noting no relationship with study retention (Table 1).

3.3 Secondary Indicators of Clinical Study Retention

We investigated ethnicity, race, smoking status, age, BMI, Charlson Index Score, DCI score, time from prostate cancer diagnosis to enrollment, and presence of a non-adherence in relation to retention (Table 1). Sixty-eight men (55%) had at least one instance of non-adherence. Of the subjects with a non-adherence, 35 (51%) subjects had one non-adherence, 25 (37%) subjects had two, 5 (7%) subjects had 3, and 3 (4%) subjects had four. All subjects in withdrawn group had at least one non-adherent event as compared to 48.1% in retained group ($p < 0.001$). The number of non-adherent events was also highly significant (range 0–4, $p < 0.001$).

3.4 Multivariate analysis:

We performed a logistic regression controlling for age, race, BMI, smoking status, days from prostate cancer diagnosis to enrollment, Charlson Index Score, and DCI score, and non-adherence. The generalized non-adherence as a categorical variable (any non-adherence yes vs. no) was not significant. However, the

number of non-adherences was a significant factor in withdrawal from the study (OR 2.5, 95% CI 3.5–40.5, $p < 0.001$).

4. Discussion

Our retrospective investigation of 123 men enrolled in a prostate cancer imaging study, found that repeat non-adherence contributed to subject withdrawal more than SES. This finding is significant because it relates to the contemporary discussion regarding increasing diversity in clinical research.

Literature has consistently shown that clinical trials lack the inclusion of marginalized groups.^{4, 14, 15} While the reasons for this are multifaceted and may be attributable to a lack of access, financial and logistical barriers, and general distrust, a significant reason may be due to provider perception. Fisher et al. suggest that “physician bias, false perceptions, and prejudices” have a significant impact on who they believe will comply with the often-demanding regimens involved with clinical research.¹⁶ Our findings show that low SES, and/or minority patients, were not at higher risk for withdrawal and should not be excluded by physicians for this reason.

In our study, we used DCI as a measure for socio-economic evaluation. Various proposed measures for SES include insurance status, race, household income or employment status or combination of these, however, the number of data points chosen to assess patients’ SES limit the ability to study true impact of SES across various studies. A comprehensive evaluation of social, economic, and financial status is necessary to estimate SES and study its impact on health disparities and clinical trials. The Economic Innovation Group, a “bipartisan public policy organization”, introduced DCI, to understand spatial distribution of U.S economic well-being. DCI combines seven distinct and complementary socio-economic indicators into a single score and creates a composite ranking by zip code. This score has been demonstrated to be an accurate measure of community’s socio-economic distress and has been found to improve risk-adjusted outcomes after surgery.¹⁷

One interesting but anticipated finding is that subjects with more than 1 non-adherent event were at a higher risk for eventually withdrawing from the research study. The majority of subjects with two non-adherences withdrew from the study, nearly all subjects with three non-adherences withdrew from study, and all subjects with four non-adherences withdrew from study. It is important to note that not all non-adherences or withdrawals were directly attributable to the subject. Coordinator phlebotomy skill, inadequate screening, and clinic scheduling processes attributed to several non-adherences or withdrawals (Supplemental Table 2).

We anticipate that future applications of our important finding would encourage real-time monitoring of non-adherent instances within clinical research studies in order to intervene early and prevent withdrawal from the study. The concept of real-time monitoring stems from successful remote monitoring to prevent and document adverse events, especially in phase 1, 2 and 3 clinical trials.^{18–21} We specifically identified that the “adherence audit” should occur after the first non-adherence to identify the barriers of the subject

or the coordinating team to implement immediate solutions. At that point, the team could assess study-team processes, environment, resources, or patient factors leading to the non-adherence and apply adaptive counter measures to prevent further issues.¹² While our results on SES are favorable to expand enrollment, the finding by no means assumes there are not barriers caused by SES in clinical trials. We agree with acknowledging and addressing the barriers up front, to prevent non-adherence in a patient centric manner.²² Dockendorf et al advocated the use of digital health technologies comprising of smart dosing, outpatient sampling and digital monitoring to increase subject retention with reduced burden on patients.²² However, further research will be required to identify common barriers and solutions encountered in real-time during clinical trial activity.

A limitation of this study is that it is limited to an observational study in older men. While we do have diversity of race and ethnicity, we lack age and gender diversity. Additionally, non-adherence data was gathered retrospectively resulting in unknown reasons for incomplete study procedures, a lack of details regarding the reason and time-point of withdrawal and therefore the decision to count any incomplete study procedure as a non-adherence regardless of retention status, and missing information regarding the barriers faced by subjects and coordinators. Future studies are needed to examine various populations and different types of clinical research studies, specifically clinical trials that include real-time non-adherence data collection.

5. Conclusion

Our findings show that low SES subjects are not at greater risk for withdrawal and researchers should actively make efforts to expand their participation in research. Our findings also highlight the importance of early intervention following a subject’s first non-adherence from the protocol to prevent withdrawal. Expanding diverse inclusion and limiting withdrawal with real-time non-adherence monitoring will lead to more efficient clinical research and greater generalizability of results.

Abbreviations

BMI-	Body Mass Index
DCI-	Distressed Community Index
IRB-	Institute Review Board
MRI-	Magnetic Resonance Imaging
SES-	Socioeconomic status

Declarations

Ethics approval and consent to participate

We enrolled men into a prostate cancer study exploring novel imaging to predict cancer outcomes from January 2016 to June 2019 under Institute Review Board, University of Texas Health, San Antonio, USA (IRB HCS20150160H). An IRB determination was obtained, HSC20200572E, to perform a retrospective chart review study to investigate risk factors for withdrawal.

Consent for publication

All patients consent

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contribution

Research conception and design: AJW, MAL

Data acquisition: AJW,HG,MAL

Data analysis and interpretation: AJW, DK, MAL

Drafting of the manuscript: AJW, HG, MAL

Critical revision of manuscript: AJW,HG,DK, AM, DP, MAL

Obtaining funding: MAL

Administrative technical or material support: MAL

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Table 1

Table 1. Patient demographics and socioeconomic stress characteristics in relation to retention.

Demographics	Retained Mean (SD) or Number (%) N=106	Withdrawn Mean (SD) or Number (%) N=17	P value*
Age	64 (6.5)	63 (5.9)	0.8
Ethnicity			0.8
Hispanic	34 (87.2%)	5 (12.8%)	-
Non-Hispanic	72 (85.7%)	12 (14.3%)	-
Race			0.4
White	77 (83.7%)	15 (16.3%)	-
African American	28 (93.3%)	2 (6.7%)	-
Asian American or Pacific Islander	1 (100%)	0 (0.0%)	-
Body Mass Index	29.1 (4.4)	30.7 (3.5)	0.1
Charlson Comorbidity Index	4.2 (0.9)	4.1 (1.0)	0.6
Smoking Status			0.8
Former smoker	38 (84.4%)	7 (15.6%)	-
Current smoker	18 (90.0%)	2 (10.0%)	-
Never smoked	49 (86.0%)	8 (14.0%)	-
Days from diagnosis to enrollment	970.8 (736.954)	951.0 (737.745)	0.9
Non-Adherence			<0.001
No	55 (100.0%)	0 (0%)	-
Yes	51 (75%)	17 (25.0%)	-
Number of Non-Adherences			<0.001
0	55 (51.9%)	0 (0%)	-
1	33 (31.1%)	2 (11.8%)	-
2	17 (16.0%)	8 (47.1%)	-
3	1 (0.9%)	4 (23.5%)	-
4	0 (0%)	3 (17.6%)	-

Socioeconomic Stress			
DCI Score	40.0 (30.7)	33.8 (34.4)	0.5
Distress Tier			0.7
Prosperous	39 (81.3%)	9 (18.8%)	-
Comfortable	19 (90.5%)	2 (9.5%)	-
Mid-Tier	15 (93.8%)	1 (6.3%)	-
At Risk	18 (90.0%)	2 (10.0%)	-
Distressed	15 (83.3%)	3 (16.7%)	-
Low SES			0.9
No	73 (85.9%)	12 (14.1%)	-
Yes	33 (86.8%)	5 (13.2%)	-

Figures

Figure 1

Cohort flow chart.

Figure 2

Percent of subjects retained or withdrawn by distress tier. We display a bar graph noting the proportion of patients that remained in the study to completion (retained) compared to those subjects who did not complete the study (withdrawn).

Figure 3

Percent of patients retained vs withdrawn in relation to the number of non-adherent events. We present a bar graph to demonstrate the number and proportions of subjects that remain in the study compared to those withdrawn from the study represented by the number of protocol non-adherent events. We note that after 1 non-adherent event the proportion of subjects that withdraw markedly increases indicated a teachable moment after the first non-adherence.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytableandfigure.docx](#)