


Leave me out: Patients' characteristics and reasons for opting out of a pragmatic clinical trial involving medication adherence

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Abstract

Opt-out procedures are sometimes used instead of standard consent practices to enable patients to exercise their autonomous preferences regarding research participation while reducing patient and researcher burden. However, little is known about the characteristics of patients who opt-out of research and their reasons for doing so. We gathered such information in a large pragmatic clinical trial (PCT) evaluating the effect of theory informed text messages on medication adherence.

Eligible patients, identified through electronic health records, were sent information about the study and provided with an opportunity to opt-out. Those opting out were asked to complete a voluntary survey regarding their reasons for doing so. Demographic data were compared among patients opting-out vs those included in the study using chi-squared tests and a log binomial regression model.

Of 9046 patients receiving study packets, 906 (10.0%) patients returned opt-out forms. Of those, 451 (49.8%) returned the opt-out survey. Patients who opted out were more likely to be older, white, and nonHispanic than those who were included in the PCT. Survey respondents expressed high levels of trust in their health care providers, research, and system. Nearly half (46.6%) reported concerns about time as a reason to opt-out.

In this PCT, 10% of patients receiving packets opted out, with significant differences in age, race, gender, and ethnicity compared to those included. Future trials should further investigate representativeness and reasons patients choose to opt-out of participating in research.

Abbreviations: CI = confidence intervals, DH = Denver Health and Hospital Authority, EHR = electronic health record, HCS = health care systems, PCT = pragmatic clinical trial, RR = relative risks, USPS = United States Postal Service, VA = VA Eastern Colorado Health Care System.

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1. Introduction

Pragmatic clinical trials (PCT) are conducted in real-world settings and populations to inform healthcare decisions and treatment effectiveness.^[1,2] PCTs generally require that data be collected from large and representative populations, which can be facilitated by minimizing the burdens for patients and clinicians associated with traditional clinical research, such as using a conventional written informed consent processes.^[3] In appropriate research contexts that involve minimal research risks, opt-out mechanisms are one means for patients' to exercise their autonomous preferences regarding research participation while reducing burdens, promoting participation, and increasing patient representativeness.^[4,5]

While an opt-out mechanism can be acceptable for minimal risk studies by patients in both urban and rural populations,^[6,7] information about opt-out processes, opt-out rates, and descriptions of which patients choose to opt-out are limited.^[8–10] Given the proliferation of PCTs,^[11–13] it is conceivable that the use of opt-out mechanisms will expand in tandem. Accordingly, data are needed to inform methodologies and practices regarding them. We describe the opt-out process developed and employed for a large, multi-center PCT evaluating medication adherence. In addition, we present demographic characteristics of patients who opted out compared to those included in the trial, their levels of trust associated with health care, and their reasons for opting out of the PCT.

2. Methods

2.1. The parent study

The parent PCT, The Nudge Study (Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications; NCT03973931),^[14] sought to improve medication adherence in patients with at least one chronic cardiovascular disease of interest who were prescribed at least 1 medication to treat that condition (Table 1) by sending theory-informed text messages, or “nudges”, to remind patients to refill their medications when a delay in refilling their prescription occurred.^[15,16] Patients were excluded if they did not speak English or Spanish, have a phone number or address in their electronic health record (EHR), or lived outside of the State of Colorado.

The Nudge Study was conducted at 2 large health care systems (HCS) in the Denver metropolitan area. The first HCS, Denver Health and Hospital Authority (DH), is a safety net system for Denver County with 9 Federally Qualified Health Centers. DH serves an estimated 1 in 4 Denver residents. Over 60% of the patients seen are members of racial and/or ethnic minority

groups. The second HCS, the VA Eastern Colorado Health Care System (VA), serves veterans across the Denver metropolitan region. Within the VA, approximately 87% of the population is white and 84% are non-Hispanic.

2.2. Opt-out process and survey

Patients meeting eligibility criteria were identified through EHRs and sent an opt-out packet through the United States Postal Service (USPS) between August 2019 and June 2020. The packet included an introductory cover letter signed by the respective site principal investigator, a “Frequently Asked Questions” document discussing the study and opt-out process, an opt-out form, an anonymous and voluntary opt-out survey for patients opting out of the study, and a self-addressed stamped envelope to return the opt-out form and survey. A phone number and email address were provided for interested patients to obtain more information about the study. The 19-item opt-out survey included: multiple choice questions regarding demographic characteristics; reasons contributing to why patients chose to opt-out; history of research participation; and, 13 five-item Likert scale questions designed, tested and validated to assess patient trust with their HCS, physicians, and researchers (Appendix I, Supplemental Digital Content, <http://links.lww.com/MD2/A738>).^[17,18] All materials were sent on letterhead and branding specific to each HCS. Materials were sent in the primary language of the patient denoted in the EHR. If no language was denoted, materials were sent in both English and Spanish. The opt-out process and materials were reviewed by the study's stakeholder panel, comprised of patients, providers, pharmacists, and healthcare staff. The study was approved by Colorado Institutional Review Board (#18-2779).

Patients were provided 4 weeks to return the opt-out form and survey. Patients were included in the study if an opt-out form was not received by the deadline printed on it. If opt-out forms were received after the deadline, patients were removed from the study at the time the forms were received. If USPS returned study packets due to an undeliverable address, patients were excluded from the study, but not considered to have opted out.

2.3. Statistical analysis

Demographic characteristics and the number of prescribed cardiovascular-related medication classes for patients who opted out vs the enrolled population were collected from the EHR. Reasons patients chose to opt-out of the study, levels of trust, and self-reported demographic characteristics associated with these responses were collected in the opt-out survey. The trust scales were scored by summing responses (with strongly disagree scored

Table 1

Inclusion criteria, cardiovascular conditions and medications classes included in the “Nudge” study.

Condition	Classes of medications
Hypertension	Beta-blockers (B-blockers), calcium channel blocker (CCB), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), or thiazide diuretic
Hyperlipidemia	HMG CoA reductase inhibitor (Statins)
Diabetes	Alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, sodium glucose transport inhibitor, meglitinides, sulfonylureas, thiazolidinediones, or statins
Coronary artery disease	P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel, ticlopidine), B-blockers, ACEi or ARB or statins
Atrial fibrillation	Direct oral anticoagulants, B-blockers, CCB

with a 1, strongly agree scored with a 5) among patients responding to all questions, with higher values indicating increased levels of trust.

Associations between patient characteristics and opting out of the study were assessed using multiple degree of freedom chi-squared tests for categorical variables and *t* tests for continuous variables, while a log binomial regression model estimated the relative risks (RR) and 95% confidence intervals (CI) of returning opt-out forms for each demographic characteristic adjusting for all other characteristics and HCS. Statistical analyses were performed using R statistical software (version 4.0.3, Vienna, Austria).

3. Results

Of 9444 potentially eligible patients sent opt-out forms, 398 (4.2%) were returned by USPS due to undeliverable addresses. Of the remaining 9046 patients, 10.0% (n=906) opted out of the study by returning an opt-out form (Fig. 1). Compared to enrolled patients, those who opted out were more likely to be older, white, and nonHispanic ($P < .001$ for all, Table 2). Patients from the VA were also more likely to opt-out compared to patients from DH (20.2% vs, 7.5%; $P < .001$). We observed a higher risk of returning opt-out forms for older age groups relative to those 50 years and younger: age 51 to 60 (RR: 1.79, 95% CI [1.30, 2.45]), 61 to 70 (RR: 3.36, 95% CI [2.52, 4.48]), 71 to 80 (RR: 4.22, 95% CI [3.15, 5.66]), and 81+ (RR: 5.29, 95% CI [3.81, 7.34]). Relative to white patients, a lower risk of opting-out was observed for black patients (RR: 0.68, 95% CI [0.56, 0.83]) and Hispanic patients (RR: 0.57, 95% CI [0.48, 0.67]). There was no difference in the mean number of prescribed cardiovascular-related medication classes between groups ($P = .28$).

Of those who opted-out, half (n=451, 49.8%) returned an opt-out survey. Among patients returning surveys and providing self-reported characteristics, 65.4% (n=295) were 61 to 80 years

of age, 65.2% (n=294) were male, 56.8% (n=256) were white, and 60.3% (n=272) were non-Hispanic (Table 2). Since these surveys were anonymous, it was not possible to compare characteristics of those returning vs not returning the survey. One quarter (25.7%) indicated they had participated in clinical research in the past. The most common reason selected for opting out was a concern the study would take too much time (46.6%; n=210), followed by feeling like they did not need the intervention because they already take their medications on time (19.5%, n=88), and being uncomfortable using technology (18.6%, n=84) (Fig. 2). Aggregated scores averaged 16.2 (scale 4–20) for trust in the HCS, 14.0 (scale 4–20) for trust in research, and 17.9 (scale 5–25) for trust in physicians, with higher scores indicating a high level of trust within each of the 3 domains (Table 3).

4. Discussion

In a PCT seeking to improve medication adherence among patients with chronic cardiovascular disease, 10.0% of patients receiving study packets opted-out. Factoring in the 4.2% of packets that could not be delivered, we had a participation rate of 86.2%. The opt-out consent process, with minimal patient enrollment burdens, likely contributed to this large participation rate. In addition, having the study team available to patients with questions allowed patients to verify the legitimacy of the study. Our results also suggest there were opportunities to improve our participation rate by addressing reasons patients chose not to participate. For instance, including a simple description of the minimal time and technological knowledge needed to participate in the study alone in the “Frequently Asked Questions” document may have increased patient understanding and improved the participation rate.

Our opt-out rate was slightly higher than 2 previously published reports regarding the use of a mailed opt-out approach: the first, a study involving colorectal cancer screening, experienced

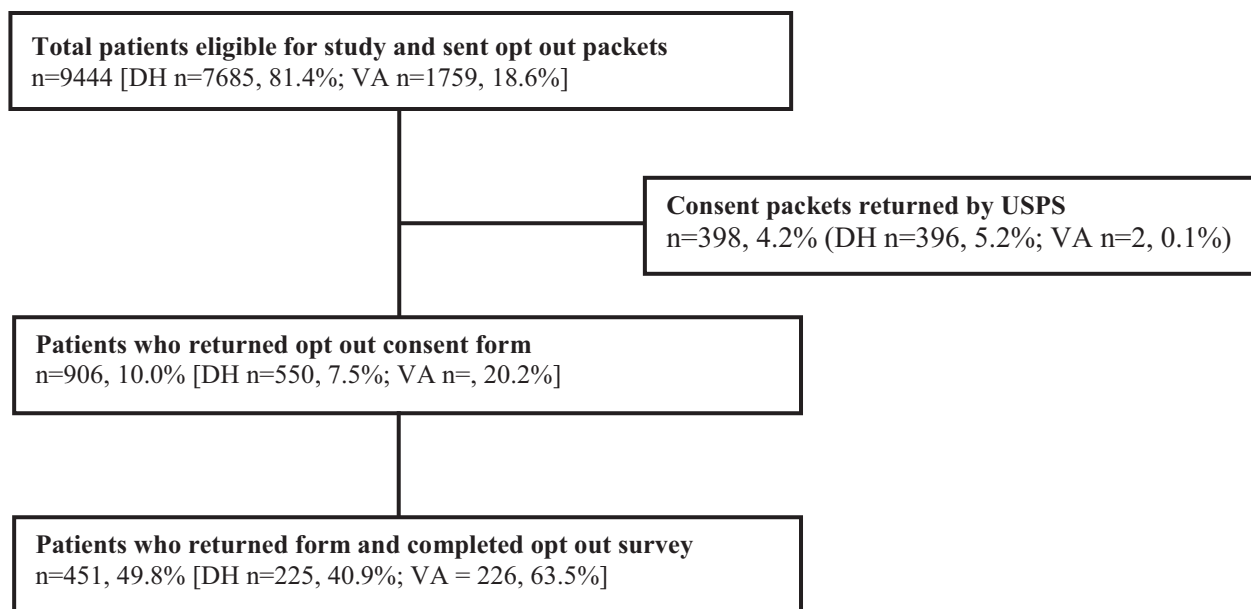


Figure 1. Participation in opt-out survey. DH = Denver Health and Hospital Authority, USPS = United States Postal Service, VA = VA Eastern Colorado Health Care System.

Table 2
Demographic characteristics for survey respondents, patients who returned opt-out forms and nonopt-out patients eligible for inclusion in the study. Reported P-values comparing the opt-out population and population eligible for enrollment are from multiple degree of freedom Chi-square tests for categorical variables and t tests for continuous variables.

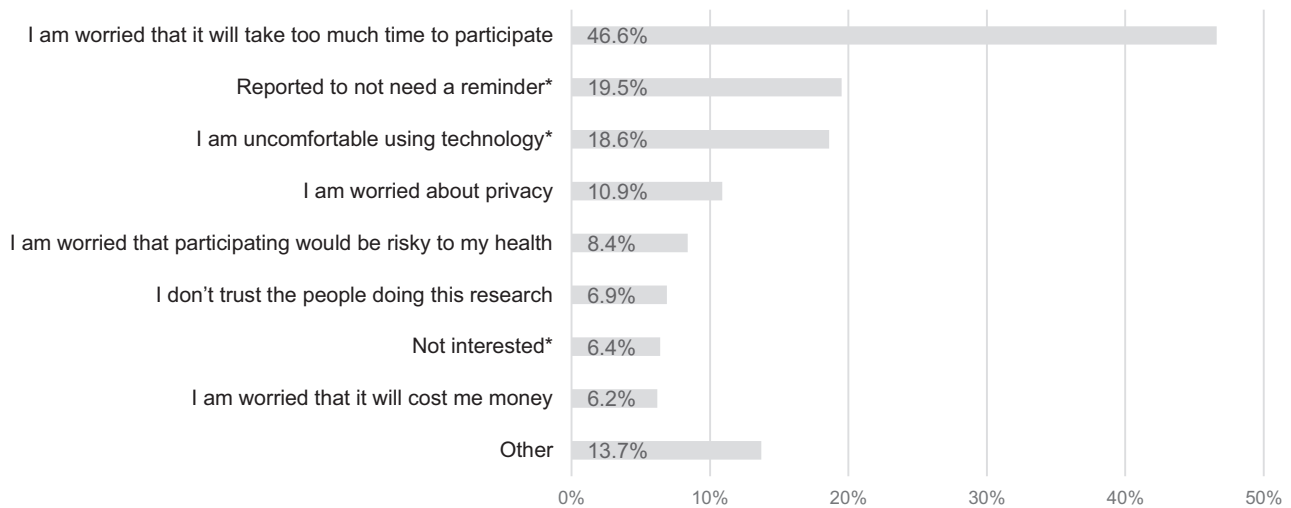
	Survey respondent N = 451	Opt-out population N = 906	Eligible for inclusion N = 8140	P-value
Age				<.001
0 to 40	0 (0)	1.5% (14)	6.3% (511)	
41 to 50	6.9% (31)	4.3% (39)	14.6% (1187)	
51 to 60	14.2% (64)	14.2% (129)	26.2% (2130)	
61 to 70	33.0% (149)	35.9% (325)	30.6% (2488)	
71 to 80	32.4% (146)	33.4% (303)	17.6% (1431)	
81+	8.6% (39)	10.6% (96)	4.8% (393)	
Missing	4.9% (22)	0 (0)	0 (0)	
Gender				<.001
Female	28.4% (128)	35.8% (324)	45.7% (3724)	
Male	65.2% (294)	63.9% (579)	54.1% (4407)	
Transgender/other	0 (0)	0.2% (2)	0 (4)	
Missing	6.4% (29)	0.1% (1)	0.1% (5)	
Race				<.001
White	56.8% (256)	76.3% (691)	72.3% (5888)	
Black	9.1% (41)	13.7% (124)	16.0% (1300)	
Multiple	2.4% (11)	0.4% (4)	0.8% (68)	
Other	8.2% (37)	5.4% (49)	9.2% (748)	
Missing	23.5% (106)	4.2% (38)	1.7% (136)	
Hispanic				<.001
Yes	29.9% (135)	33.6% (304)	54.2% (4411)	
No	60.3% (272)	63.4% (574)	44.7% (3642)	
Missing	9.8% (44)	3.1% (28)	1.1% (87)	
Number of medication classes, mean (standard deviation)*	–	2.6 (1.5)	2.6 (1.5)	.28
Healthcare system				<.001
VA	50.1% (226)	39.3% (356)	17.2% (1401)	
Denver health	49.9% (225)	60.7% (550)	82.8% (6739)	

VA = VA Eastern Colorado Health Care System.

*The number of medication classes were counted at the time of patient identification, looking 6-months back for VA patients, and 6-months or 24-months back for Denver Health patients.

a 2.5% opt-out rate compared with an opt-in rate of 23.1%^[19]; second, a texting campaign seeking to promote smoking cessation had an opt-out rate of just 1%.^[19] Of note, these studies provided a slightly smaller window of time to opt-out (3 and 2 weeks, respectively).^[9,19]

We observed significant differences in the patient population who opted out compared with those included in the study. Patients returning opt-out packets were older, white, and nonHispanic. The fact that nonWhite and Hispanic patients were more likely to participate in the study is a positive finding



*Patient write-in responses

Figure 2. Reasons contributing to opt-out decisions.

Table 3**Trust scores. Individual scores range from 1 for strongly disagree to 5 for strongly agree.**

	Proportion with response	Mean	Standard deviation
Trust in HCS			
My HCS does its best to make patients' health better.	83.6%	4.2	0.9
Patients received high quality medical care at my HCS	83.4%	4.2	0.9
My HCS gives excellent medical care	81.8%	4.1	0.9
My HCS experiments on patients without them knowing*	74.9%	3.7	1.1
Aggregate trust in HCS score (range 4–20)	74.3%	16.2	3.1
Trust in research			
Doctors who do medical research care only about what is best for each patient	78.3%	3.5	1
Doctors tell their patients everything they need to know about being in a research study	75.8%	3.5	1
Medical researchers treat people like "guinea pigs"*	74.1%	3.6	1.1
I completely trust doctors who do medical research	75.2%	3.4	1
Aggregate trust in research score (range 4–20)	70.3%	14	3.1
Trust in physicians			
Sometimes doctors care more about what is convenient for them*	76.9%	3.3	1.1
Doctors are extremely thorough and careful	79.8%	3.9	0.9
I completely trust doctors' decisions about which medical treatments are best	81.2%	3.7	1
A doctor would never mislead me about anything	79.4%	3.5	1.1
All in all, I trust doctors completely	81.4%	3.7	1
Aggregate trust in physicians score (range 5–25)	74.3%	17.9	4.1

HCS = health care system.

* Scores reversed so that strongly agree is 1 and strongly disagree is 5.

given prior evidence of disparities in clinical trials participation among racial and ethnic minority patients. Consequently, these findings may help spur new research in ways of including under-represented patient populations in clinical trials in order to increase the representativeness of clinical trial participants.

Patients opting out cited concerns around a lack of time, not needing the intervention, and being uncomfortable around technology as reasons to not participate in the Nudge study. These findings may confirm assumptions about the need to reduce burden as much as feasible to encourage participation in PCTs. Alternatively, as found by Weinfurt et al,^[20] it is possible that patients overestimated the time, effort or general burden that may be involved in a pragmatic clinical study due to a lack of understanding the study activities. Consequently, future PCTs employing an opt-out mechanism could consider conducting formative research to identify potential barriers to enrollment (such as technology or understanding) and to implement means of alleviating them.

Contrary to prior assumptions,^[20,21] lack of trust did not appear to be a motivating factor for opting out among survey respondents. Trust was high in scales measuring patient's trust of physicians, research, and HCS; and only 6.9% of patients' responses for reasons contributing to opting out included trust as a reason. However, it is possible that trust may have been different among those patients who opted-out, but did not complete a survey. Similarly, we do not know how these data compare to the perspectives of patients who were included in the trial.

Despite the usefulness of our findings regarding the opt-out process for a large number of patients asked to enroll in a multicenter PCTs, our study should be interpreted with some limitations in mind. First, as with all materials sent to patients, we were unable to verify if patients received or read them, or the extent to which the PCT was understood. Further, since surveys were returned anonymously, we were unable to compare characteristics of all of those who opted out to those who returned survey. Finally, as mentioned earlier in regard to trust,

reasons contributing to patients choosing to opt-out may have been different for the patients who did not complete the opt-out survey.

In conclusion, this report provides important data and some suggestions from a large PCT for other PCTs employing an opt-out mechanism. In addition, we have demonstrated that it is feasible to nest empirical studies related to emerging mechanisms for ethically conducting PCTs into actual trials. The data from these studies should prove useful to informing Institutional Review Boards who oversee this research as well as policies and practices for PCTs.

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