Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 7, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.10.046

Patient- and Trial-Specific Barriers to Participation in Cardiovascular Randomized Clinical Trials

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Objectives The purpose of this study was to quantitatively examine the association of patient- and trial-specific factors with participation in cardiovascular randomized clinical trials.

Background Randomized clinical trials are central to evidenced-based medicine, but low patient participation rates and potentially modifiable barriers are not well understood.

Methods At a large U.S. academic health system, we examined screening logs from December 1, 2005, to February 28, 2011, from 15 cardiovascular randomized clinical trials. We identified 655 patients who were screened and potentially eligible for participation in at least 1 trial. We used multivariable Poisson regression to quantify the risk of not participating in a trial associated with patient- and trial-specific factors.

Results The median age was 63 years (interquartile range: 54 to 72), 35% were women, and the median Charlson Index was 2 (interquartile range: 1 to 5). Forty-two percent of patients did not participate in a trial. In multivariable regression (C-Index 0.85), trial-specific factors strongly associated with not participating included intensive trial-related testing (relative risk [RR]: 1.89; 95% confidence interval [CI]: 1.63 to 2.20) and anticipated trial participation >6 months (RR: 4.10; 95% CI: 2.30 to 7.29). Patient-specific factors associated with not participating included older age (RR: 1.23; 95% CI: 1.11 to 1.36, per 10-year increase if age ≥65 years), out-of-state residence (RR: 1.26; 95% CI: 1.04 to 1.54), and female sex (RR: 1.17; 95% CI: 1.01 to 1.35). Race was not associated with participation.

Conclusions While patient-specific factors were associated with not participating in cardiovascular trials, longer trial duration and intensive trial-related testing were most strongly associated with risk for patients not participating. Innovative trial designs fostering convenience may most enhance trial participation. (J Am Coll Cardiol 2013;61: 762–9) © 2013 by the American College of Cardiology Foundation

Randomized clinical trials (RCTs) are central to evidence-based medicine. Successful RCTs require efficient recruitment of adequately sized study populations that are representative of contemporary clinical practice. However, patient recruitment is a widespread challenge across RCTs, particularly among cardiovascular RCTs conducted in the United States, and there is increasing reliance on enrollment abroad (1–4). Beyond low overall enrollment, underrepresentation of certain groups of patients from the community threatens the generalizability of RCTs (5–14).

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The developing crisis in RCT participation prompted a recent National Heart, Blood, and Lung Institute workshop on strategies for recruitment, from which several themes emerged, including the role of health care professionals as gatekeepers (15). Complementing these important initiatives, further investigation is needed to identify the most important barriers to patient participation in RCTs that can be potentially modified in future RCT designs and recruitment efforts. We quantitatively examined the association of patient- and trial-specific factors with patient participation in RCTs in a consecutive sample of patients who were

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Manuscript received August 31, 2012; revised manuscript received October 18, 2012, accepted October 23, 2012.

screened and potentially eligible for participation in at least 1 cardiovascular RCT at a tertiary medical center.

Methods

Study population and data collection. We examined screening logs from December 1, 2005, to February 28, 2011, at Duke University Medical Center (Durham, North Carolina), a high-volume tertiary academic health system in the southeastern United States. Screening logs of patients considered for RCT participation were routinely maintained to monitor for bias in selection of subjects for a RCT by investigators, the institution, and sponsors. Screening logs contained data on patients' sociodemographics, RCT eligibilities, and enrollment outcomes. If a patient considered for participation did not enroll, the primary reason for decline was documented as specifically as possible. Where possible, reasons were determined directly by patient report, while other reasons, including altered mental status, clinical instability, concern for nonadherence or substance abuse, and provider decline were based on discussion with clinical providers, review of the medical chart, and/or interview with the patient or the patient's family.

Screening logs were available for 15 ongoing or completed RCTs (16–30). Table 1 summarizes the designs of each of these trials and displays study features that were typically discussed with potential participants during informed consent. The targeted populations in these mostly phase III and IV RCTs reflected a range of clinical diagnoses, including systolic heart failure, heart failure with preserved ejection fraction, acute coronary syndromes, stable coronary disease, and patients with cardiovascular risk factors.

Abbreviation and Acronym

RCT = randomized clinical trial

We identified 667 patients who were considered potentially eligible for participation in at least 1 cardiovascular RCT after an initial screen against protocol-defined medical inclusion and exclusion criteria. Some RCTs explicitly identified an inability to follow the protocol as an exclusion criterion; however, this assessment may entail subjective determination, its importance varies based on trial follow-up requirements, and it is not well understood to what extent this type of exclusion contributes to participation outcomes. Therefore, we specifically captured information on this group, but did not consider this a reason for exclusion from the primary analyses of our study. We did exclude 12 patients with a language barrier because these patients were systematically excluded from RCTs at our institution due to the lack of availability of bilingual trial personnel as well as native language consent forms and other trial materials. Therefore, 655 patients were included in our primary analysis sample. The Duke University institutional review board approved the study and waived patient consent.

We leveraged Duke's Enterprise Data Unified Content Explorer (DEDUCE), a Web-based data query tool, to

Table 1 Trial Characteristics

Trial (Ref. #)	NCT ID	Year	Pop.	Phase	Intervention	Primary Outcome	Setting*	Size	>6 Months†	<$20‡	IT§	Sponsor
APPRAISE-2 (16)	00831441	2009	ACS	III	PO anticoagulant	MACE	H	10,848	+	−	−	I
ASCEND-HF (17)	00475852	2007	ADHF	III	IV diuretic	Combined clinical	H	7,138	−	−	−	I
ATMOSPHERE (18)	00853658	2009	sHF	III	PO renin inhibitor	Hosp/mortality	O	7,041	+	−	−	I
CARRESS (19)	00608491	2008	ADHF	III	Ultrafiltration	ΔCr/weight	H	200	−	+	−	G
DOSE (20)	00577135	2008	ADHF	III	IV furosemide	Well-being/Cr	H	300	−	+	−	G
EXACT-HF (21)	00987415	2010	sHF	IV	PO XO inhibitor	Clinical status	O	250	−	+	−	G
IMPROVE-IT (22)	00202878	2005	ACS	III	PO lipid lowering	MACE	H	18,141	+	−	−	I
RED-HF (23)	00358215	2006	sHF	III	SC epoetin	Hosp/mortality	O	2,600	+	−	−	I
RELAX (24)	00763867	2008	HF-PEF	III	PO vasodilator	Peak O_2 uptake	O	190	−	+	+	G
REVEAL (25)	00378352	2006	STEMI	II	SC epoetin	Infarct size	H	210	−	−	+	G
ROSE-AHF (26)	01132846	2010	ADHF	IV	IV pressor and diuretic	UO/cystatin C	H	360	−	+	−	G
SOLSTICE (27)	00910962	2009	NSTEMI	II	PO anti-inflam	Safety	H	500	−	−	+	I
STABILITY (28)	00799903	2008	CAD	III	PO anti-inflam	MACE	O	15,500	+	−	−	I
TRACER (29)	00527943	2007	NSTEMI	III	PO anticoagulant	MACE	H	12,946	+	−	−	I
TRA-Ocular (30)	00617123	2010	Athero	III	PO anticoagulant	Retina exam	H	200	+	−	+	I

*Recruitment setting. †More than 6 months of anticipated duration of patient participation. ‡<$20 total patient compensation for trial participation. §Intensive trial-related testing (IT), defined as cardiac magnetic resonance imaging, retinal examinations requiring extended study visits, or peak oxygen uptake measurement during exercise.

ACS = acute coronary syndrome; ADHF = acute decompensated heart failure; anti-inflam = anti-inflammatory; APPRAISE-2 = Apixaban for Prevention of Acute Ischemic Events 2; ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; Athero = atherosclerosis; ATMOSPHERE = Aliskiren Trial of Minimizing Outcomes for Patients with Heart failure; CAD = coronary artery disease; CARRESS = Cardiorenal Rescue Study in Acute Decompensated Heart Failure; Cr = creatinine; ΔCr = change in creatinine; DOSE = Diuretic Optimization Strategies Evaluation; EXACT-HF = Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients; exam = examination; G = government; H = hospital; HF-PEF = heart failure with preserved ejection fraction; Hosp = hospitalization; IMPROVE-IT = Improved Reduction of Outcomes: Vytorin Efficacy International Trial; I = industry; IV = intravenous; MACE = major adverse cardiac events; minus symbol (−) = no; NCT ID = national clinical trial identifier; NSTEMI = non–ST-segment elevation myocardial infarction; O = outpatient clinic; plus symbol (+) = yes; PO = per os; Pop. = population; RED-HF = Reduction of Events With Darbepoetin Alfa in Heart Failure; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure; REVEAL = Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction; ROSE-AHF = Renal Optimization Strategies Evaluation in Acute Heart Failure; SC = subcutaneous; sHF = systolic heart failure; SOLSTICE = Study of Losmapimod Treatment on Inflammation and Infarct Size; STABILITY = Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy; STEMI = ST-segment elevation myocardial infarction; UO = urine output; TRACER = Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome; TRA-Ocular = Trial to Assess the Ocular Safety of SCH 530348 in Patients With Atherosclerosis; XO = xanthine oxidase; Year = year of trial start.

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Table 2 Patient-Specific Factors Stratified by Participation

Factors	Did Not Participate in RCT (n = 278)	Participated in RCT (n = 377)	p Value
Sociodemographic			
Age, yrs	65.6 (55.3–75.5)	61.3 (53.5–70.2)	<0.001
Sex			
Male	165 (59.4)	263 (69.8)	0.006
Female	113 (40.7)	114 (30.2)	
Race/ethnicity*			
White	183 (65.8)	215 (57.0)	
Black	88 (31.7)	145 (38.5)	0.06
Other	7 (2.5)	17 (4.5)	
Married†	156 (56.1)	206 (54.6)	0.94
Religious affiliation	241 (86.7)	334 (88.6)	0.47
Uninsured	66 (23.7)	103 (27.3)	0.32
Employment			
Employed	48 (17.3)	68 (18.0)	
Retired	124 (44.6)	128 (34.0)	0.19
Unemployed	88 (31.7)	124 (32.9)	
Unknown	18 (6.5)	57 (15.1)	
Education, % by ZIP code, mean‡			
Did not graduate high school	23.3	23.1	0.94
High school graduate	53.1	52.9	0.77
Bachelor's degree	23.7	24.0	0.47
Income, $1,000s by ZIP code‡	38.5 (32.8–41.7)	38.5 (31.7–41.7)	1.00
Living in urban ZIP code	198 (71.2)	253 (67.1)	0.27
Out-of-state residence	37 (13.3)	29 (7.7)	0.03
Driving distance, miles§	32.0 (10.9–58.2)	35.1 (10.6–67.2)	0.34
Driving time, min§	51.8 (22.4–90.8)	52.1 (23.4–102.6)	0.48
Clinical			
Charlson Index score	2 (1–4)	3 (1–6)	0.02
Mental health disorder‖	130 (46.8)	199 (52.8)	0.13
No. of inpatient admissions in the last year			
0	99 (35.6)	115 (30.5)	
1	127 (45.7)	171 (45.4)	0.18
≥2	52 (18.7)	91 (24.1)	
≥1 outpatient encounters in the last year	197 (70.9)	292 (77.5)	0.06
No. of outpatient encounters	3 (0–10)	6 (1–15)	<0.001
Duke cardiologist	140 (50.4)	249 (66.1)	<0.001
No. of cardiology encounters	1 (0–3)	2 (0–6)	<0.001

Values are median (interquartile range) or n (%). *Self-designated; "other" race denotes Asian, Native American, or unspecified/unknown race; no Hispanic patients in primary analysis sample. †Missing data for 23 patients. ‡Extracted by ZIP code; missing data for 26 patients due to missing Census 2000 education and income data for certain ZIP codes. §Calculated from patient home address to trial center address. ‖Any mental health International Classification of Diseases 9th Revision diagnosis (codes 290–319, a broad grouping that included tobacco abuse, mild mood disorders, as well as more severe disorders) preceding the screening date.

IQR = interquartile range; RCT = randomized clinical trial.

standardize and streamline electronic medical chart review for the sociodemographic and clinical patient factors displayed in Table 2. Three variables (language, insurance, employment) were not available and were extracted in a similar electronic manner from Duke's Decision Support Repository. After this step, language data were not available for 71 patients; therefore, we performed a manual review of the medical charts and screening logs to assess for evidence of limited English proficiency.

Several variables were derived from patients' home postal addresses. We derived driving distance and driving time by referencing patients' home addresses to the address of Duke University Medical Center using CDX Technologies ZipStream (Randolph, New Jersey) integrated with Microsoft MapPoint and Excel (Redmond, Washington). Crosscheck with Google maps (Mountain View, California) showed similar driving distances and times. Based on patients' home ZIP codes, we assigned population representative values for educational attainment, median income, and rural versus urban residence using U.S. Census Bureau 2000 data (31).

Definitions. Our main outcome measure, namely, not participating in a RCT, was defined as a patient not enrolling in any of the RCTs for which he or she was screened. Definitions of patient- and trial-specific factors considered in our analyses are included in the Online Methods.

Statistical analyses. We stratified the primary analysis sample into those who participated and those who did not participate in a RCT. Demographic, clinical, and trial characteristics were compared across groups. Continuous variables are presented as median (interquartile range). Categorical variables are expressed as frequency percentages. Univariable analysis was performed using the Wilcoxon rank-sum test and Fisher's exact test for continuous and categorical variables, respectively.

Our main outcome measure occurred commonly; therefore, we used a modified Poisson regression model with a robust error variance (32) to identify the factors that were independently associated with not participating. Relative risks with 95% confidence intervals were calculated to examine the adjusted associations. Variables were selected for multivariable analysis based on clinically judged a priori importance and based on differences between the groups in univariable comparisons. Patient-specific variables in the model were age, sex, race, out-of-state residence, hospital admission, Charlson Index, and Duke cardiologist. Trial-specific variables were intensive trial-related testing, anticipated trial participation >6 months, and trial sponsor (industry versus government). The relationship between age and not participating was nonlinear; therefore, we used linear spline transformation with 1 knot at age 65 years, and the associations of increases in age with not participating were interpreted before and after 65 years of age. For modeling, Charlson Index scores were categorized into tertiles (0 to 1, 2 to 3, and 4 to 15). No covariate data were missing in the multivariable analysis.

We performed tests for interaction between age and sex on the basis of a prior report of such an interaction in heart failure trial participation (6). We also performed tests for interaction between independent risk factors with chi-square values >10. To facilitate the interpretability of the results, age was considered as a dichotomous variable (≥65 years old vs. <65 years old) in the interaction analyses. We also performed a sensitivity analysis in which we excluded 126 patients who were perceived by the trial team to have barriers to participation after reviewing the medical chart, speaking with the clinical providers, or interviewing the patient or the patient's family. This included patients with altered mental status, clinical instability, a history of or perceived risk for nonadherence, substance abuse, or cases in which the provider declined. In these cases, there was concern that the patients may have been unable to provide informed consent or were unable to follow trial protocols, and decisions regarding participation were largely made by persons other than the patient. We also performed a sensitivity analysis in which we excluded the 139 patients who were considered for multiple trials to assess whether our results were dependent on the coding scheme used for patients who were screened for multiple trials.

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). All p values are 2-sided with an alpha level of 0.05. No adjustments were made for multiple comparisons.

Results

Patient-specific factors. In the primary analysis sample, the median age was 63 years (interquartile range: 54 years to 72 years), 35% were women, and the median Charlson Index was 2 (interquartile range: 1 to 5). Patients who did not participate in a RCT represented 42% of the sample. Compared with RCT participants, those not participating were older and more commonly women, but similar in race and ethnicity (Table 2). Clinically, nonparticipants had a modestly lower comorbidity burden, and similar rates of any broadly defined mental health diagnosis and hospital admissions in the prior year. Participants had more frequent outpatient medical contact (overall and cardiology) at the study institution relative to those who did not participate. There were no significant differences in marital status, religion, insurance status, employment, and ZIP code assigned educational attainment, income levels, or urban living.

Persons who did not participate were more likely to reside out-of-state, but had similar overall driving time and distance compared with persons who participated. Specifically examining the subgroup of patients who did not participate and stated that travel distance was the primary reason for not participating (n = 22), median driving distance was 143 miles (interquartile range: 82 to 241 miles), and median driving time was 196 min (interquartile range: 150 to 277 min).

Trial-specific factors. Table 3 shows the prevalence of trial-specific factors stratified by participation status. More patients who did not participate were considered for trials with intensive trial-related testing, an anticipated participation of >6 months, industry sponsorship, and size of <1,000 participants. A smaller proportion of patients who did not participate were considered for trials that offered <$20 in total compensation or recruited in the outpatient setting.

Table 3 Trial-Specific Factors Stratified by Participation

Factors	Did Not Participate in RCT (n = 278)	Participated in RCT (n = 377)	p Value
Intensive trial-related testing*	134 (48.2)	48 (12.7)	<0.001
Trial participation >6 months	244 (87.8)	162 (43.0)	<0.001
Industry trial sponsor	252 (90.7)	227 (60.2)	<0.001
Size <1,000 subjects	158 (56.8)	169 (44.8)	0.003
Total compensation <$20	32 (11.5)	131 (34.8)	<0.001
Outpatient recruitment	43 (15.5)	115 (30.5)	<0.001

Values are n (%). *Intensive trial-related testing was defined as cardiac magnetic resonance imaging, retinal examinations requiring extended study visits, and peak oxygen uptake measurement during exercise.
RCT = randomized clinical trial.

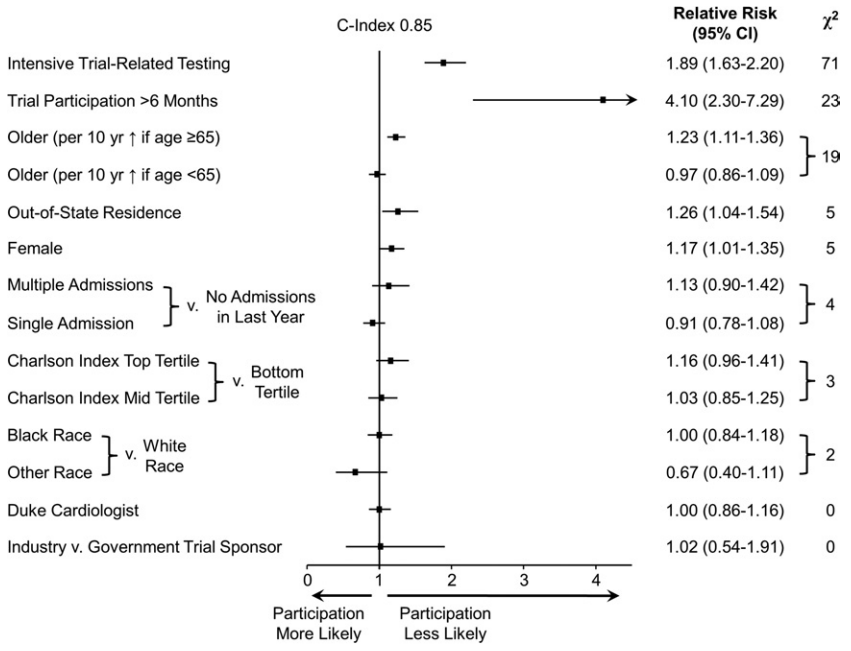

Figure 1 **Multivariable Analysis of Factors Associated With Not Participating in a Cardiovascular Randomized Clinical Trial**

The multivariable model included all of the factors in the Forest plot. Factors are ordered from top to bottom by highest to lowest chi-square. Relative risks and 95% confidence intervals (CI) are presented. The analysis included the primary analysis sample of 655 subjects without a language barrier. Intensive trial-related testing was defined as cardiac magnetic resonance imaging, retinal examinations requiring extended study visits, or peak oxygen uptake measurement during exercise. Chronic comorbidity burden was quantified by the Charlson Index. Hospital admissions were for any cause within the past year. Duke Cardiologist was defined as having an outpatient encounter within the past year with a Duke University Medical Center-affiliated cardiologist.

Factors independently associated with not participating in a RCT. In multivariable regression, intensive trial-related testing, longer trial length, and older age after 65 years were the 3 factors most strongly associated with not participating in a RCT (Fig. 1). Out-of-state residence and female sex were also independent factors. There was no independent association of participation status with industry sponsorship, Charlson Index, number of admissions, Duke cardiologist, race, or increased age before age 65 years. The C-Index for the model was 0.85.

Reasons for not participating. For the 278 patients who did not participate in a RCT, the primary reasons are categorized in Figure 2. The 4 most frequently used individual categories were unspecified reason for decline of participation, clinical instability, a history of or perceived risk for nonadherence, and patient-perceived travel barriers (distance or transportation), accounting for approximately two-thirds of the reasons for not participating. Travel barriers were especially common in patients who were considered for lengthier trials and among the elderly (Online Results).

Supplemental analyses. Sensitivity, interaction, and subgroup analyses (Online Results) were largely consistent with our primary results. In sensitivity analyses (Online Figs. 1 and 2), the 3 factors most strongly associated with not participating in a RCT remained intensive trial-related testing, longer trial length, and older age after 65 years.

Discussion

Trial-specific factors were more strongly associated with not participating in RCTs than patient-specific factors in our study, which is unique in the granularity of patient- and trial-specific factors simultaneously considered. Two trial-specific factors, intensive trial-related testing and an anticipated participation of >6 months, were most strongly linked with lack of participation. Patient-specific factors that were independently associated with not participating included older age after 65 years, female sex, and out-of-state residence.

Under-participation in RCTs: a longstanding systemic challenge in the United States. Between 1997 and 2009, U.S. federally funded RCTs of coronary artery disease populations required ~50% enrollment abroad (3). The United States is not alone in its recruitment problems: among 114 trials in the United Kingdom conducted between 1994 and 2002, >2 in 3 failed to recruit the target sample size within the planned time period (2). Slow or incomplete enrollment can undermine trial completion, statistical power, and the timely availability of results to guide clinical practice, and adds expense, limiting funding

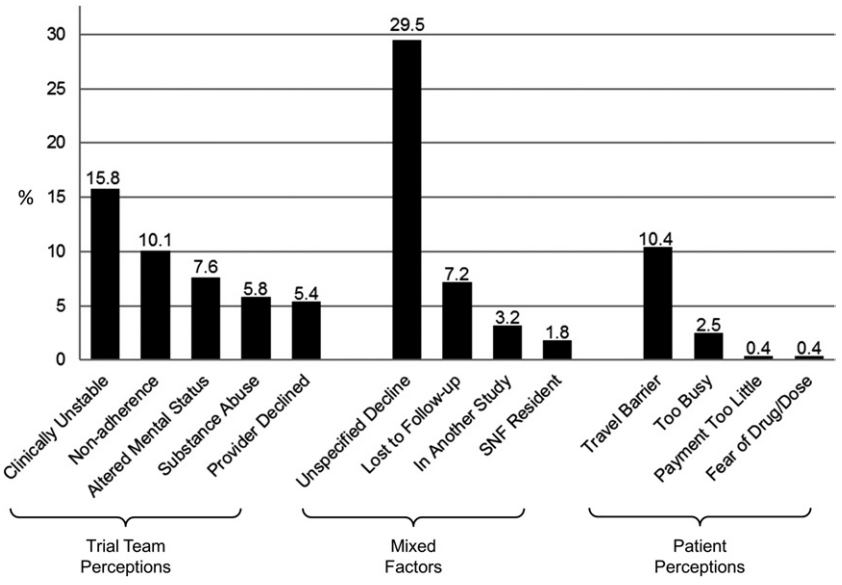

Figure 2 **Distribution of Primary Reasons for Not Participating in a Cardiovascular Randomized Clinical Trial**

In the 278 subjects without a language barrier who did not participate in a trial, the primary reasons for not participating were grouped into trial team perceptions, mixed factors, and patient perceptions. Within these groups, the **bar plots** show the percentage of patients who were contained within the selected categories of primary reasons for not participating, as documented in the screening logs. Altered mental status includes dementia and delirium. Unspecified decline indicates that no specific reason for decline of participation was identified. Travel barrier included travel distance and transportation barriers. SNF = skilled nursing facility.

for other important trials. These challenges also decrease site and sponsor interest in future RCTs.

Beyond impeding trial operations, under-representation of certain community patient groups in RCTs challenges the generalizability of the trial results. We are approaching the 2-decade mark since the National Institutes of Health Revitalization Act called for greater representation of women and minorities in RCTs (5). Under-representation of women has been shown in a number of studies (5–13), with women comprising only ~27% on average of the participants in cardiovascular RCTs (9,13) and National Institutes of Health initiatives failing thus far to improve on this (9). In our study, female sex was independently associated with not participating in cardiovascular RCTs, yet interestingly, race was not. Although the elderly were not a focus group of the Revitalization Act, or national guidelines on inclusiveness in clinical trials that followed in 1994 (11), we found that older age was a risk factor for not participating in a RCT, independent of comorbidities. Patients with limited English proficiency represent another vulnerable group that was systematically excluded from RCT participation in our study because of the lack of necessary resources for native language communication. There is wide variability across institutions in the availability of such resources, although a case can be made for greater resource allocation to support consistent inclusion of this growing segment of the population in clinical research (14).

Patient factors and provider perceptions as barriers to RCT participation. Among patient-reported reasons for not participating in RCTs, inconvenience and inability to complete study requirements are common themes. In targeted interviews conducted during an earlier study from our institution (33), 27% of patients cited inconvenience as their primary reason for deciding against RCT enrollment. In our study, travel distance and difficulty arranging transportation clustered in patients who were considered for longer trials and in the elderly. The inconvenience of in-person visits likely reaches beyond travel distance and transportation arrangements alone; for example, in women especially, there may be the need to arrange child care to attend a study visit (15).

Many patients in our study did not provide specific reasons for declining RCT participation, suggesting that patients are often not transparent in their attitudes toward RCTs in practice. Patient fear of random assignment to treatment (decision made by "the computer") and research risks, engrained with elements of mistrust, present formidable challenges in RCT recruitment (33). In women, particularly, the perceived risk of harm from research has been linked to reluctance to participate in RCTs (34,35). Given that public exposure to research may be skewed by sensational media reports of error or duplicity, a continuing mission of the research community is to provide a more balanced perspective by raising awareness regarding the robust mechanisms in place to protect human research subjects and ensuring that they are implemented.

In many cases, trial team and provider perceptions of a patient may play a primary role in the participation outcome, including perceptions regarding adherence, substance use, clinical status, or other factors, which together accounted for 45% of patients who did not participate in a RCT in our sample. Limiting enrollment of such patients, who may be less likely to adhere to the study protocol, is an important consideration in many RCTs. However, it is important to note that barriers to RCT participation perceived by the trial team and providers are often based on overall impressions rather than formal criteria, and their importance varies based on trial follow-up requirements. Ultimately, targeting these issues in future RCTs may promote more balanced representation of patient subgroups and strengthen the efforts of the American College of Cardiology's Coalition to Reduce Disparities in Cardiovascular Care and Outcomes (CREDO) group aimed at achieving equitable care and outcomes for all patients, regardless of race, ethnicity, sex, and age (36).

Implications for future clinical trial design and conduct. Given our results, it is important for the clinical trial community to consider whether a study question could be reliably answered with less intensive testing or through a study of shorter duration. If this is not possible, minimizing inconvenient in-person visits could potentially improve participation. For example, a recently launched longitudinal study is using centralized follow-up telephone interviews instead of multiple patient trips to the research center (37). In the modern era, creative follow-up solutions can be explored; for example, patients may directly interact via Internet and mobile technologies to efficiently and conveniently provide follow-up information.

Practical solutions to trial design and conduct that integrate the research enterprise with clinical care and medical education will likely be most successful. For instance, using trial activities as a venue to provide clinical information to patients, providers, and community members enhances health care quality in real time (36). Informatics systems that integrate trial data with existing electronic medical records could augment the availability of patient information at the point of care while increasing the efficiency of research data collection. Such integration may allow for efficient tracking of patient status and reassessment of trial candidacy after clinical stabilization, as well as more objective identification of likely nonadherent patients (e.g., no-show rate for outpatient appointments). A further advantage of informatics systems that bridge the clinical and research enterprises is the increased ability to expose and engage physicians early in their medical education to clinical research. In appropriate circumstances, research participation might become part of routine care (38) or randomization may be clustered at the site level (39) to alleviate the burden of additional work associated with informed consent.

Study limitations. First, our study setting was a single academic medical center in the southeastern United States with a high volume of cardiovascular RCT research, and we explored only participation in cardiovascular RCTs. Therefore, our results may not be generalizable to other institutions in other locations in the United States or abroad or to participation in RCTs in other therapeutic areas. Second, all patients in our study had access to a RCT; we did not address challenges to enrollment at the provider level (i.e., providers as gatekeepers). Third, this was an observational study, precluding direct assessment of causality, and unmeasured confounders are possible in this observational analysis. Fourth, regarding variables themselves, educational attainment and income were based on population representative levels according to ZIP code as opposed to direct report by patients.

Conclusions

Among patients presenting to a high-volume academic medical center in the southeastern United States who were considered potentially eligible for RCT participation after an initial screen against medical eligibility criteria, we identified multiple potentially actionable barriers to participation. While age, sex, and state of residence were associated with not participating, longer trial duration and intensive testing were the factors most significantly related to RCT participation. One major implication of our study is the need for innovative RCT designs using integrative approaches and emerging technologies to foster convenience and thereby facilitate greater RCT participation.

Acknowledgments

The authors thank Duke's Cardiovascular Research Study Coordinators, including Carolyne Rotich, Chandra McNeill, and Bernadette Druken, and Duke's Decision Support Repository Team for helping compile the data for this study.

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Key Words: trial enrollment ■ trial participation ■ trial representation.

APPENDIX

For supplemental Methods, Results, and References section, as well as a figure, please see the online version of this article.