



## **Trends in Consent for Clinical Trials in Cardiovascular Disease.**

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# Trends in Consent for Clinical Trials in Cardiovascular Disease

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**Background**—Cardiovascular clinical trials depend on patient enrollment. Enrollment rates appear inadequate, but little is known about how frequently patients accept or decline offers of enrollment. The objective of this study was to assess trends and predictors of patient acceptance of offers to enroll in clinical trials for cardiovascular disease.

**Methods and Results**—We utilized an established database containing all randomized, controlled trials ( $n=1224$ ) in cardiovascular disease published between 2001 and 2012 in the 8 highest-impact general medical and cardiology journals. Studies were eligible if the number of patients approached and number of patients declining enrollment could be ascertained from published materials. All studies were screened for eligibility. Each eligible study was reviewed by 3 co-authors. All discrepancies were resolved by the group. The main outcome was acceptance rate, defined as the number of patients enrolled divided by the number patients who were eligible and approached. Only 21.7% ( $n=266$ ) of studies provided information sufficient to assess patient enrollment and refusals. The median acceptance rate across trials was 83.2%. Significant predictors of higher enrollment included: enrollment in the acute setting ( $P=0.031$ ); geographical region ( $P<0.001$  for group); and trial sponsorship ( $P=0.006$  for group).

**Conclusions**—Rates of reporting data sufficient to calculate acceptance rates are low. This compromises the ability to identify drivers of low enrollment and assess trial generalizability. However, the high rates of acceptance observed suggest that factors other than patients' decisions may be the primary drivers of declining rates of trial enrollment. (*J Am Heart Assoc.* 2016;5:e003582 doi: 10.1161/JAHA.116.003582)

**Key Words:** clinical trial • informed consent • recruitment • research ethics • trials

Evidence-based medicine depends upon patient enrollment and retention in clinical trials. Unfortunately, there are alarming challenges. According to a recent Institute of Medicine report, 40% of National Cancer Institute–funded trials do not complete enrollment.<sup>1</sup> Enrollment rates in cardiovascular trials have also declined.<sup>2</sup> The Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction trial, for example, enrolled an average of only 1 patient per center every 6.25 months.<sup>3</sup> Poor enrollment delays valuable data, compromises generalizability, can skew outcomes, and can drive outsourcing of research.<sup>4</sup>

Potential sources of low enrollment include rising costs, competing demands on clinicians, regulatory barriers, restrictive eligibility criteria, and cultural attitudes toward research. Most directly, eligible patients may decline enrollment.<sup>5</sup> Some data suggest that factors such as intensive testing or long trial duration may discourage enrollment.<sup>6</sup> However, the frequency with which patients decline participation in cardiovascular trials and reasons for these decisions remain understudied. This information is critical to addressing low enrollment and has important ethical implications regarding informed consent and shared decision making. In this study, we examined rates of patient acceptance in cardiovascular trials over a 12-year period.

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## Methods

### Clinical Trial Identification

We utilized a database of randomized, controlled trials in cardiovascular disease published in the 8 highest-impact general medicine and cardiology journals between 2001 and 2012.<sup>7</sup> As previously described, researchers selected publications through a PubMed search of “trial” AND “random” and through a manual search of each journal by issue between 2001 and 2012. This yielded 4524 publications. A total of

3300 were excluded because they were observational studies, secondary publications, phase I trials, or pilot trials. The final database contained 1224 studies.

All 1224 studies were reviewed for this project. A study was eligible for inclusion if acceptance rate—the number of enrolled patients divided by number of eligible patients approached—could be identified from the manuscript or supplementary materials.

## Data Abstraction

Each eligible study was reviewed by 3 co-authors. Discrepancies in categorization were resolved by consensus with the senior author. The following data were abstracted.

*Enrolled patients* were enrolled in the trial. Patients who were subsequently excluded or withdrew after initial consent were considered enrolled.

*Decliners* were approached, but did not enroll. Patients ineligible for inclusion, considered incapacitated, or never approached were not considered decliners.

*Eligible patients approached* were patients who were eligible and approached for inclusion. Where not directly reported, the sum of decliners and enrolled patients was used.

*Enrollment setting* referred to location of enrollment decisions (inpatient, outpatient, or both).

*Acute trials* were those in which an initial enrollment decision was explicitly required or reasonably expected within 24 hours of diagnosis or admission.

*Study type* was defined by whether the study compared existing treatments, assessed a new indication, or assessed a novel treatment. Only studies of medical or procedural interventions were categorized this way.

The following additional data had been previously abstracted and defined: *disease/condition under study*, *intervention type*, *geographical region*, *funding source*, and *trial size*.<sup>7</sup> Minor refinements to the *disease/condition under study* and *intervention type* categorization systems were made in order to increase precision. Only eligible studies were reclassified.

## Statistical Analysis

Analysis was performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC). Descriptive statistics were tabulated for each characteristic. Acceptance rate was calculated by dividing the number of enrolled patients by the number of patients eligible and approached. In order to examine associations between acceptance rates and study characteristics, tests for nonparametric data were performed (Wilcoxon Mann–Whitney for dichotomous variables and Kruskal–Wallis for variables with 3 or more levels). For all analyses,

significance testing was 2-sided.  $P < 0.05$  was considered statistically significant.

## Results

Acceptance rate was determined in 266 of 1224 trials (21.7%). The frequency with which studies reported data sufficient to calculate an acceptance rate increased from 2001 (8.8%) to 2002 (26.4%), but then remained relatively constant across the 12-year period (range, 18.8–28.6%; Table 1). Reporting of these data varied appreciably across journals (range, 11.3–70.8%; mean, 21.7%; Table 2). Among journals publishing more than 100 cardiovascular trials during this period, the highest frequency of reporting was 38.7%.

The most common study conditions were coronary artery disease (21.4%) and cardiovascular risk prevention (18.4%; Table 3). More than half (53.8%) involved comparing existing treatments. Enrollment for most trials occurred in the outpatient setting (76.7%). The most common interventions studied were medications (45.5%) and procedures (18.1%). The most common geographical locations were Western Europe (43.6%) and North America (29.7%). Funding sources were evenly distributed over time.

Median acceptance of enrollment was 83.2% (Figure). Rates of acceptance were similar across journals and remained relatively constant throughout the 12-year period. No significant differences were observed based on study condition, enrollment setting, trial size, or study type (Table 3). Studies testing behavioral interventions exhibited numerically lower acceptance than those involving other types of interventions, but this difference was not significant.

**Table 1.** Temporal Trends in Reporting of Data Sufficient to Assess Acceptance Rate

Year	No. of Articles	No. Reporting	Percentage
2001	91	8	8.8
2002	103	27	26.2
2003	109	22	20.2
2004	112	23	20.5
2005	122	24	19.7
2006	101	19	18.8
2007	88	18	20.5
2008	83	22	26.5
2009	99	23	23.2
2010	117	27	23.1
2011	93	23	24.7
2012	106	30	28.3
Total	1224	266	21.7

**Table 2.** Journal-Level Frequency of Reporting Data Sufficient to Calculate Acceptance Rate

	Percent of Trials Reporting Data Sufficient to Calculate Acceptance Rate	No. of Trials Reported in 12-Year Period*
#1	68.4	n<100
#2	70.8	
#3	12.7	n>100 <sup>†</sup>
#4	13.1	
#5	18.1	
#6	19.5	
#7	21.3	
#8	38.7	
Total	21.7	1224

\*Journals grouped based on publication of greater than or fewer than 100 articles during the study period. Names withheld in order to protect journal identity.

<sup>†</sup>Chi-square test for trend;  $P<0.001$ .

Acceptance was higher in studies where enrollment occurred in acute settings (86% vs 77%;  $P=0.031$ ). Acceptance was highest in Western Europe (83%) and lowest in North America (69%;  $P<0.001$  for group comparison). Acceptance was also higher in trials sponsored by industry (80%) or with mixed funding (79%) compared to those sponsored by government (72%) or institutions (71%).

The distribution of disease/condition under study—using the previous categorization scheme, which had been applied to all studies—was compared among studies reporting and not reporting acceptance rates. Among those reporting acceptance rates, there were fewer studies focusing on acute coronary syndrome, coronary artery disease, and heart failure, and there were more “general” studies, many of which were prevention focused (Table 4).

## Discussion

Using a large database of trials published in high-impact journals, this study provides novel insights into rates of acceptance of enrollment in cardiovascular trials. Most important, it demonstrates that reporting is poor. Acceptance rates could be calculated in fewer than 22% of studies and was variable across journals. Given concerns about declining enrollment, the dependence of evidence-based progress on trials, and the relevance of acceptance rates for interpreting generalizability, this finding is problematic. Notably, this information is contained in the recommended CONSORT (Consolidated Standards Of Reporting Trials) diagram, though it may be overlooked because it is not in the CONSORT checklist.<sup>8</sup> The key data that need to be present in order to facilitate assessment of acceptance rates within trials are: the

number of patients determined to be eligible for inclusion; the number approached to participate; and the number (among those eligible and approached) who declined to participate. Common problems encountered in this study included considering consent as an eligibility criterion and “bundling” of the number who declined to participate with other reasons for exclusion. Many of these problems are easily addressable through more granular reporting.

This analysis did demonstrate surprisingly high rates of acceptance among studies reporting relevant data. Similar data have not been published in cardiovascular disease, and there are limited published comparative data from other fields. One meta-analysis of acute lung injury trial enrollment suggests an acceptance rate (enrolled/enrolled+declined) of 71%.<sup>9</sup> However, reported acceptance rates in oncology trials appear to be generally under 50%.<sup>10</sup> Infrequent reporting likely biases our study’s sample and complicates assessments of whether these rates reflect reality. In addition, some patients who elect not to participate in a trial will not be captured by traditional reporting. For example, protocols may record acceptance rates based only on participants that present for screening visits and may not include individuals who choose not to be screened. Similarly, if a patient’s primary cardiologist recognizes that a patient with stable angina is eligible for an ongoing trial, but the patient does not want to be referred for the trial, that patient will not be represented. Reported acceptance in these studies may thus be inflated, because individuals who are never formally screened and asked to participate will not be counted as decliners. Nonetheless, our data do raise questions about whether patient refusal is really driving systemically low enrollment. If these data are at all representative, it appears that other factors may be more important. These may include: lack of motivation or conflicting duties of clinicians; inadequate funding, incentives, or infrastructure for investigators; failure to integrate trials into care delivery; negative perceptions of industry; and inadequate incentives for study staff.<sup>5</sup>

Several relationships warrant further study. First, acceptance was highest in acute settings. This may have been driven by lower representation of behavioral studies in the acute setting, and behavioral studies’ lower acceptance rates may be a result of the fact that they often require greater “agency” on the part of the participant. However, an increased rate of acceptance in acute studies also coheres with observations that decision making and the nature of consent likely differ in more-acute settings.<sup>11,12</sup> Specifically, the presence of significant time pressure, stress, and physical symptoms likely limits patients’ understanding of clinical trials for which they are eligible and may change the nature of their decision making. Second, markedly different acceptance between Western Europe and the United States underscores perceptions that cultural factors play a role in enrollment

**Table 3.** Characteristics of Randomized, Controlled Cardiology Trials Between 2001 and 2012 Reporting Enrollment Statistics (n=266)

	N (%)	Acceptance Rate (SD)	P Value
<b>Disease</b>			
Acute coronary syndrome	31 (11.7)	0.80 (0.19)	0.214
Arrhythmias	29 (10.9)	0.79 (0.22)	
Coronary artery disease	57 (21.4)	0.80 (0.19)	
Heart failure/cardiomyopathy	20 (7.5)	0.74 (0.18)	
Hypertension	19 (7.1)	0.73 (0.24)	
Stroke	4 (1.5)	0.63 (0.23)	
Venous thromboembolism	20 (7.5)	0.82 (0.19)	
Valvular	3 (1.1)	0.89 (0.08)	
Vascular	21 (7.9)	0.77 (0.18)	
Prevention	49 (18.4)	0.72 (0.22)	
Other	13 (4.9)	0.84 (0.14)	
<b>Acuity</b>			
Not acute	236 (88.7)	0.77 (0.21)	0.031
Acute	30 (11.3)	0.86 (0.17)	
<b>Enrollment setting</b>			
Inpatient	55 (20.7)	0.80 (0.16)	0.248
Outpatient	204 (76.7)	0.77 (0.21)	
Both	7 (2.6)	0.78 (0.16)	
<b>Intervention</b>			
Device	10 (3.8)	0.83 (0.09)	0.085
Medication	121 (45.5)	0.79 (0.20)	
Procedure	48 (18.1)	0.80 (0.33)	
Surgery	20 (7.5)	0.78 (0.17)	
Testing/imaging	14 (5.3)	0.80 (0.21)	
Behavioral	33 (12.4)	0.69 (0.20)	
Other	20 (7.5)	0.71 (0.20)	
<b>Year</b>			
2001	8 (3.0)	0.82 (0.18)	0.747
2002	27 (10.2)	0.77 (0.20)	
2003	22 (8.3)	0.74 (0.21)	
2004	23 (8.7)	0.78 (0.15)	
2005	24 (9.0)	0.77 (0.26)	
2006	19 (7.1)	0.83 (0.15)	
2007	18 (6.8)	0.80 (0.13)	
2008	22 (8.3)	0.80 (0.18)	
2009	23 (8.7)	0.71 (0.23)	
2010	27 (10.2)	0.74 (0.23)	
2011	23 (8.7)	0.79 (0.24)	
2012	30 (11.3)	0.81 (0.19)	

Continued

**Table 3.** Continued

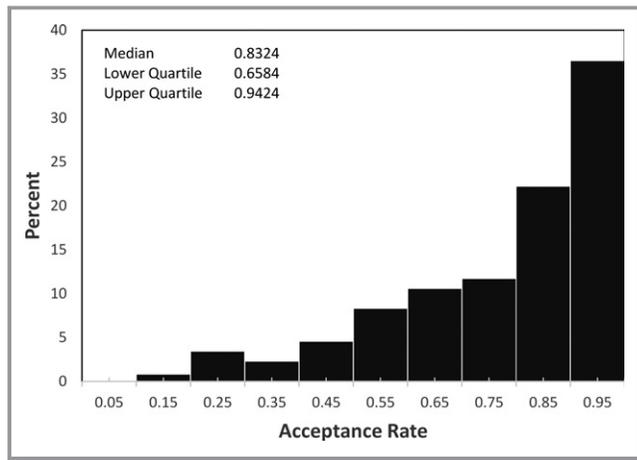
	N (%)	Acceptance Rate (SD)	P Value
<b>Region*</b>			
Central/South America	3 (1.1)	0.65 (0.16)	<0.001
Mixed	49 (18.4)	0.81 (0.18)	
North American	79 (29.7)	0.69 (0.22)	
Western Europe	116 (43.6)	0.83 (0.18)	
Eastern Europe	1 (0.4)	0.83	
Rest of the World	18 (6.8)	0.78 (0.20)	
<b>Trial size</b>			
15 to 130	65 (24.4)	0.77 (0.22)	0.642
131 to 341	68 (25.6)	0.79 (0.20)	
342 to 825	66 (24.8)	0.75 (0.21)	
≥826	67 (25.2)	0.80 (0.17)	
<b>Sponsor</b>			
Industry	74 (29.6)	0.80 (0.20)	0.006
Government	55 (22.0)	0.72 (0.22)	
University/organization	86 (34.4)	0.71 (0.20)	
Mixed <sup>†</sup>	35 (14.0)	0.79 (0.18)	
Missing	16 (6.0)		
<b>Design</b>			
Superiority vs treatment	168 (63.2)	0.78 (0.19)	0.961
Noninferiority	11 (4.1)	0.80 (0.16)	
Superiority vs placebo	87 (32.7)	0.76 (0.22)	

\*Trials were categorized by the region(s) in which study site(s) were located. "Rest of the world" is defined as countries outside of Europe or the Americas.

<sup>†</sup>If 2 or more of the listed sources were identified.

decisions and highlights the need to expand education in the United States regarding the importance of trials to health system improvement. Third, enrollment rates did not differ based on whether trials were testing existing or novel therapies. This finding is interesting in the context of ongoing discussion about whether patients view consent for comparative effectiveness studies, for example, differently from other trials.<sup>13–16</sup> Finally, observed higher rates of acceptance in industry-funded trials compared with trials funded by government or other traditionally nonprofit entities warrant further study to assess the extent to which this is driven by structural considerations, such as clinical site reimbursement.

The most practical implication of these data is a need for routine reporting of acceptance rates in order to assess generalizability and identify successes and challenges in recruitment. These data can be easily included in CONSORT diagrams, and variability in inclusion of these data suggests the potential to address this issue, to a large extent, at the journal level. Although individuals who do not come to



**Figure.** Observed rates of patient acceptance of trial enrollment.

screening visits or are never formally “approached” will never be captured by this mechanism, these data would be of substantial value to the scientific community.

The principal finding—the low rate of reporting relevant acceptance data—is this study’s principal limitation and can be remedied only by addressing this problem. Whereas the key data to facilitate assessment of acceptance rates should be straightforward to report, an important element of improving reporting may be the provision of adequate support to ensure rigorous and consistent documentation of screening activities. A second potential limitation is the restriction to high-impact journals. However, infrequent reporting suggests that patient acceptance rate is unlikely to drive publication

decisions, and there is no reason to suppose that lower-impact journals are more likely to require these data. Third, differences in distribution of conditions under study between reporting and nonreporting studies may reveal some selection bias; however, all major categories of conditions were reasonably represented in both groups. Fourth, we do not have data from studies that were never published, and we did not specifically examine relationships between acceptance rates and premature termination. Fifth, we did not extract detailed data regarding study features, such as frequency of follow-up, the nature of study-required procedures, or length of participation that may affect willingness to participate. Finally, these data are insufficiently granular to analyze individual enrollment decisions or site-level variability. As a result, they cannot provide specific guidance regarding recruitment practices for individual patients or populations. Embedding prospective studies within future trials could substantially enrich understanding in these areas by identifying patient-level drivers of acceptance or refusal and identifying practices that optimize enrollment and alignment of decisions with patients’ preferences.

In conclusion, rates of reporting data regarding trial acceptance are problematically low and should be improved in order to understand the extent to which patients’ decisions drive patterns of trial enrollment and the extent to which trial populations are generalizable. However, the high rates of acceptance observed suggest that other systemic issues may play a larger role in driving patterns of low enrollment.

**Table 4.** Distribution of Disease Categories by Complete Acceptance Data Versus Incomplete Acceptance Data

Disease	Complete Acceptance Data (n=266)	Incomplete Acceptance Data (n=958)
	N (%)	N (%)
Acute coronary syndrome	27 (10.2)	158 (16.5)
Arrhythmias	30 (11.3)	85 (8.9)
Coronary artery disease	54 (20.3)	257 (26.8)
General	66 (24.8)	127 (13.3)
Heart failure	19 (7.1)	130 (13.6)
Hypertension	18 (6.8)	35 (3.7)
Stroke	1 (0.4)	22 (2.3)
Venous thromboembolism	20 (7.5)	50 (5.2)
Vascular	16 (6.0)	39 (4.1)
Lipids	15 (5.6)	55 (5.7)
Total	266	1224

Fisher exact test; P=0.041.

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