

# Reporting the Recruitment Process in Clinical Trials: Who Are These Patients and How Did They Get There?

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**Background:** A common criticism of randomized, controlled trials (RCTs) is that the enrollment process may be highly selective and those who enroll may not represent persons in the general population. The recruitment process reported in published RCTs has not been systematically evaluated.

**Objective:** To determine whether published RCTs report information about how their study sample was assembled and to describe the proportion of potential study participants who were actually enrolled.

**Design:** Cross-sectional explicit review of RCTs published in four high-impact medical journals between 1 April 1999 and 1 April 2000. All RCTs involved interventions in humans.

**Measurements:** The number of persons who were screened for eligibility, the number who were eligible, and the number who were enrolled in each RCT.

**Results:** A total of 172 RCTs were reviewed. Ninety (52%) re-

ported the number of persons who were evaluated by the investigators for eligibility, and 74 (43%) reported the number of persons who were actually eligible for participation. Of the studies that reported quantitative recruitment information, the median proportion of screened persons who were eligible for participation was 65% (interquartile range, 41% to 82%) and the median proportion of eligible persons who enrolled was 93% (interquartile range, 79% to 100%). Some trials reportedly enrolled every person screened for eligibility; others screened as many as 68 people for each person finally enrolled.

**Conclusions:** Many RCTs published in major medical journals do not provide information about the patient recruitment process. As a result, it is difficult for readers to gauge the extent to which participants may represent a highly selected subgroup.

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Randomized, controlled trials (RCTs) are frequently hailed as the gold standard of study designs for determining the efficacy of different interventions (1). The adequacy of reporting in RCTs has received increased attention during the past decade, because some reviews have suggested that investigators often do not report enough methodologic information to allow readers to effectively assess their studies (2–5). Meetings held by journal editors and investigators in the mid-1990s culminated in the publication of the Consolidated Standards of Reporting Trials (CONSORT) statement in 1996 (6). These guidelines primarily focused on information relevant to the internal validity of trials. They required detailed information about entry criteria, method of randomization, patient follow-up, outcome assessment, and analytic plan (6–8).

The CONSORT initiative has been criticized for underemphasizing the issue of external validity by failing to require authors to report information about the source population, when feasible (9). Before using the results of an RCT for treating an individual patient, a clinician must determine whether his or her patient differs from those who participated in the trial in a meaningful way. Therefore, it is important to evaluate how the RCT sample was assembled from the general population (10). This trial recruitment process can be described with qualitative and quantitative data, both of which can contribute important information about the generalizability of the RCT.

After selecting a condition of interest, investigators must decide which people are potentially eligible to participate, that is, the target population. The definition of the target population can have a significant impact on the gen-

eralizability of the study. For example, when recruiting people for a study of hypertension, investigators could target patients in hypertension clinics, the patients of primary care physicians, or previously undiagnosed persons who were identified as being hypertensive at community screenings. After defining the target population, the investigators must engage a subgroup of this population by identifying and approaching these potential participants (Figure).

The next steps in the recruitment process, which can be described with readily available quantitative data, can also have a significant impact on generalizability (Figure). If only a small proportion of potential participants eventually enroll in a study, the concern arises that participants differ from nonparticipants as a result of eligibility criteria or other factors. Potential participants undergo eligibility screening to determine who is eligible for participation (this proportion is termed the *eligibility fraction*) (Table 1). Persons who are eligible for participation (Figure) are then asked to provide informed consent and enroll in the study (this proportion is termed the *enrollment fraction*). The product of these two fractions represents the proportion of potential participants who actually enrolled in the study (termed the *recruitment fraction*) (Table 1).

Using a standardized abstraction instrument, we assessed whether the quantitative enrollment experience was being reported clearly in RCTs published in four high-impact medical journals. We also analyzed the available data to estimate whether trial enrollees represented a highly selected population and to gain insight into the methods for reporting the recruitment process.

## METHODS

### Sources of Data

Using four journals and selecting only investigations involving interventions in humans, we reviewed all RCTs published in a 1-year period starting 1 April 1999. We conducted a manual search of all articles published under the following headings: articles (*Annals of Internal Medicine*), original contributions (*The Journal of the American Medical Association*), original research (*The Lancet*), and original articles (*The New England Journal of Medicine*). Because we wanted to study the enrollment process on an individual basis, only RCTs that involved individual people as the unit of randomization (rather than a hospital or region, for example) were included. Subgroup or follow-up analyses of a previously published study, reports of the results of multiple RCTs in a single article, and investigations of diagnostic strategies (rather than therapeutic interventions) were also excluded.

### Data Collection

Articles were screened, selected, and abstracted by two independent investigators using a standardized abstraction instrument. Results were compared by a third party, and disagreements were resolved by consensus. We recorded the following information: journal, sources of support, type of intervention, clinical area, and number of people who were screened (to determine whether they were eligible). We used a strict definition of the number of people screened in our quantitative analysis of the eligibility and recruitment fractions. Only RCTs that reported the number of potential participants in a specific target population were included in this portion of the analysis. For example, in a trial of antihypertensive therapy, investigators evaluated 10 000 adults in the general population and identified 1000 with hypertension who were then evaluated for trial eligibility. We used 1000 as the number of patients screened.

### Context

The value of randomized, controlled trials often depends on generalizability of the findings. However, persons recruited for these studies may not be representative of the population of interest.

### Contribution

Randomized, controlled trials recently published in four high-impact medical journals were reviewed to evaluate the recruitment process. Only half of the trials reported the number of persons who were evaluated for eligibility, and 43% reported how many were actually eligible. The proportion of screened potential participants who were eligible and actually enrolled varied widely.

### Implications

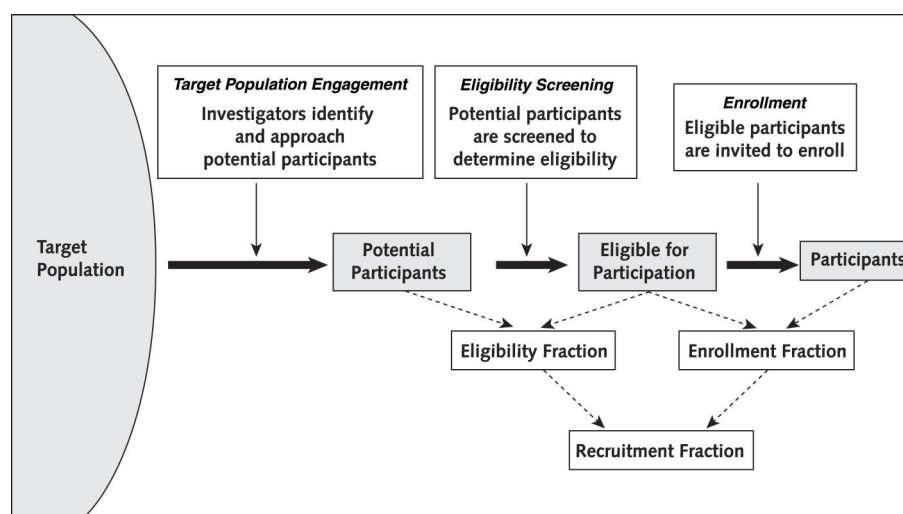
Because the patient recruitment process is often poorly delineated, it is difficult to judge the generalizability of findings reported in many randomized, controlled trials.

—The Editors

We also abstracted information on the number of patients who were eligible, the number who were eligible but declined enrollment, the number who actually enrolled, and the mortality rate in the control group. Information about eligible nonparticipants was also recorded, when available. The type of intervention for each trial was categorized as pharmaceutical therapy, behavioral therapy, surgery, nonsurgical procedures, and other. Studies were also categorized by source of support: pharmaceutical industry, government, foundation, and other.

The eligibility and enrollment fractions were defined, and the recruitment fraction was defined as the product of these fractions (Table 1 and Figure): the proportion of potential participants who were approached by the investi-

Figure. The trial enrollment process.



**Table 1. Trial Recruitment Terminology**

Term	Definition
Target population	Location and characteristics of potentially eligible persons; represents the individuals to whom the trial's results are expected to apply
Eligibility fraction	Proportion of potential participants who undergo screening and are eligible to enroll
Enrollment fraction	Proportion of people who are eligible for participation and who actually enroll
Recruitment fraction	Proportion of potential participants who actually enroll

gators and who subsequently enrolled. The number needed to screen to identify one person who would actually enroll in a trial was calculated by dividing 1 by the recruitment fraction. Finally, to develop a proxy for disease severity, we grouped the RCTs according to the mortality rate in their control groups.

### Statistical Analysis

Results were summarized and reported as proportions; a chi-square test was used to evaluate differences among groups. We used an adaptation of the Wilcoxon rank-sum test as a nonparametric test for trend across ordered groups to determine whether there was an association between recruitment fraction and mortality rate in the control group (11). We used Spearman rank correlation coefficients as well as *t*-tests to determine whether the number needed to screen for each patient enrolled was related to study size, source of funding, or type of control intervention. We also used an analysis of variance (ANOVA) model for multiple group comparison tests to identify differences in the number needed to screen among groups.

## RESULTS

We identified 215 RCTs. A total of 43 were excluded for the following reasons: They were subgroup analyses or follow-up studies of previously reported RCTs ( $n = 24$ ), the unit of randomization was not individual persons ( $n = 11$ ), multiple studies were reported simultaneously ( $n = 5$ ), diagnostic strategies were investigated ( $n = 2$ ), or in vitro methods were used ( $n = 1$ ). The analysis comprised the remaining 172 RCTs (Table 2). The median number of participants was 257 (range, 18 to 54 654). Approximately two thirds of the studies were carried out in several settings (multicenter), and about half were sponsored by industry. Pharmaceutical agents (70% of the studies) were by far the most common intervention used.

### Reporting the Recruitment Process

About one half of the published RCTs (90 of 172) reported information about the number of potential participants that were screened by the investigators for eligibility; the rate of reporting did not differ across the four journals (Table 2). We found no significant association between reporting the number of people screened and the size of the study (number of participants) or whether trials

were multicenter in design, industry sponsored, or performed by investigators outside the United States. However, we found that trials in which the mortality rate in the control group was less than or equal to 5% were significantly more likely to provide some screening information (59%) than other trials (37% and 40% for the intermediate and highest mortality groups, respectively) ( $P = 0.04$ ).

The number of people who were eligible for participation was reported in 74 studies (43%). Larger studies were less likely to report this information, although the difference was not significant. Multicenter trials were much less likely to report the number of eligible participants (34%) than were single-center trials (59%) ( $P = 0.002$ ). Reporting this information was not associated with industry sponsorship, type of intervention, whether the study was done outside the United States, or mortality rate in the control group. Few trials systematically screened all people in a specific location; we found that 31 of the RCTs (18%) screened a "consecutive series" of people who presented to the investigators' institutions for care.

### Recruitment Data

Only 49 trials (28%) reported enough data to calculate the eligibility fraction. In these studies, the median proportion of potential participants who were found to be eligible for enrollment was 64.6% (interquartile range, 41.3% to 82.2%) (Table 3). In the 74 studies that reported eligibility data, a median of 93.2% of eligible people enrolled (interquartile range, 78.8% to 100%) (Table 3). A total of 20 studies reported that 100% of eligible patients enrolled. There was no association between 100% participation and the number of eligible people ( $P > 0.2$ ), the number of enrolled people ( $P > 0.2$ ), or mortality rate in the control group ( $P > 0.2$ ). Only 40 of the remaining 54 studies provided complete information about the people who were eligible but did not enroll. Declining to participate was the most common reason for nonenrollment (mean, 86% of nonenrolled people in these studies), followed by loss to follow-up (5.8%), clinical deterioration before randomization (4.9%), and physician refusal (0.6%).

The overall recruitment fraction varied greatly across studies. In the 81 RCTs (47%) that provided adequate data for analysis, the median recruitment fraction was 54.0% (interquartile range, 32.0% to 77.1%). The median number needed to screen to identify one enrollee was 1.8 (range, 1 to 68). In summary, some investigators reported that they enrolled every potential participant screened, whereas other investigators needed to screen as many as 68 potential participants for each person they finally enrolled.

We also investigated whether the recruitment fraction was associated with characteristics of the studies or the conditions under investigation. We found no significant relation between recruitment fraction and the type of intervention studied, type of control intervention, industry sponsorship, study size, or involvement of multiple (rather

Table 2. Reporting of Enrollment Process by Study Characteristic

Characteristic	Total Trials	Trials That Reported Number of Patients Screened*	
		n (%)	
Total	172 (100)	90 (52)	74 (43)
Journal			
<i>Annals of Internal Medicine</i>	9 (5)	6 (67)	4 (44)
<i>The Journal of the American Medical Association</i>	25 (15)	15 (60)	12 (48)
<i>The New England Journal of Medicine</i>	58 (34)	26 (45)	16 (28)
<i>The Lancet</i>	80 (47)	43 (54)	42 (52)
Number of enrollees			
<110	45 (26)	20 (44)	22 (49)
110–260	42 (24)	28 (67)	22 (52)
260–650	44 (26)	21 (47)	17 (39)
>650	41 (24)	21 (51)	13 (32)
Multicenter trial			
Yes	111 (63)	55 (50)	38 (34)
No	61 (37)	35 (57)	36 (59)
Industry sponsored			
Yes	91 (53)	45 (49)	35 (38)
No	81 (47)	45 (56)	39 (48)
Study location			
United States	65 (38)	37 (57)	27 (42)
Other countries	78 (45)	42 (54)	35 (45)
United States and other countries	29 (17)	11 (38)	12 (41)
Intervention studied			
Surgery	6 (4)	3 (43)	4 (67)
Nonsurgical procedure	11 (6)	7 (64)	5 (45)
Pharmaceutical therapy	120 (70)	57 (48)	46 (38)
Behavioral therapy	27 (16)	18 (67)	13 (48)
Other	8 (5)	5 (62)	6 (75)
Control group mortality rate			
≤5%	117 (68)	69 (59)	52 (44)
5%–20%	30 (17)	11 (37)	11 (40)
≥20%	25 (15)	10 (40)	10 (40)

\*  $P = 0.038$  for multigroup comparisons for control group mortality rates (analysis of variance).

†  $P = 0.032$  for multigroup comparisons for journals (analysis of variance).  $P = 0.002$  for multicenter trials (chi-square test).

than single) centers; comparisons were made by using an analysis of variance model (Table 4). However, we found a relation between recruitment fraction and study mortality rate. Studies with the highest mortality rate in the control group had a significantly higher median number needed to screen (3.6) than those with intermediate (number needed to screen, 1.7) or low (number needed to screen, 1.8) mortality rates ( $P = 0.016$  for multigroup comparison).

## DISCUSSION

We found sporadic and incomplete reporting of the recruitment process in many RCTs. This would make it difficult for readers to gauge the generalizability of the trial results. Only 52% of the RCTs that we reviewed reported the number of people screened for eligibility, and only 43% reported the number of people who were eligible. In the few articles that provided a quantitative assessment of their recruitment process, we found marked variation in the proportion of people who were eligible and the proportion who were enrolled. This variation underscores the importance of making these valuable data available to all persons involved with health care, including clinicians, patients, and policymakers.

One of the RCTs in our sample provides an excellent example of how a thorough description of a trial's recruitment process can inform subsequent decision making. In the Prolyse in Acute Cerebral Thromboembolism (PRO-ACT) II trial, patients with acute ischemic stroke of less than 6 hours in duration were randomly assigned to an intra-arterial thrombolysis group or a control group (12). The patients who were assigned to the thrombolysis arm of the study experienced a superior clinical outcome at 90 days. The investigators provided meticulous detail about the patient recruitment process, describing how 12 323 patients with acute ischemic stroke were screened. Patients were excluded ( $n = 10\,893$  [83% of total]) if they presented more than 6 hours after the onset of symptoms

Table 3. Actual Recruitment and Enrollment

Data	Trials That Reported Data	Median	Interquartile Range
	n	%	
Eligibility fraction	48	64.6	41.3–82.2
Enrollment fraction	74	93.2	78.8–100
Recruitment fraction	81	54.0	32.0–77.1

Table 4. Relation between the Number of Patients Needed to Screen for Enrollment and Trial Characteristics

Characteristic	Total Trials, <i>n</i>	Median Number Needed to Screen to Identify One Participant (Interquartile Range)	<i>P</i> Value*
Total	81	1.8 (1.3–3.1)	
Journal			0.2
<i>Annals of Internal Medicine</i>	6	2.1 (1.7–2.4)	
<i>The Journal of the American Medical Association</i>	12	2.8 (1.7–4.3)	
<i>The New England Journal of Medicine</i>	37	1.6 (1.2–2.2)	
<i>The Lancet</i>	26	2.4 (1.6–3.8)	
Number of enrollees			>0.2
<110	20	1.7 (1.3–2.6)	
110–260	26	2.0 (1.3–3.3)	
260–650	19	2.4 (1.5–3.9)	
>650	16	1.7 (1.1–2.8)	
Multicenter trial			0.16
Yes	49	2.3 (1.5–3.6)	
No	32	1.7 (1.3–2.4)	
Industry sponsored			>0.2
Yes	42	2.2 (1.3–3.3)	
No	39	1.7 (1.3–2.9)	
Intervention studied			>0.2
Surgery	2	1.4 (1.0–1.7)	
Nonsurgical procedure	7	2.4 (1.2–2.8)	
Pharmaceutical therapy	53	2.2 (1.3–3.4)	
Behavioral therapy	15	1.6 (1.3–2.5)	
Other	4	2.0 (1.5–2.5)	
Type of control intervention			0.14
Inactive or placebo	43	1.8 (1.3–3.3)	
Active	38	2.0 (1.3–3.1)	
Control group mortality rate			0.016
≤5%	62	1.8 (1.3–2.8)	
5%–20%	10	1.7 (1.3–2.4)	
≥20%	9	3.6 (2.5–5.4)	

\* *P* values for multigroup comparisons were obtained by using analysis of variance.

(*n* = 4053), had mild or rapidly improving deficits (*n* = 2410), were older than 85 years of age (*n* = 696), or met any of several other clinical exclusion criteria. After an additional 8% were excluded on the basis of findings from computed tomography scans and 6% were excluded for “other” reasons, 474 patients underwent diagnostic angiography. More patients were excluded on the basis of angiographic findings, and the remaining 180 patients were enrolled. For each of these 180 trial participants, the investigators had to screen approximately 68 people.

This recruitment information provides an important framework to help clinicians and other interested parties interpret this trial. The implications for clinicians caring for patients in the “real world” are that most of their patients with severe strokes may differ from trial enrollees in important ways and that they should be extremely cautious when selecting candidates for thrombolysis. These enrollment data can also be informative for policymakers. For example, persons interested in the development and application of interventions for acute stroke, either in the general population or in their own institutions, would note that the vast majority of people who have had strokes are not candidates for this intervention. It is also important to note that even after clinical exclusion, patients in the PRO-ACT II trial were far more likely to be excluded on the basis of imaging data (1413 patients) than to be eligible for

enrollment (180 patients). This emphasizes the importance of accurate and careful radiographic assessment. Public health practitioners would also benefit from the knowledge that approximately one third of patients who have had strokes arrived at the hospital too late to be considered for thrombolysis therapy, and that optimal implementation of this intervention would require aggressive social marketing to increase knowledge about strokes.

It is of concern that 20 studies reported enrolling 100% of eligible patients, because this seems implausible. An earlier survey of RCTs found that many clinical investigators defined people who declined to participate as “ineligible” (13). Therefore, it is possible that the “eligibility” criteria in some of the studies in our sample included patient willingness to enroll. This is not appropriate. Earlier studies have suggested that patients who are eligible but do not enroll may differ from trial participants in important ways (13–17).

Previous work has suggested that investigators infrequently reported enough methodologic information for readers to assess the validity of the study design or the generalizability of the results (2–5, 13, 18). After the CONSORT criteria were published in 1996, the quality of reporting in published RCTs improved substantially (19). However, the focus of these efforts was on ensuring a valid assessment of each trial’s internal validity. It is equally im-

portant to allow readers to assess generalizability, because clinicians will be more comfortable applying RCT results to their patients when the trial participants are similar to patients in the community.

The recent revision of the CONSORT guidelines encourages authors to discuss the generalizability of their results. It also includes a modified flow diagram containing the number of patients who were assessed for eligibility (20). Although this is a welcome step, it is important to note that in a recent review, only one half of published RCTs included a flow diagram (18). We suggest that the CONSORT guidelines be modified to incorporate both qualitative and quantitative information to help readers assess generalizability. The CONSORT checklist should require authors to include a definition of the study's target population. To whom do the investigators expect the results of the trial to apply? How does this target population compare with what is known about the full spectrum of people in the population with a particular condition?

It is important to understand that the eligibility fraction is based on two factors: the actual eligibility criteria and the group of patients to which these criteria are applied. For example, a study of refractory hypertension would have drastically different eligibility fractions if potential participants were screened from a hypertension clinic instead of a primary care clinic. Therefore, the CONSORT guidelines should advise investigators to describe the settings and methods used to engage potential participants as well as the rationale and implications of this choice.

Finally, the CONSORT guidelines should require investigators to make every effort to provide quantitative data about the recruitment process. It is not always feasible for all investigations, especially in large multicenter trials, to gather data about every step of the recruitment process. However, investigators should at least document how many people were identified as eligible for enrollment and report the enrollment fraction. Whenever possible, the eligibility fraction and the number of potential participants that needed to be screened to identify one enrollee should also be reported. In addition, the CONSORT guidelines should emphasize that eligibility and willingness to participate are distinct entities and should be recorded as such.

It is important to note that our review was restricted to RCTs published in four medical journals; thus, it is unclear whether our findings are generalizable to RCTs published in other journals. Nevertheless, we expect that the trials with the greatest impact would be published in these journals. Additional work, with larger sample sizes, may detect other important relationships between study characteristics and the recruitment process.

In conclusion, our analysis demonstrated that many RCTs published in high-impact journals did not provide quantitative recruitment data. To understand the internal validity of RCTs, a reader needs data that are qualitative (such as the definition of outcome measures and the

method of randomization) and quantitative (such as the proportion of participants who received their assigned treatment and were analyzed for primary outcome). Similarly, the external validity of RCTs could be more readily assessed if investigators reported qualitative information (such as the definition of the target population and the engagement process) as well as quantitative data that describe what happened when the investigators tried to recruit participants. The translation of research into practice could be done with greater confidence if patients, clinicians, and policymakers had more information about the extent to which people in the community differ from trial participants. Careful documentation of qualitative and quantitative aspects of the trial recruitment process could provide this information.

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