ECRI Evidence Report

Patients' Reasons for Participation in Clinical Trials and Effect of Trial Participation on Patient Outcomes

April 2002. Issue No. 74.

Policy Statement

This report is a short-form evidence report designed to provide a rapid and accurate overview of some aspects of patient behavior regarding clinical trials and a comparison of patient outcomes inside and outside of clinical trials. The information contained in this report derives from the currently available published, peer-reviewed scientific literature, and studies chosen for inclusion were limited to English-language publications. The recommendations and conclusions must be interpreted cautiously and judiciously. The data on which they are based often do not permit unequivocal resolution of the scientific and clinical issues most relevant to patient care. ECRI implies no warranty and assumes no liability for the information, conclusions, and recommendations in this evidence report.

ECRI believes that the sources of information used in this report are reliable and has used its best professional judgment in analyzing the data obtained, but cannot assume any liability for the accuracy or completeness of the studies undertaken by others. ECRI makes no recommendations about the applicability for an individual patient or the appropriateness of an individual insurance coverage decision. Such decisions are the responsibility of the patient, his or her physician, and the insurance carrier. This report should not be used to judge the economic value or marketplace dynamics associated with a technology for investment or other business purposes. There may be little relationship between the clinical value of a technology and the financial performance of companies associated with the technology.

The conclusions and recommendations of this report and the studies on which it is based are highly perishable and reflect the state of the art at the time this report was compiled. A multidisciplinary staff of life and physical scientists and health professionals produced this report. This report was carefully reviewed by other professionals within ECRI as well as by qualified extramural reviewers in pertinent fields before being issued as a final report. Neither ECRI nor its employees accept gifts, grants, or contributions from or consult for medical device or pharmaceutical manufacturers. This report reflects the judgment of ECRI and not necessarily those of outside reviewers.

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Overview

Participation in Clinical Trials

This report is an evidence-based supplement to ECRI's *Patient Reference Guide for Adults with a Serious or Life-Threatening Illness: Should I Enter a Clinical Trial?* (Freely available online at ECRI's Web site "Patient Information" tab at www.ecri.org.) Patients may have several questions and concerns as they consider enrolling in a clinical trial. The patient reference guide is an educational resource that explains concepts and terms that may be unfamiliar to patients, such as the phases of trials, weighing risks and benefits of trial participation, randomization, placebo controls, and double-blinding. In addition, it contains practical resources designed to assist patients with the decision of whether to participate (such as a list of questions to ask a physician). Furthermore, the guide informs patients of key issues that affect patients entering trials, such as informed consent, patient protection mechanisms, and the right to withdraw from the trial at any time.

The patient reference guide refers to research relevant to the enrollment decision. This report contains a detailed summary and analysis of that research evidence on two particular questions:

(1) *What reasons do patients give for participating and not participating in clinical trials?*
(2) *Do patients in clinical trials have better treatment outcomes than similar patients who were not in clinical trials?*

These questions do not exhaust the set of evidence-based questions that are important to patients in the decision-making process. We selected them because in our judgment they are important questions, and because our literature searches uncovered evidence that bears directly on them.

An evidence-based approach is important because it does not rely the impressions or memories of individuals. Impressions and memory are imperfect and may be subject to the biases of a particular person. This report relies on information that has been systematically collected by researchers as part of an implicit effort to overcome these imperfections and possible biases. We therefore excluded information that is potentially biased. As such, the evidence upon which this report is based is derived not merely from studies that have been published in the medical literature, but from the highest-quality studies in that literature.

For clarity of terminology, in this report we have distinguished between a "study" and a "trial." Research articles that addressed the first question are referred to as "studies." For example, a "study" might report the reasons that patients cited for why they participated in any of three cancer trials. By contrast, research articles that addressed the second question are referred to as "trials." For example, a patient might enroll in a "trial" of a new chemotherapeutic drug for the treatment of cancer.

Evidence Base

Identification of Clinical Studies

One characteristic of a good evidence-based analysis is a systematic and comprehensive search for information. Such searches distinguish ECRI's assessments from traditional literature reviews. With a less rigorous approach to identifying and obtaining literature, it is possible for a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias because we obtained and included articles according to explicitly determined a priori criteria.

We excluded some articles that we obtained because of their relatively low methodological quality. This is because the results of these articles can be misleading. We document these exclusions in the "Study Selection" section of this report. Articles that we included are discussed in the "Results" section.

To identify information for this report, we searched the following databases:

Bioethicsline (through November 2001)
Cochrane Library (through 2001, Issue 3)
ECRI Library Catalog (through December 2001)
PubMed (includes Medline, PreMedline, and HealthSTAR) (1988 through November 2001)
U.K. National Health Service (NHS) Centre for Reviews and Dissemination Web site (through November 2001)
U.S. National Institutes of Health (NIH) Web site (through November 2001)
U.S. National Library of Medicine (NLM) LocatorPlus (through November 2001)

The search strategies employed a number of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts:

Main concept: Clinical trials

Additional concepts: altruism; altruistic; attitude; attitude to health; benefit; beneficial; conflict of interest; control group; cooperative behavior; decision-making; enlist; enroll; equipoise; ethics; financial disclosure; financial ties; finder's fees; fraud; join; Helsinki; human experimentation; informed consent; insider dealing; institutional review boards; IRB; medical errors; motivation; patient acceptance of healthcare; patient compliance; patient participation; patient satisfaction; patients; physician-patient relationships; placebo effect; random allocation; recruit; risk; social perception; social values; survival; treatment outcome; truth disclosure; voluntary workers; volunteers; well-being

In addition, we hand-searched the following bibliography:

National Library of Medicine. Ethical issues in research involving human participants. National Library of Medicine. Bethesda (MD):1999; 296 p. (Current Bibliographies in Medicine; 99-3).

This resource contains 4,640 citations published between January 1989 and November 1998. It is available at http://www.nlm.nih.gov/pubs/cbm/hum_exp.html.

What reasons do patients give for participating and not participating in clinical trials?

The primary audience for the patient reference guide is patients who are considering whether to enroll in a clinical trial. We posed this question because such patients may find it helpful to know the reasons that other patients give for their decisions. We considered reasons *for* participation as well as reasons *against* participation to provide a balanced analysis.

Study Selection

We selected studies based on predetermined objective criteria. We employed these criteria to ensure that we selected articles in an unbiased manner. The criteria that we used were specifically designed to include only those studies that were most likely to have valid conclusions and be most relevant to patients considering enrollment in a clinical trial. A research analyst evaluated study design and quality of reporting without reference to the specific results reported by the study. We required studies to meet the following four criteria for inclusion in our analysis:

- Studies included mentally competent patients with an acute or chronic life-threatening illness. Only studies of life-threatening illnesses were considered because the intended audience for the patient reference guide is patients with a life-threatening illness who are considering enrollment in clinical trials.
- All patients were at least 18 years old. Parents and caregivers make decisions for entering children into clinical trials, and the reasons for such proxy decision making may not be representative of reasons given by individual adult patients.
- All patients had been asked to participate in an actual clinical trial. Studies based on patients' hypothetical decision making were not included because patients' reasons for making hypothetical choices may not accurately reflect their reasons for real decisions.
- Patients were asked to provide their own reason(s) for participating or not participating in a clinical trial. We did not consider the opinions of physicians, caregivers, family members, or any other parties regarding patients' reasons for participation. Their opinions may be different from the reasons stated by patients themselves; for this report, we adopted a purely patient-oriented approach.

Seventeen studies met the above inclusion criteria. We excluded 3 of the 17 for reasons listed in **Table 1**. These studies were qualitative and did not report numbers or percentages of patients who cited each reason.

The remaining 14 studies (**Table 2**) reported information gathered from 2,189 patients who provided reasons for participating in a trial, and 6,498 patients who provided reasons against participating in a trial. Eleven studies reported reasons for trial participation, and four studies reported reasons against trial participation (one study reported reasons for and against participation). Six studies asked questions in an open-ended format (e.g., "Why did you decide to participate?"), and nine studies asked questions in a closed-ended format (e.g., "Among the reasons listed below, select the one that describes why you decided to participate"). One study used both open- and closed-ended questions.

Seven studies permitted patients to list more than one reason, but only one of these (Hutchison(1)) asked patients to rank-order their reasons. In the remaining six studies, patients

were not asked about the relative importance of the listed reasons. Five studies addressed participation in phase I trials, and seven studies addressed participation in phase II or phase III trials (one did not report trial phase(s), and another contained a mix of phase I and non-phase I trials).

Table 1. Excluded Studies

Study	Reason for exclusion
Huizinga et al.(2)	Did not report the number or percentage of patients who gave each reason
Schutta and Burnett(3)	Did not report the number or percentage of patients who gave each reason
Searight and Miller(4)	Did not report the number or percentage of patients who gave each reason

Table 2. Study Characteristics

Author and year	Disease	n	Mean age	% female	Reasons for participation	Reasons against participation	Open-ended question	Closed-ended question	>1 reason per patient	Phase I
Taylor and Leitman (2001)(5)	Cancer	5,972	NR	NR		✓	✓		✓	NR
Jenkins and Fallowfield (2000)(6)	Cancer	185[a]	NR	69.6%[b]	✓	✓		✓		
Ling et al. (2000)(7)	Cancer	163	60[b,c]	65%[b]		✓	✓			Mix
Tomamichel et al. (2000)(8)	Cancer	31	57[c]	29%	✓			✓		✓
Yuval et al. (2000)(9)	MI	150	NR	NR	✓			✓		
Hutchison (1998)(1)	Cancer	28	55.4	39.3%	✓			✓		✓
Itoh et al. (1997)(10)	Cancer	32	58[c]	53.1%	✓			✓	✓	✓
Daugherty et al. (1995)(11)	Cancer	27	58[c]	29.6%	✓		✓	✓	✓	✓
Henzlova et al. (1994)(12)	LVD	1,162	NR	NR	✓			✓	✓	
Wilcox and Schroer (1994)(13)	Heart disease	40	65.8	45%	✓		✓		✓	
Smith and Arnesen (1988)(14)	MI	178	64[b]	31%[b]		✓		✓	✓	
Mattson et al. (1985)(15)	MI	380	54[b]	NR	✓		✓		✓	
Penman et al. (1984)(16)	Cancer	144	NR	52%	✓			✓		
Rodenhuis et al. (1984)(17)	Cancer	10	NR	40%	✓		✓			✓

Author and year	Disease	n	Mean age	% female	Reasons for participation	Reasons against participation	Open-ended question	Closed-ended question	>1 reason per patient	Phase I
Totals	**Cancer: 9 Heart: 5**	**8502**	**59**	**45%**	**11**	**4**	**6**	**9**	**7**	**5**

[a]—Jenkins and Fallowfield(6) reported 138 patients who gave reasons for participation and 47 patients who gave reasons against participation
[b]—Based on the total number of patients in the study, not the number of patients for whom reasons were reported
[c]—Median age

Mix—Ling et al.(7) included 19 trials: two were phase I, nine were phase II or later, and for eight, study phase could not be determined
n—Number of patients for whom reasons were reported

LVD—Left ventricular dysfunction; MI—Myocardial infarction; NR—Not reported

Key Study Results

The included studies reported several different kinds of results, but not all of these results were directly relevant to the question. Therefore, we only considered the relevant subset of results. These results were comprised of: (1) a set of reasons cited by patients for or against participation, and (2) for each reason, the percentage of patients who cited that reason.

Results

Reasons for participation

Table 3 shows each reason for participating in a clinical trial and the percentage of patients who reported it. Studies often used different verbal descriptions of the same general reason category. For example, Jenkins and Fallowfield(6) found that 16.3% of patients gave the reason "I thought the trial/study offered the best treatment available," whereas Tomamichel et al.(8) reported that 59% of patients participated because of the "possibility of medical benefit." Both of these reasons can be assigned to the general category "potential health benefit." In order to compare the results of different studies, ECRI assigned each specific reason to one of three general categories: potential health benefit, physician influence, and potential benefit to others (i.e., altruism). Another ECRI research analyst independently checked these assignments, and all disagreements were resolved by discussion. The category assignments appear in the rightmost column of **Table 3**.

Some studies reported more than one reason within a single general category. For example, Yuval et al.(9) found that 31% of patients gave the reason "Hoped for better treatment" and 12% of patients gave the reason "Hoped for better follow-up." ECRI assigned both of these reasons to the general category "potential health benefit." We added the two percentages to yield 43% as the percentage of patients in the Yuval et al. study who gave a reason within the general category of potential health benefit. We performed similar computations in other studies where appropriate.

Some studies permitted each patient to list more than one reason, thus the percentages in the study added to more than 100%. Due to the possibility of counting the results from a given patient more that once (which biases the data towards the reasons given by that patient), we did not add percentages in the aforementioned manner. Instead, for these studies we adopted a conservative approach and used only the highest relevant percentage for the general category. For example, in the study by Itoh et al.(10), 28% of patients cited "trust in doctor" as one of their reasons for participation and 22% cited "advice of doctor" as one of their reasons. Some patients may have cited both of these reasons. To avoid double-counting patients' reasons, we used 28% as the percentage for the general category "physician influence." We used this same process in all other studies that permitted multiple reasons per patient.

Figure 1 plots the percentages of patients (with 95% confidence intervals) who cited potential health benefit as a reason for participation. The corresponding plots for physician influence and potential benefit to others appear in **Figure 2** and **Figure 3**, respectively. These plots demonstrate the wide variability in study results. The range of percentages was 16% to 100% for potential health benefit, 0% to 70% for physician influence, and 0% to 65% for potential benefit to others. We did not include the study by Hutchison(1) in these plots because it

employed a ranking method that did not yield percentages. Daugherty et al.(11) asked both an open-ended question and a closed-ended question, so it appears twice in the figures.

To measure whether the studies reported similar results, we computed a statistic called the Q statistic. This statistic allows one to determine whether the differences among study results ("heterogeneity") are statistically significant. The value of Q increases as the heterogeneity increases. We computed Q separately for each of the three general categories: potential health benefit, physician influence, and potential benefit to others. All three values of Q were statistically significant (388.10 for potential health benefit, 72.48 for physician influence, and 964.25 for potential benefit to others; all p values <0.000001).

These statistically significant values for Q indicate that the percentage of patients who gave these reasons was different in different studies. These differences may have been caused by differences in patient characteristics or study designs. We next investigated seven potential sources of heterogeneity:

- Whether patients had cancer or heart disease
- Average age of patients
- Gender distribution of patients
- Number of patients in the study
- Whether the study used an open-ended format or a closed-ended format
- Whether patients were permitted to cite more than one reason for participation
- Whether patients had been asked about participation in a phase I trial or in a phase II or later trial

To address each of the above potential sources of heterogeneity, we conducted analyses of subgroups. As an example, consider patients' disease as a possible explanation of heterogeneity. We placed the six studies of cancer patients in one subgroup, and the four studies of heart disease patients in another subgroup. Then we computed the Q statistic separately for each subgroup. We performed similar subgroup analyses for each of the other six sources listed above.

In **Table 4**, the shaded cells indicate subgroups for which there was significant heterogeneity. For example, there was statistically significant heterogeneity among the cancer studies ($Q = 93.20$, $p < 0.000001$) as well as among the heart disease studies ($Q = 278.40$, $p < 0.000001$) regarding the percentage of patients who cited potential health benefit as a reason for participation. Based on these tests, we conclude that patients' disease was not a sufficient explanation for why the studies' results differed. We drew similar conclusions for the other six sources of heterogeneity because all analyses contained a subgroup of studies with statistically significant heterogeneity. There were some instances in which one of the two subgroups did not have statistically significant heterogeneity. However, in all of these cases, the complementary subgroup did have statistically significant heterogeneity. Therefore, no subgrouping fully eliminated all of the heterogeneity. Based on these results, we conclude that none of the seven potential explanations of heterogeneity are, by themselves, sufficient to explain the differences among the results of these studies.

The preceding analyses of subgroups considered only one variable at a time. It would be possible to investigate multiple variables simultaneously in an attempt to explain the large differences between studies' results. For example, patients' disease and patients' age could be used together to account for differences in study results, even though neither variable on its

own was sufficient. However, given the relatively small number of studies, we were unable to perform such an analysis.

Despite the heterogeneity between studies, it is informative to estimate the "typical" percentages of patients who gave reasons within the three general categories. These estimates can be reached by combining the results of the studies. A simple average, however, would not be meaningful. As shown by the heterogeneity tests, the studies' outcomes were too different to justify a simple combination of their results. Instead, we performed a more complex computation that was based on a "random effects" statistical model. This calculation allowed us to obtain crude averages in the presence of heterogeneity. We estimated average percentages of 45% for potential health benefit, 27% for physician influence, and 18% for potential benefit to others (see **Figure 4**).

Table 3. Reasons for Participation

Author	n	Reported reasons for participation	Percent of patients[a]	Reason category assigned by ECRI
Jenkins and Fallowfield(6)	147	I feel that others with my illness will benefit from the results of the trial	23.1%	Potential benefit to others
		I trusted the doctor treating me	21.1%	Physician influence
		I thought the trial/study offered the best treatment available	16.3%	Potential health benefit
		Other	41.5%	Other
Tomamichel et al.(8)	31	Possibility of medical benefit	59%	Potential health benefit
		Trust in institutional oncologist	26%	Physician influence
		Contribution to research	3%	Potential benefit to others
		Other	12%	Other
Yuval et al.(9)	150	To help research	35%	Potential benefit to others
		Hoped for better treatment	31%	Potential health benefit
		Don't know	14%	Other
		Hoped for better follow-up	12%	Potential health benefit
		Was frightened to refuse	8%	Other
Hutchison(1)	28	Might help you	Median rank 1[b]	Potential health benefit
		I had nothing to lose	Median rank 3[b]	Other
		Doctor advised you	Median rank 3[b]	Physician influence
		Might help others	Median rank 3[b]	Potential benefit to others
		Family advised you	Median rank 5[b]	Other
Itoh et al.(10)	32	No treatment benefit to myself, but wish to participate anyway	63%	Other
		Trust in doctor	28%	Physician influence[c]
		Advice of doctor	22%	Physician influence[c]
		Some treatment benefit for myself	19%	Potential health benefit[c]
		Better option than no treatment	9%	Potential health benefit[c]
		To help future cancer patients	6%	Potential benefit to others
		Family's advice	0%	Other
Daugherty et al.(11) open-ended	27	Possible therapeutic benefit	85%	Potential health benefit
		Advice or trust in a physician	11%	Physician influence
		Family pressures	4%	Other
		Altruistic reasons	0%	Potential benefit to others
Daugherty et al.(11) closed-ended	27	Possibility of medical benefit	100%	Potential health benefit[c]
		Not having a better option	89%	Potential health benefit[c]
		Trust in institution oncologist	70%	Physician influence[c]
		Trust in institution	67%	Other
		Trust in referring physician	63%	Physician influence[c]
		Trust in institutional oncology nurses	37%	Other
		Wanting to help future cancer patients	33%	Potential benefit to others[c]
		Family wanted it	30%	Other
		To be a part of research	22%	Potential benefit to others[c]

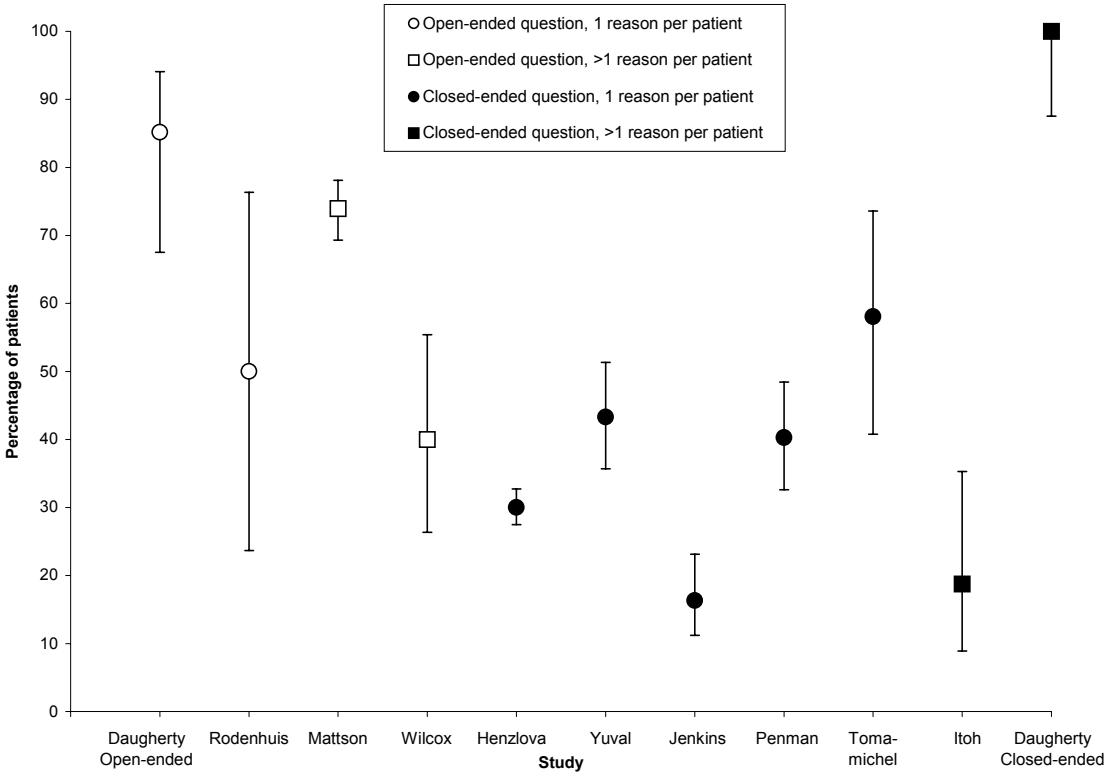
Author	n	Reported reasons for participation	Percent of patients[a]	Reason category assigned by ECRI
Henzlova et al.(12)	1162	Primary physician recommended	29%	Physician influence
		Contribute to medical science	18%	Potential benefit to others
		Live longer	18%	Potential health benefit
		Help others	10%	Potential benefit to others
		Feel better	12%	Potential health benefit
		Free care and medication	1%	Other
		Other	12%	Other
Wilcox and Schroer(13)	40	Physician influence	47.5%	Physician influence
		Improved health	40%	Potential health benefit[c]
		Coordinator influence	17.5%	Other
		Altruism	15%	Potential benefit to others
		Free care	5%	Other
		Advantage of being closely watched	2.5%	Potential health benefit[c]
		Choice of medication over surgery	2.5%	Potential health benefit[c]
		Friend	2.5%	Other
Mattson et al.(15)	380	Self-directed motivations (medical monitoring, reassurance, physical improvement)	74%	Potential health benefit
		Altruistic motivations (help others, help heart patients, research participation)	65%	Potential benefit to others
		Influence of the medical profession	20%	Physician influence
		Free medical services	16%	Other
		"Harmless"	7%	Other
		Curiosity/"Give it a try"	5%	Other
		Have time available	3%	Other
		Other/Don't know	2%	Other
Penman et al.(16)	144	Trust in physician	31%	Physician influence
		Physician's information	18%	Physician influence
		It will fight illness	15%	Potential health benefit
		It will cure illness	13%	Potential health benefit
		Will get worse without it	8%	Potential health benefit
		No better treatment	4%	Potential health benefit
		Other physicians agree	3%	Physician influence
		Trust in hospital	1%	Other
		Willing to accept the offer	1%	Other
		Family wanted it	1%	Other
		Consent form information	1%	Other
		Prior treatment same hospital	1%	Other
		Other	1%	Other
		Benefits outweigh risks	0%	Potential health benefit
		To be a part of research	0%	Potential benefit to others
		Prior treatment same physician	0%	Physician influence
		Least expensive	0%	Other

Author	n	Reported reasons for participation	Percent of patients[a]	Reason category assigned by ECRI
Rodenhuis et al.(17)	10	Hope of improvement of their diseases	50%	Potential health benefit
		Husbands had urged them to go along	30%	Other
		Not able to formulate an explicit motivation	20%	Other

[a]—In some studies, the percentages add to more than 100% because patients were permitted to list more than one reason.
[b]—Henzlova et al.(12) asked patients to rank five reasons in order of importance to the decision. The authors reported only the median rank for each reason.
[c]—Patients in this study were permitted to list more than one reason. Thus, due to the possibility of double-counting patients, we did not add the percentages within any general category. Instead, we used the study's highest relevant percentage as our estimate of the percentage of patients who gave the general reason (see text).

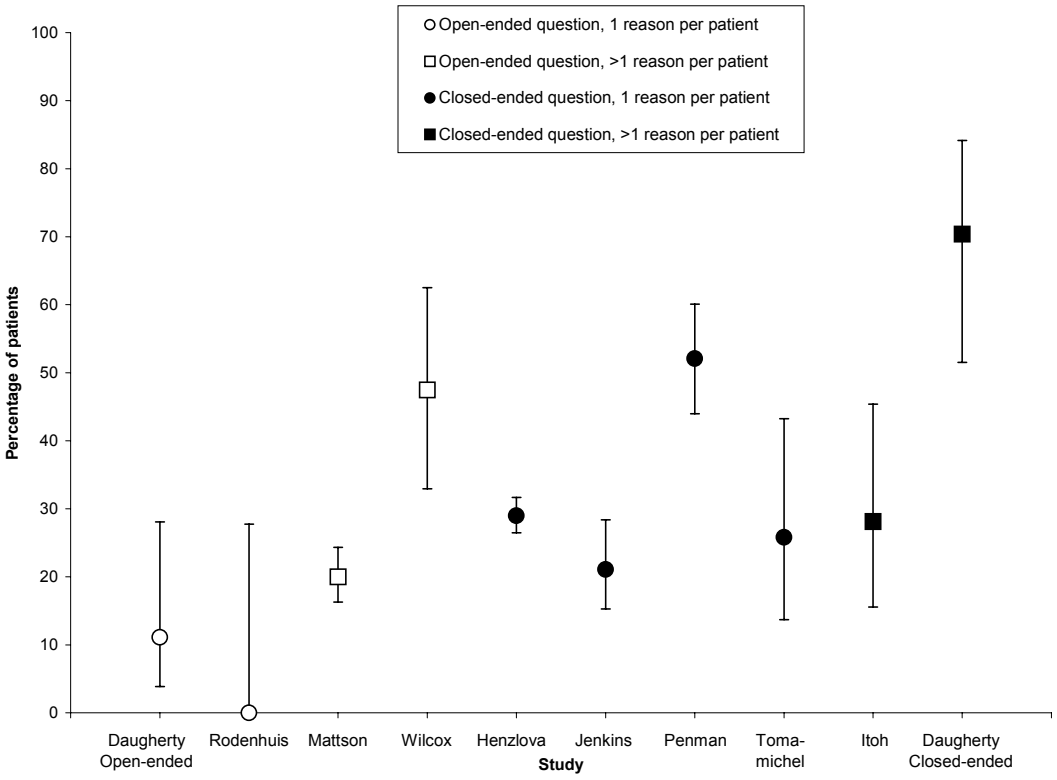
n—Number of patients for whom reasons were reported.

Figure 1. Potential Health Benefit as a Reason for Participation



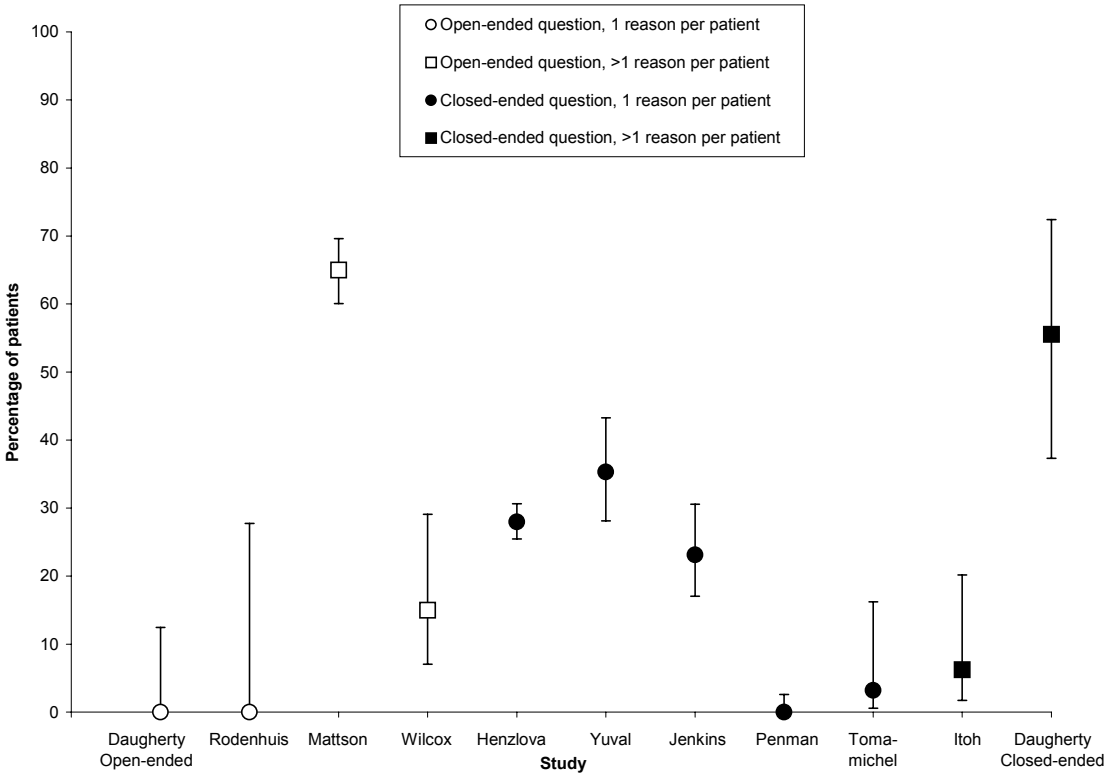
Error bars represent 95% confidence intervals using the Wilson score method.(18)

Figure 2. Physician Influence as a Reason for Participation



Error bars represent 95% confidence intervals for proportions using the Wilson score method.(18)

Figure 3. Potential Benefit to Others as a Reason for Participation



Error bars represent 95% confidence intervals for proportions using the Wilson score method.(18)

Table 4. Heterogeneity Analyses of Subgroups on Reasons for Participation

Shaded cells indicate subgroups for which there was statistically significant heterogeneity. The p values do *not* refer to significant differences between subgroups. Instead, they refer to heterogeneity of studies *within* a subgroup. See explanation in text.

	Q statistic (p value)[a]		
	Potential health benefit	**Physician influence[b]**	**Potential benefit to others**
All studies	388.10 (p <0.000001)	72.48 (p <0.000001)	964.25 (p <0.000001)
Subgroup analyses			
Cancer	93.20 (p <0.000001)	52.24 (p <0.000001)	42.71 (p <0.000001)
Heart disease	278.40 (p <0.000001)	19.90 (p = 0.000048)	188.50 (p <0.000001)
Mean age <58[c]	3.21 (p = 0.73255)	0.41 (p = 0.522061)	150.27 (p <0.000001)
Mean age ≥58[c]	41.91 (p <0.000001)	11.65 (p = 0.002951)	4.60 (p = 0.100476)
<50% female[d]	18.11 (p = 0.000418)	17.95 (p = 0.000451)	4.62 (p = 0.201967)
≥50% female[d]	22.17 (p = 0.000015)	33.18 (p <0.000001)	42.38 (p <0.000001)
<100 patients	42.74 (p <0.000001)	18.46 (p = 0.001002)	4.85 (p = 0.303012)
≥100 patients	337.75 (p <0.000001)	52.19 (p <0.000001)	951.30 (p <0.000001)
Open-ended	22.27 (p = 0.000057)	17.60 (p = 0.000533)	262.50 (p <0.000001)
Closed-ended	47.63 (p <0.000001)	35.27 (p <0.000001)	428.51 (p <0.000001)
One reason per patient	99.47 (p <0.000001)	52.33 (p <0.000001)	432.82 (p <0.000001)
More than one reason per patient	65.00 (p <0.000001)	11.04 (p = 0.004008)	143.57 (p <0.000001)
Phase I trials	40.60 (p <0.000001)	6.82 (p = 0.077819)	1.07 (p = 0.784923)
Phase II and later trials	337.76 (p <0.000001)	57.98 (p <0.000001)	951.83 (p <0.000001)

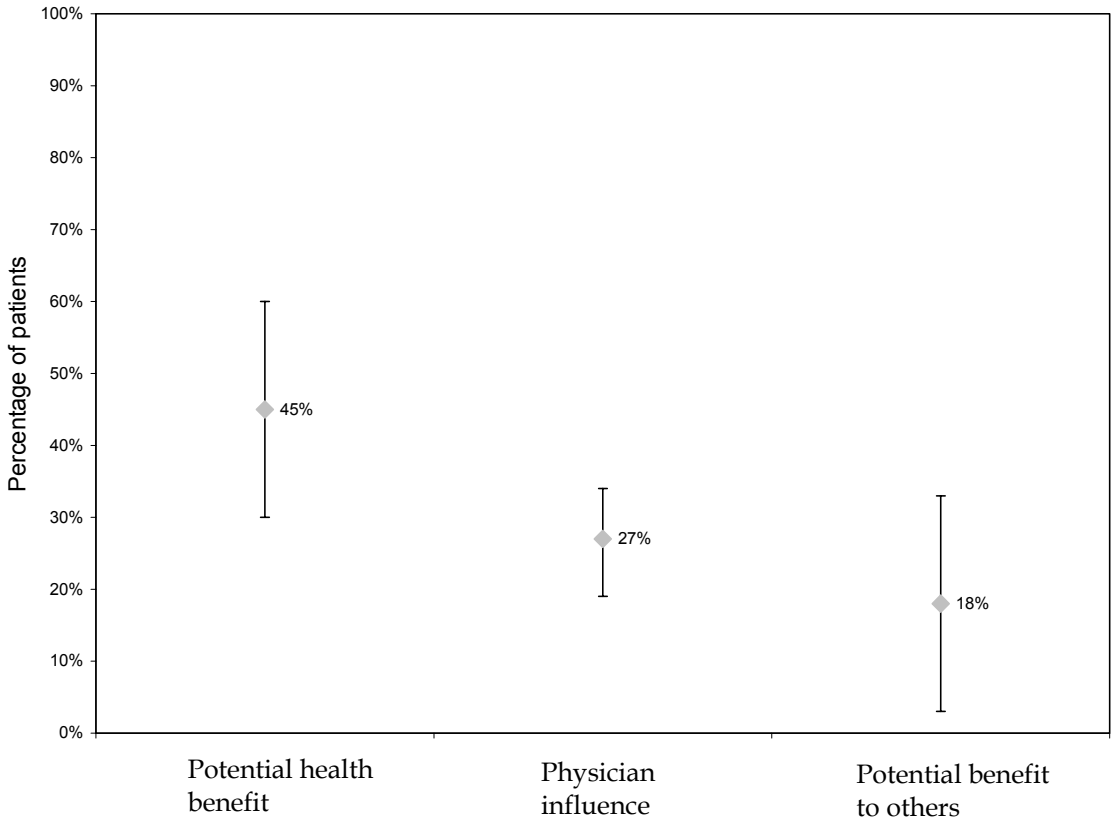
[a]—For each subgroup, we measured between-study heterogeneity using the Q test. See explanation in text.

[b]—The percentage of patients who cited physician influence as a reason for participation was reported in all studies except Yuval et al.(9) Thus the overall Q statistic for physician influence was based on 9 studies, whereas the overall Q statistics for potential health benefit and potential benefit to others were each based on 10 studies. The study by Hutchison(1) was not included in any heterogeneity analyses because it reported a unique rank-order methodology.

[c]—Only five studies of reasons for participation reported the mean or median age of patients. The overall Q statistics for potential health benefit, physician influence, and potential benefit to others were 71.38, 13.71, and 335.39, respectively (all p values <0.05).

[d]—Only seven studies of reasons for participation reported the sex distribution of patients. The overall Q statistics for potential health benefit, physician influence, and potential benefit to others were 94.08, 57.30, and 47.94, respectively (all p values <0.05).

Figure 4. Results of Random-Effects Calculations: Reasons for Participation



Error bars represent 95% confidence intervals.

Reasons against participation

Four studies asked patients why they decided not to participate in trials (**Table 5**). As with the reasons for participation, ECRI assigned a general category to each specific reason in order to permit comparisons between studies. The general categories were: "inconvenience", "concern over experimentation", "potential lack of health benefit", and "physician influence." Another research analyst independently checked the category assignments, and disagreements were resolved through discussion. The category assignments appear in the rightmost column of **Table 5**. As before, we combined the relevant percentages in studies that permitted only one reason per patient.

The resulting percentages for each of the four categories appear in **Figure 5**. None of the percentages exceeded 37%, indicating little agreement between patients regarding reasons against participation. As in the section on reasons for participation, we conducted heterogeneity analyses of subgroups in attempting to explain the differences among the results of different studies. However, statistically significant heterogeneity was present in all of the subgroup analyses. To estimate typical percentages of patients citing these reasons against participation, we conducted another set of random-effects calculations (**Figure 6**). We estimated average percentages of 25% for inconvenience, 20% for concern over experimentation, 19% for potential lack of health benefit, and 14% for physician influence.

Table 5. Reasons Against Participation

Author	n	Reported reasons against participation	Percent of patients[a]	Category assigned by ECRI
Taylor and Leitman(5)	5,972	Belief that they would be better off taking "the standard treatment"	37%	Potential lack of health benefit[b]
		Fear that they might get a placebo rather than actual treatment	31%	Potential lack of health benefit[b]
		Belief that the "standard treatment" would be more effective	30%	Potential lack of health benefit[b]
		Fear of being treated "like a guinea pig"	22%	Concern over experimentation
		Distance they would have to travel to obtain treatment	21%	Inconvenience[b]
		Belief that the cost of treatment would not be covered by insurance	20%	Other
		Amount they would have to pay out-of-pocket	18%	Other
		Fear that their doctor would not be able to choose treatment	18%	Potential lack of health benefit[b]
		The effort involved in the informed consent process	6%	Inconvenience[b]
Jenkins and Fallowfield(6)	51	I trusted the doctor treating me	21.6%	Physician influence
		The idea of randomization worried me	19.6%	Concern over experimentation
		I wanted the doctor to choose my treatment rather than be randomized by a computer	17.6%	Potential lack of health benefit
		Other	41.2%	Other
Ling et al.(7)	196	Patient prefers to wait before entry	17%	Other
		Too unwell/Deterioration in condition	16%	Other
		Lives too far away	11%	Inconvenience
		Patient "didn't want to"/"Not interested"	8%	Other
		Transfer to hospice/hospital/discharge	6%	Inconvenience
		Unable to give informed consent	6%	Other
		Family objection	5%	Other
		Objection to medication	4%	Other
		Not willing/unable to complete forms	3%	Other
		Doctor error/objection	3%	Physician influence
		Too many pills	2%	Other
		Too anxious	2%	Other
		Weekend/evening admission (research nurse unavailable)	1%	Inconvenience
		Placebo fear	1%	Potential lack of health benefit
		Previous participation in trials	1%	Other
		Declined consent reason unknown	17%	Other

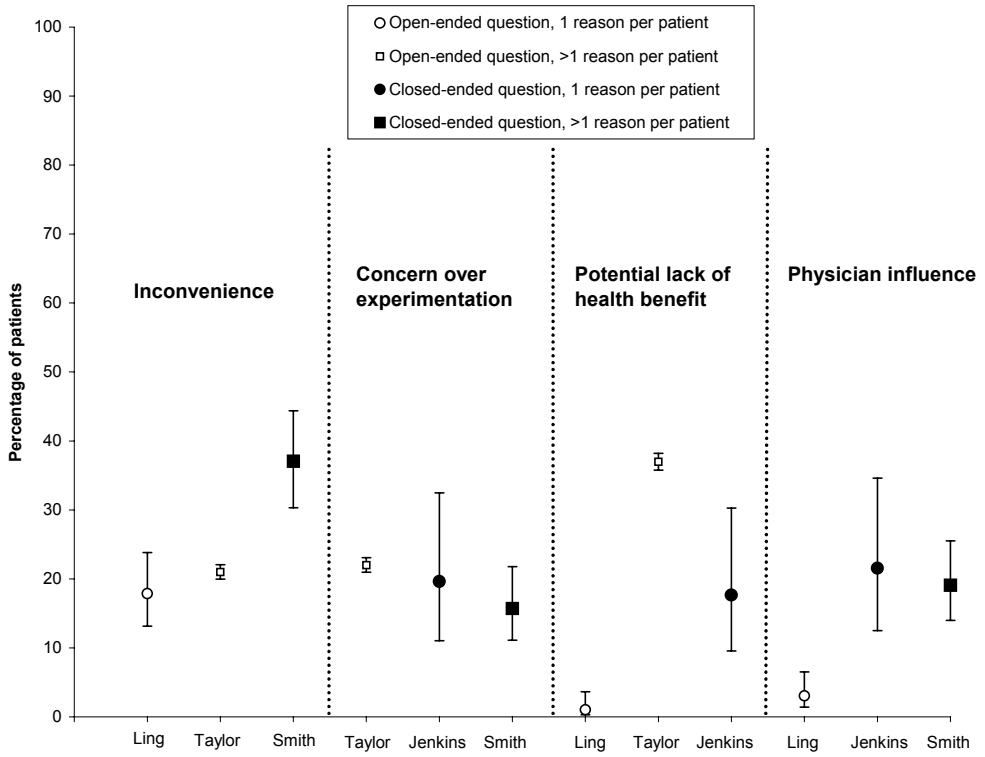
Author	n	Reported reasons against participation	Percent of patients[a]	Category assigned by ECRI
Smith and Arnesen(14)	178	Transportation problems	37%	Inconvenience[b]
		Not willing to see other doctors	19%	Physician influence
		Against taking part in experiments	16%	Concern over experimentation
		Insufficient information	11%	Other
		Inconvenient	10%	Inconvenience[b]
		Disliked focusing on disease	8%	Other
		Lack of time	8%	Inconvenience[b]
		Other specified	13%	Other

[a]—In some studies, the percentages add to more than 100% because patients were permitted to list more than one reason.

[b]—Patients in this study were permitted to list more than one reason. Thus, due to the possibility of double-counting patients, we did not add the percentages within any general category. Instead, we used the study's highest relevant percentage as our estimate of the percentage of patients who gave the general reason (see text).

n—Number of patients for whom reasons were reported.

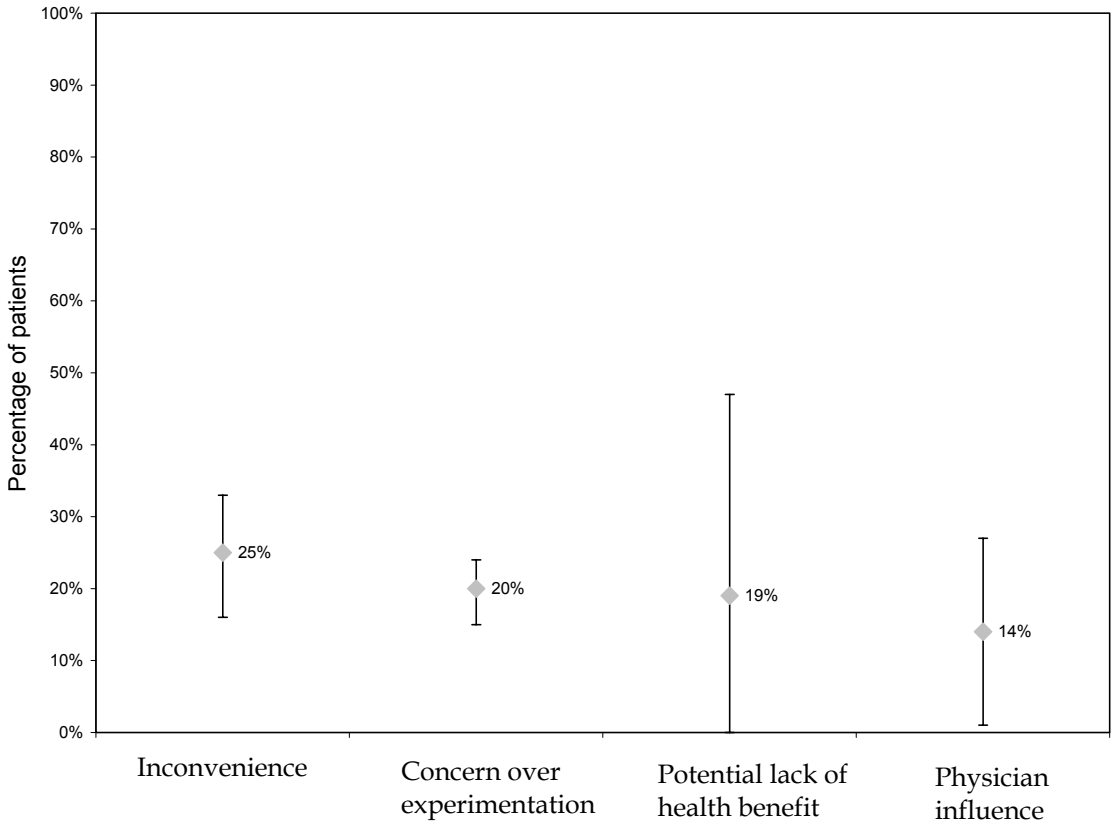
Figure 5. Plot of Reasons Against Participation



Error bars represent 95% confidence intervals for proportions using the Wilson score method.(18)

Study

Figure 6. Results of Random-Effects Calculations: Reasons Against Participation



Error bars represent 95% confidence intervals

Conclusions

Of 14 studies we identified on reasons for participating and not participating in clinical trials, 11 studies cited patients' reasons for participating. These studies reported widely varying results for why patients chose to participate in clinical trials. Although there were differences in patient characteristics and study designs, these differences did not explain why the results of these studies were so different. We used random-effects calculations to combine the studies and estimate the typical percentages of patients who cited reasons in three general categories: potential health benefit (45%), physician influence (27%), and potential benefit to others (18%).

Four studies asked patients why they decided against participation in clinical trials. As with the analyses of reasons for participation, we observed statistically significant heterogeneity in the results that could not be explained by patient characteristics or study designs. Random-effects calculations yielded estimated percentages of 25% for inconvenience, 20% for concern over experimentation, 19% for potential lack of health benefit, and 14% for physician influence.

Do patients in clinical trials have better treatment outcomes than similar patients not in clinical trials?

For patients with a serious or life-threatening illness, a key factor in the decision-making process about trial participation is whether participating will improve the chance of long-term survival and quality of life (QoL). There can be no certain answer to this question, however, because a clinical trial is by definition experimental. Its very existence means that researchers do not know for certain whether the novel treatment has any effect, beneficial or harmful.

Nevertheless, it is possible to examine the health outcomes of the patients who have participated in trials. To place this information in proper context, however, we must also examine the health outcomes of similar patients who were eligible for trials but did not participate in them. It may be informative to compare the health outcomes of patients in these two groups in an attempt to measure the effect of trial participation.

However, there are several potential pitfalls in trying to make this comparison. First, researchers rarely track the progress of patients who did *not* participate in clinical trials. Thus, for most trials, the data are unavailable. Second, clinical trials vary widely in numerous ways (e.g., trial design, patient populations, kinds of treatments), and the effect of participation in past clinical trials may not be generalizable to current or future clinical trials. Third, patients cannot be randomly assigned to either the trial group or the group without trials. Ethically, patients must consent to participate in a clinical trial. Because of the nonrandom assignment, selection biases greatly complicate the comparison of the two groups. For example, if the patients in the trial group were significantly younger than the patients not in trials, then one would expect a priori that the trial group would survive longer. In this situation, it would not be clear whether an observed difference in survival was due to age, trial participation, or both factors.

Despite these pitfalls, we attempted to answer this question by locating trials that compared the health outcomes of patients in each of two groups: patients who participated in a clinical trial, and patients who were eligible for that trial but did not participate. Of particular interest were trials that attempted to control for selection bias when comparing the two groups.

Trial Selection

To be included in analyses of this question, our a priori selection criteria required that a trial meet all of the following inclusion criteria:

- Include mentally competent patients with an acute or chronic life-threatening illness. Only trials of life-threatening illnesses were considered because the intended audience for the patient reference guide is patients with a life-threatening illness who are considering enrollment in a clinical trial.
- Report data for each of two groups of patients: one group in a clinical trial and another group not in any clinical trial. Both groups are necessary in order to assess the influence of trial participation on health outcomes.
- Report survival data, quality-of-life data, or both. Survival data could be reported as survival curves, percentage surviving to a specific time (e.g., three-year survival), and could be reported as either overall survival or disease-free survival. QoL data were considered differently for different diseases.

Patient age 18 years or older was not a requirement for this question. The effect of trial participation on children's health outcomes is relevant to an adult's decision about his/her own trial participation because it may reflect widely applicable advantages or disadvantages of being in a trial.

Seventeen trials met the inclusion criteria. Eight of these trials, however, were excluded for reasons listed in **Table 6**. Six of the excluded trials reported data from a group of nontrial patients in which some patients were not eligible for the trial (or the trial did not report whether patients not in the trial were eligible). Clinical trials often employ stringent inclusion criteria that require a minimum level of health. If patients in the nontrial group were not eligible for the trial, then they might not be comparable to patients in the trial group. Therefore, any differences in posttrial health outcomes between the two groups could be attributed solely to the fact that some patients not in the trial failed the eligibility criteria. The goal of this analysis was to determine the health outcome effects strictly due to trial participation, not to other factors.

Two trials were excluded for other reasons. The trial reported by Smith and Arnesen(19) was excluded because the trial group only included patients who received the placebo arm. As patients decide whether to enter a randomized trial, they do not know which arm of the trial they will be assigned to. Therefore, the overall effect of participating in a trial can only be measured by including data from all arms of that trial, not selected arms. Furthermore, if we examined only the placebo arm, then it would be impossible to measure any effects of the novel treatment, which is the basis for conducting the trial. The trial reported by Meadows et al.(20) was excluded because patients in one group had received research protocols that had already been proven effective. Therefore, these protocols were not experimental, and one would expect a priori that protocol patients would have better health outcomes than other patients who did not receive the protocols due to inadequate access or poor adherence.

Nine trials remained after these exclusions (**Table 7**). These trials reported on a total of 1,793 patients in trials and 2,654 patients not in trials. The trial by Bertelsen(21) is listed twice in the table because authors reported data separately for each of two trials: one on stage I/II ovarian cancer, and another on stage III/IV ovarian cancer. Therefore, the evidence base consisted of 10 trials. Eight trials investigated cancer patients, and two investigated patients who had heart conditions. Only one trial included children (Lennox et al.(22)). Four trials were conducted in the United States. None of the trials were phase I trials.

Table 6. Excluded Trials

Trial	Reason for exclusion
Cottin et al.(23)	95% of patients in the group not in the trial were not eligible for the trial.
Hjorth et al.(24)	80% of patients in the group not in the trial were not eligible for the trial.
Jha et al.(25)	Authors did not report whether patients in the group not in the trial were eligible for the trial.
Meadows et al.(20)	Nonexperimental research protocols (treatment effectiveness had been established in earlier trials).
Quoix et al.(26)	Some patients in the group not in the trial (unreported percentage) were not eligible for the trial.
Smith and Arnesen(19)	All patients in the trial group had received a placebo, and trial patients who had received the experimental treatment were not reported.
Stiller and Draper(27)	Authors did not report whether patients in the group not in the trial were eligible for the trial.
Stiller and Eatock(28)	Authors did not report whether patients in the group not in the trial were eligible for the trial.

Table 7. Trial Characteristics

Trial	Disease	Country	Number of trials	Number of patients in trials	Number of patients not in trials	Mean age of trial patients	Mean age of patients not in trials	Percent of females in trials	Percent of females not in trials
Antman et al.(29)	Sarcoma	U.S.	1	42	48	NR	NR	40%	60%
Bertelsen(21)	Ovarian cancer, stage I/II	Denmark	1	72	48	NR	NR	100%	100%
Bertelsen(21)	Ovarian cancer, stage IIII/IV	Denmark	1	265	96	NR	NR	100%	100%
Boros et al.(30)	Leukemia	U.S.	3	46	46	NR	NR	NR	NR
Brown et al.(31)	Myocardial infarction	U.K.	2	140	329	61.5	64.9	31.4%	33.1%
CASS(32)	Coronary artery disease	U.S.	1	780	1,315	51.2	50.9	9.7%	9.4%
Davis et al.(33)	Nonsmall-cell lung cancer	U.S.	4	78	152	NR	NR	NR	NR
Lennox et al.(22)	Nephro-blastoma	U.K.	1	98	104	NR	NR	NR	NR
Ward et al.(34)	Stomach cancer	U.K.	1	217	493	63[a]	64[a]	30%	31%
Winger et al.(35)	Brain cancer	Canada	1	55	23	52	55	NR	NR
Totals	**Cancer: 8 Heart: 2**	**U.S.: 4 U.K.: 3 Other: 3**	**1: 7 >1: 3**	**1,793**	**2,654**	**56.9**	**58.7**	**52%**	**56%**

[a]—Ward et al.(34) reported median ages

MI—Myocardial infarction; NR—Not reported; U.K.—United Kingdom; U.S.—United States

Key Study Results

Only survival and QoL were considered for this question. These are the outcomes that are most important to patients. Other outcomes, such as biologic details of cells and cell counts, were not included because they are surrogate outcomes that are only indirectly related to patients' key concerns.

Survival

Reporting of survival included Kaplan-Meier survival curves, and percentage surviving to a specific time point (e.g., three-year survival). Trials were required to report survival for each of the two groups: patients in trials and eligible patients not in trials.

Quality of Life

Because QoL is a subjective concept that was measured differently for different diseases in the trials we examined, we considered each trial separately when assessing QoL. Trials were required to report QoL for each of the two groups.

Results

Survival

As discussed earlier, one problem with comparing the health outcomes of clinical trial patients to those of patients not in trials concerns the potential for selection bias. Because patients cannot be randomly assigned to these groups, there may be important differences in patient characteristics that influence survival. An example in cancer trials is stage of disease: suppose that among patients in the trial, 30% had advanced metastatic cancer, whereas among eligible patients not in the trial, 60% had advanced metastatic cancer. Obviously, one would expect the average survival of trial patients to be longer than that of patients not in the trial *purely as a result of the different distributions of disease stage*, and not necessarily as a result of trial participation.

To compensate for patient differences, a well-designed trial could use statistical techniques to control for differences in patient characteristics such as disease stage. Ideally, the effect of trial participation on survival would be examined in isolation after factoring out other characteristics that may influence survival. An example of a statistical technique that can achieve this goal is multiple logistic regression. Several predictor variables are used to predict a dichotomous survival outcome (e.g., whether a patient survives for at least four years). Using this technique, it is possible to estimate the *independent* influence of trial participation on survival by simultaneously accounting for other factors.

All 10 trials compared characteristics of patients in trials with patients not in trials (see **Table 8**). Statistically significant differences were found in 8 of the 10 trials. Of these eight trials, only three used statistical techniques to control for these differences when examining the effect of trial participation on survival. A fourth trial (the Bertelsen(21) trial on stage III/IV ovarian cancer) found that the two groups were not significantly different in any of five patient characteristics. Therefore, in that trial, a comparison of the survival rates of the two groups may be acceptable even without statistically controlling for patient characteristics. A fifth trial (the Davis et al.(33) trial on nonsmall-cell lung cancer) used a "matched control" group in which

patients not in the trial were matched to trial patients based on cancer-related prognostic factors.

These five trials are shaded in the table, and they represent the highest-quality trials in our evidence base. We extracted the survival results from these five trials only. Results of other trials were not extracted because it was impossible to determine (based on published reports) whether survival effects were due to trial participation or to significant differences in patient characteristics. In the five extracted trials, survival effects could be attributed solely to trial participation.

The survival results appear in **Table 9** and **Figure 7**. Four of the five trials found that patients in trials survived significantly longer than patients not in trials. In another trial, by Brown et al.(31), the difference was in the same direction but was not statistically significant. To provide an appreciation of the size of the survival difference, we estimated three-year overall survival rates for the two groups of patients. This was the only survival outcome reported by one of the trials (Lennox et al.(22)), and we could estimate it from survival curves in three of the other four trials. The range of three-year overall survival was 19% to 80% for patients in trials and 4% to 70% for patients not in trials. We could not conduct heterogeneity analyses of the survival data because authors did not report sufficient data to permit such analyses.

Quality of Life

Only 1 of the 10 trials reported QoL outcomes. Brown et al.(31) enrolled patients who had heart attacks, and authors measured the extent of chest pain and breathing difficulty in patients who had participated in clinical trials and patients who had not. However, there were significant differences in pre-study patient characteristics between the groups, and the QoL comparisons did not account for these differences. Thus, one cannot clearly interpret such comparisons within this study.

Table 8. Controls for Differences in Patient Characteristics

Shaded rows indicate trials of highest quality from which we extracted survival data (see explanation in text).

Author	Disease	Which patient characteristics were compared between the groups?	Which showed a significant difference between the groups?	Did the authors control for this characteristic in the survival comparison?	What additional characteristics did the authors control?
Antman et al.(29)	Sarcoma	Age, gender, tumor location & size, stage	Cancer stage	No	None
Bertelsen(21)	Ovarian cancer, I/II	Stage and type of cancer, residual tumor, presence of ascites, tumor cells in ascites	Residual tumor Presence of ascites	No No	None
Bertelsen(21)	Ovarian cancer, III/IV	Stage and type of cancer, residual tumor, presence of ascites, tumor cells in ascites	None	NA	None
Boros et al.(30)	Leukemia	Age, leukocyte count, platelet count, LDH value, uric acid, bilirubin, SGOT findings, performance status, bone marrow cellularity, preleukemic symptoms, fever	Age Leukocyte count	Yes Yes	Platelet count, LDH value, performance status, antibiotics, preleukemic symptoms, fever
Brown et al.(31)	Myocardial infarction	Age, gender, previous MI, previous RV, infarction type, Killip class, management	Age	Yes	Gender, previous MI, type of infarction, Killip class
CASS(32)	Coronary artery disease	Age, gender, race, work status, angina, cigarette use, previous MI, hypertension, congestive failure, diabetes, stroke, peripheral arterial disease, use of nitroglycerin, use of nitrates, use of beta-blockers, use of antiarrhythmic agents, Q-wave MI on ECG, ST depression on ECG, T-wave inversion on ECG, normal ECG, diseased vessels, left-main CA disease, proximal LAD disease, left ventricular score, ejection fraction	Angina Cigarette use Hypertension Diabetes Stroke Use of beta-blockers Q-wave MI on ECG ST depression on ECG Diseased vessels Left-main CA disease Proximal LAD disease	No No No No No No No No No No No No	None
Davis et al.(33)	Nonsmall-cell lung cancer	Nodal involvement, tumor size, tumor histology	None	NA	Age, gender, radiation
Lennox et al.(22)	Nephroblastoma	Age, stage of disease	Age	Yes	Stage of disease

Author	Disease	Which patient characteristics were compared between the groups?	Which showed a significant difference between the groups?	Did the authors control for this characteristic in the survival comparison?	What additional characteristics did the authors control?
Ward et al.(34)	Stomach cancer	Age, gender, symptom duration, disease stage, intent of surgery, residual tumor, metastases, tumor site, number of sites, type of gastrectomy, size of tumor, other pathologic findings	Age Symptom duration Tumor site Number of sites Gastrectomy Size of tumor	No No No No No No	None
Winger et al.(35)	Brain cancer	Age, tumor type, performance status	Performance status	No	None

CA—Coronary artery
ECG—Electrocardiogram
LAD—Left anterior descending coronary artery
LDH—Lactic dehydrogenase
MI—Myocardial infarction
NA—Not applicable because the study did not find differences in patient characteristics
RV—Revascularization
SGOT—Serum aspartate aminotransferase

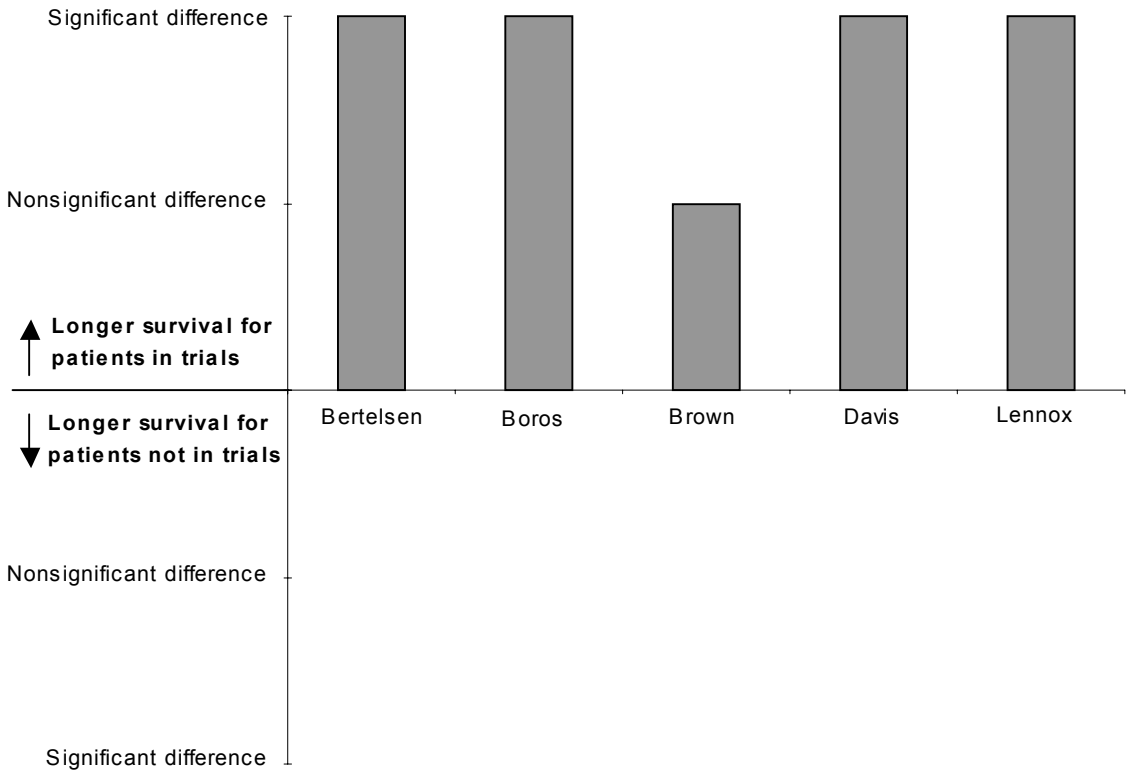
Table 9. Statistics for Survival Comparison

	Reported survival curves?	Statistical test	Value of test statistic	Confidence interval	Three-year overall survival	
					Percent of patients in trials	Percent of patients not in trials
Bertelsen(21) Stage III/IV	Yes	Mantel-Haenzel test	NR	NR	35%[b]	23%[b]
Boros et al.(30)	Yes	Cox regression slope for trial participation	-0.774[c]	NR	19%[b]	4%[b]
Brown et al.(31)	Yes	Adjusted[a] odds ratio for four-year OS	1.60	0.97-2.63	80%[b]	70%[b]
Davis et al.(33)	No	Relative mortality risk for trial participation	0.39	0.18-0.83	NR	NR
Lennox et al.(22)	No	Adjusted[d] chi square for three-year OS	11.67	NR	77%	58%

[a]—Brown et al.(31) performed a multiple logistic regression in order to adjust for patient characteristics.
[b]—Estimated by ECRI based on published Kaplan-Meier survival curves. One cannot infer the numbers of surviving patients from these percentages due to unreported censoring in the survival data.
[c]—A negative slope in the Cox regression performed by Boros et al.(30) indicated that patients in trials survived longer than patients not in trials.
[d]—Lennox et al.(22) did not report the method of adjustment.

NR—Not reported.
OS—Overall survival.

Figure 7. Plot of Survival Comparison



Conclusions

Based on the available evidence, we conclude that some evidence shows that patients in phase II/III trials survive longer than similar patients who are not in trials. One cannot have great confidence in these results, however, due to the small evidence base.

We identified five trials that controlled for differences in patient characteristics (or found no differences in patient characteristics) when comparing the survival of patients in clinical trials with that of eligible patients not in clinical trials. In four of five trials, patients in trials survived significantly longer than those not in trials.

Only one trial compared the QoL of patients in trials with that of patients not in trials. However, one cannot interpret the results due to differences in patient characteristics between the two groups. Appropriately controlled studies are needed to shed light on the potential effect of trial participation on QoL.

None of the 10 trials analyzed addressed participation in a phase I trial. A phase I trial is not necessarily intended to improve the health of patients in that trial, but rather to determine appropriate dosing levels and measure adverse effects. Of course, it is possible that current patients may themselves benefit from the new treatment, but such an outcome is not the primary intent of a phase I trial. By contrast, a phase II or later trial is intended to improve the health of patients in the trial. All trials in our evidence base for this question related to participation in phase II or later trials. *Consequently, we emphasize that the results for this question are only relevant to patients considering enrollment in phase II or later trials, not to patients considering enrollment in phase I trials.* In other words, the finding that trial patients survived longer in four of five trials cannot be construed by potential phase I trial participants as direct evidence in favor of participation. Instead, we found no evidence relevant to the influence of phase I trial participation on health outcomes.

There are two additional caveats to our results on this subject. Even though some authors controlled for some patient characteristics, one cannot be certain that *all* important characteristics were considered in these trials. There may have been additional characteristics related to survival that were not considered or reported by the authors. Second, statistical significance is an unreliable basis for deciding whether to control for a patient characteristic. Smaller trials are less likely to detect a statistically significant difference between groups. Ideally, a trial would control for patient characteristics *regardless* of whether there were statistically significant differences. However, none of the trials controlled for *all* patient characteristics, and so use of this latter criterion would yield no analyzable trials. Therefore, we extracted data from all trials that attempted to control for observed differences in patient characteristics.

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