

Accrual Experience of National Cancer Institute Cooperative Group Phase III Trials Activated From 2000 to 2007

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A B S T R A C T

Purpose

Recent reports have suggested that 40% or more of National Cancer Institute (NCI) –sponsored Cooperative Group phase III trials failed to achieve their accrual goals. We examine in detail the accrual experience of the Cooperative Group phase III trials.

Patients and Methods

All Cooperative Group phase III trials activated from 2000 to 2007 were examined for their accrual experience. For trials that stopped accrual with < 90% of their accrual goal, the reasons for having < 90% accrual were documented. We focus on trials that ended with < 90% accrual because of inadequate accrual rates rather than for other reasons, such as an interim monitoring analysis by an independent data monitoring committee that stops the trial early because one treatment is clearly superior.

Results

There were 191 trials activated from 2000 to 2007. We project that 22.0% of these trials will have < 90% accrual because of inadequate accrual rates. We project that there will be 176,627 patients eventually accrued on the 191 trials (current accrual, 154,579) and that 2,991 of these patients will be on trials that have < 90% accrual because of inadequate accrual rates (1.7%). For nonpediatric cancer trials, the corresponding percentages are 26.7% and 2.0%.

Conclusion

We find that insufficient accrual rates are not as high as previously reported and that only a small proportion of patients were enrolled on trials that ended with insufficient accrual because of an inadequate accrual rate. NCI has implemented new procedures to reduce the number of trials that fail to reach their accrual goals and to minimize the number of patients accrued on these trials.

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INTRODUCTION

The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) supports phase III clinical trials primarily through the NCI Clinical Trials Cooperative Group program. There are currently approximately 100 such trials actively accruing patients. Although many Cooperative Group phase III trials have led to major advances in the treatment of cancer patients,¹ a proportion of trials are never completed because they do not achieve a sufficient accrual to meet their scientific objectives. Such trials represent loss of the resources that went into designing the trials, getting them activated, and treating the patients accrued on the trials, as well as not utilizing the efforts of the participating patients. In addition, an ongoing trial may preclude opening other trials in the same disease setting that might have been successfully completed. As part of ongoing

efforts to improve the efficiency of the NCI clinical trials program, we have performed an in-depth review of the accrual experience from Cooperative Group phase III trials activated from 2000 to 2007.

PATIENTS AND METHODS

Trial Information

All CTEP-supported phase III trials led by an NCI-sponsored Cooperative Group or conducted as part of an international collaboration with a Cooperative Group that were activated in the years 2000 to 2007 were identified. Trials were categorized as having accrual finished or not, with the latter category including trials that were temporarily closed to accrual. The accrual goal of the trial was taken from the latest CTEP-approved version of the trial protocol. The percent accrued for the trial was calculated as the current or final accrual divided by the accrual goal of the trial. Closed trials with < 90% accrued were considered not fully accrued. Trials not fully accrued were categorized for the reason they stopped accruing by using the

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following categories: (a) external information (eg, results of another clinical trial that answered the current trial question or rendered it irrelevant), (b) formal interim monitoring of the current trial by an independent data monitoring committee (either for showing one of the trial arms superior or for futility/inefficacy of the experimental treatment arm), (c) unacceptable toxicity, (d) drug supply issues, or (e) inadequate accrual rate. Information for performing the categorization was obtained from administrative documents (eg, protocol amendments and protocol status updates), trial publications, and CTEP investigators. Trials were additionally categorized by the primary disease site, whether or not the trial involved a randomization (some pediatric phase III trials use historical controls), and whether or not the trial involved an investigational new drug agent.

Statistical Analyses

Trials that were closed to accrual with < 90% of their accrual goal were considered to have insufficient accrual, with the 90% figure chosen prospectively before the analysis was begun. Considering that the statistical power of a trial is typically based on an estimated number of events that will be observed (which depends on the length of the follow-up), we believe that trials that achieve $\geq 90\%$ of their accrual goal can be considered successfully accrued from a statistical point of view. One parameter of interest is the probability that a trial activated from 2000 to 2007 will have insufficient accrual because of an inadequate accrual rate (category (e) above). Since not all trials activated from 2000 to 2007 have completed accrual, this parameter needs to be estimated. If one estimates solely from trials that have closed to accrual, then the estimator will be subject to sampling bias. (This is the same type of bias one would observe by trying to estimate median patient survival in a clinical trial by using the median survival of only those patients who have died.) To avoid sampling bias, statistical methods for survival data that account for censored observations were used that adjust for actively accruing trials. In particular, (1) the unit of analysis is the trial, (2) "time" on study is the percentage accrued for the trial, (3) the trial is considered as having the "event of interest" if the trial stopped accruing with < 90% accrued because of inadequate accrual, (4) trials that stopped with < 90% accrual for other reasons (eg, interim monitoring) are considered a competing risk, and (5) trials that are still actively accruing are treated as censored observations. (Trials that have accrual temporarily suspended are considered active). In this framework, the parameter of interest is the crude cumulative incidence² evaluated at 90% percent accrued.

Other parameters of interest are a projection of the number of patients who will be accrued to trials that will have insufficient accrual because of an inadequate accrual rate and the proportion of such patients compared with the total number of patients who will be accrued to all trials. To obtain estimators of these parameters, survival methods were applied with the analyses weighted by the accrual goal for each trial (details are found in the Appendix, online only).

RESULTS

One hundred ninety-one phase III trials were activated from 2000 to 2007 (Table 1). Figure 1 displays a histogram of the percentage accrued for the 133 trials for which accrual has finished; trials having an inadequate accrual rate are shown in gold. The estimate of the proportion of trials that have insufficient accrual because of an inadequate accrual rate is 22.0%. This estimate is remarkably similar to the naive proportion of trials that had an inadequate accrual rate (21.5%; 41 of 191), which would be an appropriate estimator if we knew that all actively accruing trials would eventually achieve at least 90% accrual. The reason for this is that practically all of the actively accruing trials are already past the point (in terms of percent accrued) at which trials that are going to stop because of inadequate accrual would have stopped (Fig 2). In particular, 85% (35 of 41) of the trials that closed for inadequate accrual rates had < 20% accrued (Fig 1), and 91% (53 of 58) of the trials still accruing already have > 20% accrued (Fig 2).

Table 1. Accrual Status and Reasons for < 90% Accrued in CTEP-Sponsored Phase III Trials Activated From 2000 to 2007 (191 trials)

Status	No. of Trials
Accrual not over	58
$\geq 90\%$ accrued so far	9
< 90% accrued so far	49
Accrual over	133
$\geq 90\%$ accrued	68
< 90% accrued	65
Reasons for < 90% accrued	
Interim monitoring	12*†
External information	9*
Drug supply issues	2
Unacceptable toxicity	3
Inadequate accrual rate	41

Abbreviation: CTEP, Cancer Therapy Evaluation Program.

*Includes two trials that had < 90% accrued because of both interim monitoring and external information.

†Two of the 12 trials were stopped for superiority monitoring; the other 10 were stopped for futility monitoring.

The estimate of the proportion of patients enrolled on trials that had insufficient accrual because of an inadequate accrual rate is 1.7%, representing a projected 2,991 patients of a projected 176,627 that will eventually be accrued to all 191 trials. This low percentage reflects the obvious point that trials stopped for inadequate accrual will tend to have only a small number of patients accrued.

When examined by primary disease site (Table 2), the pediatric cancer trials have a smaller proportion of trials with inadequate accrual rate leading to < 90% accrued than the adult cancer trials. In fact, only two of the 42 pediatric trials had < 90% accrued because of an inadequate accrual rate. For the adult cancer trials, the breast cancer trials appear to have fewer trials with inadequate accrual rates. None of the 15 phase III trials with nonrandomized designs had < 90% accrued because of an inadequate accrual rate (Table 3); these trials were all pediatric cancer trials. There is no substantial difference in the proportion of inadequately accruing

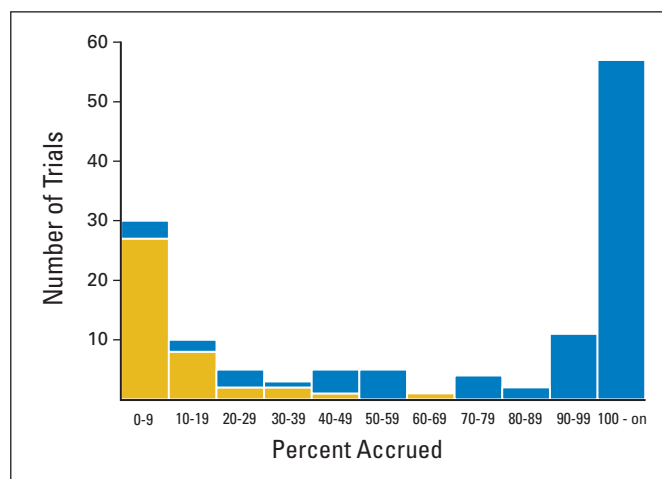


Fig 1. Histogram of percent accrued for 133 trials that are closed to accrual (gold indicates trials with inadequate accrual rate).

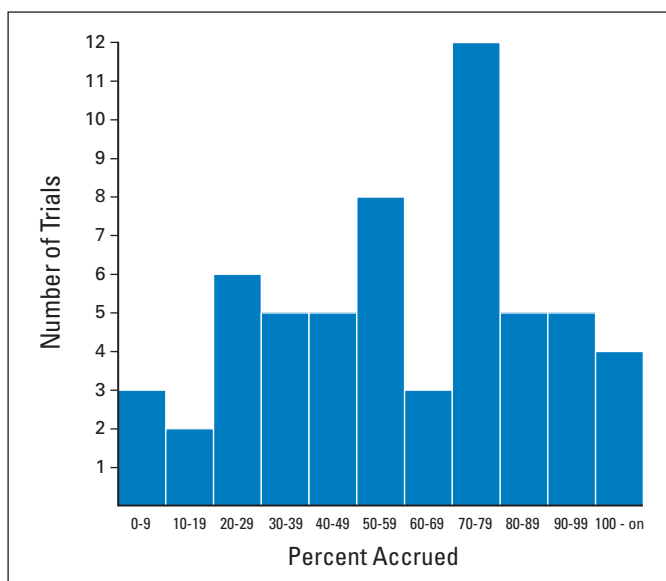


Fig 2. Histogram of current percent accrued for the 58 trials that are not closed to accrual.

trials depending on whether or not the trial involved an investigational new drug agent (Table 3).

Although $\geq 90\%$ accrual was the prospectively defined cutoff for sufficient accrual, similar results are obtained by using a 95% cutoff. Using a 95% cutoff, the estimate of the proportion of trials that have insufficient accrual because of an inadequate accrual rate is 22.8% (instead of 22.0%), and the estimate of the proportion of patients enrolled on trials that had insufficient accrual because of inadequate accrual rate is 2.2% (instead of 1.7%).

DISCUSSION

Cheng et al³ report 49.2% (30 of 61) of CTEP-approved nonpediatric phase III trials failed to achieve at least 25% of accrual goals. Recently, the Institute of Medicine reported that 40% of CTEP-approved phase III trials failed to achieve minimum accrual goals,⁴ a figure that has been repeated elsewhere.⁵⁻⁷ We report here that we estimate that 28.3% of such nonpediatric trials will fail to achieve at least 90% of their accrual goals because of inadequate accrual, based on data from 149 trials (Table 2). The difference between the results can be attributed to exclusion of actively accruing trials by Cheng et al³ (leading to sampling bias) and their inclusion, as failures to achieve accrual goals, of trials that ended for other reasons besides inadequate accrual.⁴ We have chosen not to consider trials that failed to achieve at least 90% of their accrual goals because of formal interim monitoring, unacceptable toxicity, or drug supply issues as failures. This is an obvious decision for trials that closed because of interim monitoring, and one could argue for the other categories that failure to fully accrue was beyond the control of the investigators.

Overall, we estimate that 22.0% of all trials (adult and pediatric) will end with insufficient accrual because of inadequate accrual rates, and 1.7% of the total number of patients accrued on all trials will be on these trials. It is possible that a trial that ends with accrual $< 90\%$ of projected because of an inadequate accrual rate can still provide useful clinical information. For example, the Eastern Cooperative Oncology Group (ECOG) E4201 trial,⁸ which closed to accrual with 74 of 332 patients accrued, demonstrated the major advance of treating locally inoperable pancreatic cancer with radiation therapy in addition to gemcitabine.⁹ Another example is given by the Radiation Therapy Oncology Group (RTOG) 9813 trial, which closed to accrual with 201 of 454 patients accrued and is in follow-up. This trial, which compares temozolomide plus radiation versus nitrosourea plus radiation for

Table 2. Estimated Proportion of Trials That Had Insufficient Accrual Because of an Inadequate Accrual Rate and the Estimated Proportion of Patients on These Trials, by Primary Disease Site

Primary Disease Site	Trials		Patients			
	No. Activated	Estimated Proportion With Inadequate Accrual Rate (%)*	No. of Patients Accrued to Date	Projected No. Accrued When All Trials Are Closed*†	Projected No. on Trials With Inadequate Accrual Rate*†	Estimated Proportion on Trials With Inadequate Accrual Rate (%)*
Adult						
Breast	31	13.0	69,936	76,382	362	0.5
Hematopoietic	25	28.8	6,795	7,108	240	3.4
GI	18	28.6	18,437	20,316	746	3.7
Female reproductive	16	37.5	10,174	11,304	193	1.7
Lung	14	22.6	5,652	7,198	640	8.9
Prostate	16	25.0	8,951	11,204	150	1.3
Other‡	29	34.9	10,988	11,470	523	4.6
Subtotal	149	26.7	130,933	147,742	2,930	2.0
Pediatric						
Nonhematopoietic	26	7.7	6,024	8,845	25	0.3
Hematopoietic	16	0.0	17,622	19,471	0	0.0
Subtotal	42	4.8	23,646	28,955	28	0.1
Total	191	22.0	154,579	176,627	2,991	1.7

*These proportions and numbers are estimated using survival analysis methodology.

†Because projected numbers for subgroups are based on within-subgroup survival curves, numbers do not add up exactly to totals.

‡Includes seven head and neck cancer, four distant metastases (unspecified origin), three melanoma, three astrocytoma, three renal, three soft tissue sarcoma, three bladder, one testicular, one neuroendocrine, and one breast/colorectal cancer trials.

Table 3. Estimated Proportion of Trials With Insufficient Accrual Because of an Inadequate Accrual Rate and the Estimated Proportion of Patients on These Trials, by Randomization-In-Design Status and Whether or Not the Trial Involves an IND Agent

Randomization-in-Design Status	Trials		Patients			
	No. Activated	Estimated Proportion With Inadequate Accrual Rate (%)*	No. of Patients Accrued to Date	Projected No. of Patients Accrued When All Trials Closed*†	Projected No. on Trials With Inadequate Accrual Rate*†	Estimated Proportion on Trials With Inadequate Accrual Rate (%)*
Randomized design						
IND agent	60	18.5	50,947	59,174	1,073	1.8
No IND agent	116	26.7	100,882	112,716	1,864	1.7
Subtotal	176	23.9	151,829	172,488	2,983	1.7
Nonrandomized design	15	0.0	2,750	4,370	0	0.0
Total	191	22.0	154,579	176,627	2,991	1.7

Abbreviation: IND, investigational new drug.

*These proportions and numbers are estimated using survival analysis methodology.

†Because projected numbers for subgroups are based on within-subgroup survival curves, numbers do not add up exactly to totals.

treating anaplastic astrocytomas or mixed gliomas, may still provide relevant clinical information. Much more likely, trials that end early because of inadequate accrual will provide little useful clinical data. Although the number of patients involved in these trials is small (compared with the number of patients on all trials), there are still considerable resources involved in opening a trial, whether or not it accrues.

Should one aim for a clinical trials program to open only trials in which one is positive that they will accrue successfully? We would argue no, because this would preclude starting trials that address important questions but in which it is known at the start that accrual will be challenging. For example, the Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT; American College of Surgeons Oncology Group [ACOSOG] Z0070), comparing radical prostatectomy versus brachytherapy in early-stage prostate cancer, accrued only 56 of a required 1,980 patients. Another example is given by the Southwest Oncology Group S0521 trial, which compared maintenance chemotherapy versus observation in patients with previously untreated low- and intermediate-risk acute promyelocytic leukemia. It accrued only 95 of a required 500 patients. Yet experts often cite the strong need for clinical trials for both these questions.

Although we believe it is important to attempt to perform important trials that may be a challenge for enrollment, it is also important to minimize the time and number of patients involved in trials that turn out to have insufficient accrual. One strategy is to examine characteristics of inadequately accrued trials to help inform trial prioritization.¹⁰

A second strategy is to open a trial first in a limited number of institutions to assess accrual feasibility. This strategy was used in the Surveillance Therapy Against Radical Treatment (START) trial (National Cancer Institute of Canada Clinical Trials Group [NCIC CTG] PR.11), testing radical prostatectomy or radiotherapy versus active surveillance for favorable-risk prostate cancer.

A third strategy is to stop trials early when it is apparent they will never reach their accrual goals because of inadequate accrual rates. To this end, we developed CTEP early-stopping guidelines¹¹ that apply to slow-accruing phase III Cooperative Group trials activated after April 1, 2004 (trials that have < 20% of their projected accrual rates in quarters 5 and 6 after their activation are closed). (Twenty-six of the 41 trials that had inadequate accrual rates in Table 1 were activated before April 1, 2004.) These guidelines were based on historical data that demonstrated that trials with poor accrual in this time interval would

be extremely unlikely to ever reach their accrual goals.¹² Our experience with the CTEP early-stopping guidelines will be reported when we have further follow-up of the trials activated after April 1, 2004.

A fourth strategy is to simplify the enrollment process and expand patient entry onto trials. To this end, CTEP has developed the Cancer Trials Support Unit (CTSU),¹³ which allows for a larger number of institutions to enter patients into different Cooperative Group trials in an efficient manner. This strategy appears to be successful, because CTEP data (not shown) indicate that cross-Group accrual (enrollments from Groups other than the lead Group) has increased from an average of 20% in the pre-CTSU 1990s to 40% in the post-CTSU 2000s.

A fifth strategy is to simplify the data collection required for patients on trials, which may encourage physicians to participate. CTEP is working with the US Food and Drug Administration to reduce certain types of adverse event reporting, which may help in this regard.¹⁴

Finally, because slow development of a trial concept to a protocol ready for enrollment is associated with its ability to achieve its accrual goal,³ CTEP, working in concert with the Cooperative Groups, developed the Central Institutional Review Board for faster protocol review¹⁵ and has recently instituted new timelines for all phases of trial development.¹⁶ The target timelines to move from a trial concept to a protocol ready for accrual for phase II and III Cooperative Group trials have been reduced to 7 and 10 months, respectively, a > 50% reduction from current timelines. If these target timelines are achieved, then we will be able to determine whether this promising approach is indeed successful in reducing the number of trials that fail to meet their accrual goal.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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