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Journal of Clinical Epidemiology 54 (2001) 877–883

Journal of Clinical Epidemiology

Patterns of patient enrollment in randomized controlled trials

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Received 25 August 2000; received in revised form 27 November 2000; accepted 1 February 2001

Abstract

We aimed to describe enrollment patterns in a large cohort of randomized controlled trials (RCTs) and evaluate whether early recruitment predicts the ability of RCTs to reach their target enrollment. We considered all 77 efficacy RCTs initiated by the AIDS Clinical Trials Group between 1986 and 1996 (28,992 patients enrolled until November 1999). Thirteen RCTs (17%) failed to reach half their target recruitment. Enrollment trajectories showed that the initial rate of accrual determined the subsequent rates of enrollment. The target sample size was attained by 7/8, 11/14, 15/35 and 4/20 of trials with very rapid, rapid, moderate and slow enrollment during the first 3 months, respectively ($P < 0.001$). Enrollment during the first month or two strongly correlated with subsequent accrual ($P < 0.001$). The patient pool, the eligibility criteria, the attractiveness of a trial and adequacy of the network of clinical sites may influence RCT enrollment. Early enrollment offers strong evidence on the feasibility of a trial and is indicative of its future pace of recruitment.

Keywords: HIV; Modeling; Patient enrollment; Randomized controlled trials; Sample size; Study design

1. Introduction

Recruiting an adequate number of patients as determined by sample size calculations is traditionally considered a prerequisite for the successful conduct of randomized controlled trials (RCTs). The recruitment of patients is routinely recorded in all clinical trials and it is thought to be an important indicator of a trial's progress over time [1,2]. However, there is no strong empirical evidence on how the progress of recruitment should be interpreted. Important questions may be posed: Are there specific patterns of patient enrollment? More specifically, is it possible to predict from early recruitment the ability of randomized trials to reach their target enrollment eventually? These issues are particularly important in efficacy trials, which often require large sample sizes.

Insight into these issues may be gained empirically from databases that collect prospectively information about the conduct of several RCTs. In this article we used detailed information from a comprehensive database of clinical trials performed by a large multicenter clinical trials group in human immunodeficiency virus (HIV) infection. The database included information on the enrollment dates of patients and study design factors of registered trials. This allowed assessment of the natural history of patient enrollment in a large number of randomized efficacy trials and the examination of predictors that determine the ability of trials to reach or not reach their target sample size.

2. Material and methods

We used data on the accrual of patients in clinical trials which were initiated by the AIDS Clinical Trials Group (ACTG) between October 10, 1986 and October 10, 1996. All patients enrolled until November 12, 1999 were considered. Studies that were also jointly funded from other organizations such as pharmaceutical companies or the Terry Beirn Community Programs for Clinical Research on AIDS or the Studies from Ocular Complications in AIDS research were excluded whenever the ACTG database included only ACTG-funded patients, unless the ACTG-funded patients were the large majority (accounting alone for more than 80% of the target enrollment). For the main analysis, we considered then only the randomized controlled efficacy trials which had been designated as phase II, II/III, or III by their investigators, as previously described [3]. Observational, nonrandomized, pharmacokinetic and safety phase I and phase I/II studies were excluded as well as substudies of the main protocols. Qualification for inclusion was based on examination of the complete protocols [3].

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0895-4356/01/$ – see front matter
PII: S0895-4356(01)00353-5

ACTG is sponsored by the Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID) and it represents the largest network for the conduct of clinical trials on HIV infection and its complications worldwide. ACTG performs trials both in adults (Adult ACTG) and in children (Pediatric ACTG). It uses the clinical resources of 30 university sites across the United States as well as other collaborative clinical units. Statistical expertise is offered for the design of all protocols through the Center for Biostatistics in AIDS Research (CBAR) at the Harvard School of Public Health, and sample size estimates for target enrollment are obtained for randomized efficacy trials before a trial is launched.

On-study dates were used to calculate the total enrollment duration and the number of patients enrolled over time for each trial. The date of starting enrollment for each trial was defined as the date the first patient entered the study in any of the participating sites.

Descriptive statistics (mean, median, skewness, modes and early peaks) and histograms of the percentage of patients enrolled every month compared to the original target enrollment were used to describe the recruitment characteristics. We arbitrarily divided trials into the following categories based on the percentage of target (the estimated final enrollment anticipated according to the study protocol) attained in the first 3 months: (1) extremely rapid enrollment ($>$ 50% of target sample size enrolled in 3 months); (2) rapid enrollment (25–50% of target sample size enrolled in 3 months); (3) moderate enrollment (5–25% of target sample size enrolled in 3 months) and (4) slow enrollment ($\leq$5% of target sample size enrolled in 3 months). This classification did not take into account the anticipated total duration of enrollment, because this was not clarified in many of the protocols. Using the chi-square test adjusting for trend we evaluated whether these characteristic patterns were related to the ability of the trial to reach its target sample size. We also compared the eventual proportion of target enrollment among the different characteristic patterns (slow, moderate, rapid, very rapid) using Kruskal-Wallis ANOVA. Furthermore, the cumulative proportion of target enrollment (the proportion of cumulative accrual every month compared to the target sample size) was plotted separately for each study.

Non-parametric (Spearman) correlation coefficients were estimated for the relationship between parameters of very early enrollment and the total or total remaining accrual. Total accrual contains also the very early enrollment, while the total remaining accrual excludes the very early enrollment. Thus the correlation between very early enrollment parameters and remaining accrual is more strictly appropriate. We considered the following parameters of very early enrollment: (1) the number of patients accrued the first month; (2) the number of patients accrued the second month; (3) the number of patients accrued the first 2 months; (4) the ratio of patients accrued the second over first month (acceleration of enrollment); (5) the ratio of patients accrued the first month over the target sample size; and (6) the ratio of patients accrued the first 2 months over the target sample size. Subgroup analyses were conducted according to the population (adult or pediatric), the trial domain (complications of HIV, including opportunistic infections and neurologic complications, or antiretroviral therapy) and the masking (double-blind versus single-blind or unmasked). The mean proportion of target achieved was also compared within these subgroups. Statistical analyses were conducted in SPSS 9.0 (SPSS Inc., Chicago, IL). All reported P-values are two-tailed.

3. Results

A total of 324 clinical studies, of which 96 were randomized efficacy trials, were initiated by the ACTG between October 10, 1986 and October 10, 1996. Of those we excluded 33 studies (including 19 randomized efficacy trials), because they had been performed jointly with a significant patient contribution from other trial groups without on-study dates being available on non-ACTG patients. During the 10-year period 77 qualifying randomized efficacy trials started with total enrollment of 28,992 patients until November 12, 1999. Seventy-four RCTs were performed by the ACTG alone, while there was a small contribution of patients from other organizations in three trials. Only one of the 77 trials was still open as of November 12, 1999. This study accrued 56% of its target sample size after 57 months of enrollment and very few patients were being enrolled in the last months.

Considering all 77 efficacy trials, the median enrollment time ranged from 0.5 to 25.5 months and the total duration from 2 to 57 months. Of these trials, 23 were significantly right skewed and 7 were significantly left skewed. The peak monthly enrollment occurred within the first 6 months in 41 of the 77 trials.

In particular, studies with target or actual sample size greater than 500 patients are summarized in Table 1. Most of these trials were significantly right skewed except for ACTG 076 [4], ACTG 081 [5], ACTG 155 [6] and ACTG 185 [7], where significant left skewness was observed. ACTG 076 [4] and ACTG 185 [7] were both studies on maternal–infant HIV-1 transmission and they depended on the availability of new cases of pregnant HIV-infected women. The other two trials with left skewness (one trial on antiretroviral therapy [6] and one on *Pneumocystis carinii* pneumonia prophylaxis [5]) showed some acceleration over time. The distribution of enrollment was unimodal in all but two studies. However, in eight studies, there were also additional peaks in the enrollment which were $\geq$ 90% of the mode monthly enrollment. In most studies, the peak monthly enrollment during the first 6 months was very close, if not identical, to the peak monthly enrollment during the whole trial duration. Few exceptions did occur, primarily in perinatal transmission trials (ACTG 076 and

Table 1
Enrollment parameters in studies with target or actual sample size greater than 500 patients

ACTG Protocol	Actual enrollment *n*	Target enrollment *n*	Mean (SD) (months)	Median (months)	Total duration (months)	Significant skewness	Mode[a] (months)	Peak in the first 6 months (ratio to mode)
002	575	482	5.79 (3.15)	5.7	12	—	6, [5]	6 (1.00)
016	716	538	10.53 (5.90)	10.0	21	—	10, 21, [4]	4 (0.94)
019	3236	3200	11.84 (6.98)	12.2	25	+ (right)	7	5 (0.60)
036	193	538	7.67 (4.00)	7.0	17	+ (right)	6, [5]	6 (1.00)
076	1039	1496	19.29 (8.95)	19.3	35	+ (left)	19, [16,24]	3 (0.57)
081	843	600	7.83 (3.81)	8.0	13	+ (left)	13	5 (0.60)
118	615	660	8.47 (5.45)	7.9	18	—	4, [2]	4 (1.00)
152	839	819	13.57 (6.32)	13.1	25	—	13, [11]	6 (0.69)
155	1001	750	5.60 (1.83)	6.0	8	+ (left)	8	6 (0.48)
175	2495	2100	4.58 (2.04)	4.5	10	+ (right)	5	5 (1.00)
185	1039	1600	25.60 (9.97)	25.5	42	+ (left)	25	4 (0.27)
193	1314	1292	11.66 (8.91)	11.0	29	+ (right)	2	2 (1.00)
196	1216	1100	4.62 (2.32)	4.7	10	—	7	4 (0.73)
204	1227	1200	9.08 (6.26)	8.6	22	+ (right)	2	2 (1.00)
254	383	690	13.96 (12.99)	8.7	57	+ (right)	4	4 (1.00)
261	549	471	6.82 (4.00)	6.4	16	+ (right)	5, [3]	5 (1.00)
277	857	700	3.01 (2.00)	2.6	7	—	1	1 (1.00)
300	649	740	9.61 (6.11)	8.8	24	+ (right)	4, [3]	4 (1.00)
320	1178	1750	3.94 (2.82)	3.1	13	+ (right)	2	2 (1.00)
981	428	500	10.10 (5.93)	9.2	46	+ (right)	5, 7, 13	5 (1.00)

ACTG: AIDS Clinical Trials Group; SD: Standard deviation
[a]Months with enrollment ⩾90% of the enrollment during the mode month are shown in brackets.

ACTG 185) as well as in ACTG 019 [8], ACTG 081 [5] and ACTG 155 [6].

The relationship of the characteristic enrollment patterns with the eventual proportion of target enrollment is shown in Table 2. It is evident that the faster the early enrollment, the more likely were the trials to reach their target sample size ($P < 0.001$). Almost all of the very rapid studies reached their target (88%), except for one (ACTG 333). This study was restricted to patients on the old saquinavir formulation and offered them the option of changing therapy to better, newer drugs. Most patients were accrued in the first 3 months, as patients on the old saquinavir formulation were immediately eager to switch to better options. However, the pool of patients on the old formulation who would switch treatment was probably rapidly depleted. Conversely, only four of 20 (20%) efficacy trials with slow early accrual achieved their target sample size eventually. Among these four studies, two targeted a pediatric population and the other two sought to enroll patients with newly diagnosed opportunistic infections. Of the 20 RCTs with slow early enrollment, 13 (65%) kept recruiting patients for more than a year and 10 (50%) were recruiting for more than 2 years. The mean eventual proportion of target enrollment significantly differed among the characteristic enrollment patterns ($P < 0.001$). On average, studies with rapid or very rapid enrollment eventually reached significantly closer to the target than studies with moderate or slow enrollment (102% or 103% versus 89% or 53%, respectively) (Table 2).

In Figure 1, trajectories of the cumulative proportion of target enrollment are presented. The graphs categorize studies with target sample size < 200 (32 studies), 200–500 (27 studies) and ⩾ 500 (18 studies) to allow a better visualization of trajectories for specific trials. The graphs show that

Table 2
Association of characteristic early enrollment patterns with the eventual proportion of target enrollment

Characteristic early enrollment patterns	Reached target			Proportion of target eventually achieved				
	n/N	(%)	P[a]	Mean	(SD)	Median	(IQR)	P[b]
Slow	4/20	(20.0)	<0.001	0.53	(0.40)	0.64	(0.83)	<0.001
Moderate	15/35	(42.9)		0.89	(0.30)	0.93	(0.37)	
Rapid	11/14	(78.6)		1.02	(0.20)	1.08	(0.22)	
Very rapid	7/8	(87.5)		1.03	(0.18)	1.06	(0.13)	

SD: standard deviation, IQR: interquartile range.
[a]chi-square test adjusting for linear trend.
[b]Kruskall-Wallis test.

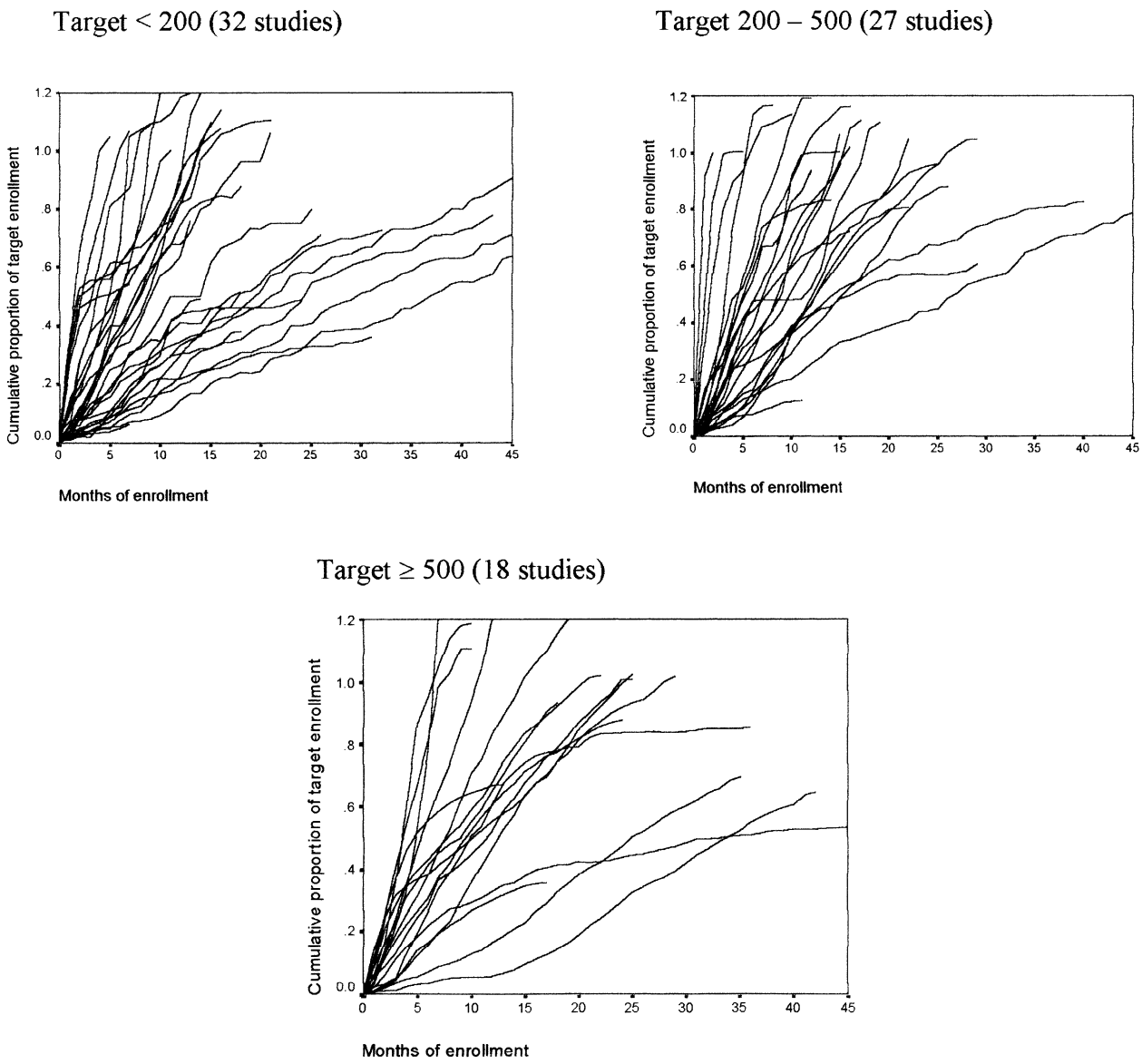

Fig. 1. Trajectories of the cumulative proportion of target enrollment

in most cases the initial rate of enrollment also determined the subsequent pace in each trial. This was true regardless of the absolute number of patients set as the target sample size. All studies that had recruited < 30% of their target sample size after 10 months failed to reach this target eventually. No studies showed marked acceleration of accrual over time. Overall, there were 48 (62%) studies that accomplished ⩾ 80% of the target enrollment and 16 (21%) studies reached between 50% and 80% of the target.

Thirteen trials failed to reach even half the target sample size during their conduct. Although, several reasons may have contributed to the relative recruitment failure of each of these trials, the key reasons were the following: five trials studied syndromes that might have been relatively uncommon to find enough patients to enroll (including toxoplasmosis, neurosyphilis, peripheral neuropathy, AIDS dementia complex [two trials]); three trials set eligibility criteria that might have been too limiting given the requested sample size (*P. carinii* pneumonia refractory to standard treatment; history of hemophilia; children with mild to moderate symptoms only); one trial used tight eligibility criteria and was also limited to patients who had previously participated in a specific prior protocol (roll-over); one trial was interrupted early due to evidence suggesting increased mortality from the tested intervention; and for three trials the tested regimens were probably soon considered rather outdated given the rapid evolution in antiretroviral therapeutics.

Table 3 shows the correlation between very early and late enrollment parameters. Enrollment during the first month or two strongly correlated with the ability of a trial to accrue patients eventually and reach its target enrollment. The acceleration of enrollment in the first 2 months (the ra-

Table 3
Spearman correlations between very early and late enrollment

	Total accrual		Total remaining accrual	
Very early accrual parameters	Absolute enrollment	Proportion of target enrollment	Absolute enrollment	Proportion of remaining target enrollment
1st month accrual	0.601[a]	0.471[a]	0.536[a]	0.460[a]
2nd month accrual	0.751[a]	0.516[a]	0.600[a]	0.503[a]
1st + 2nd month accrual	0.699[a]	0.526[a]	0.533[a]	0.508[a]
2nd/1st month accrual	0.507[a]	0.265[b]	0.513[a]	0.259[b]
1st/target accrual	−0.040	0.374[b]	−0.107	0.360[b]
1st + 2nd/target accrual	0.152	0.517[a]	−0.007	0.503[a]

[a] $P < 0.001$.
[b] $0.001 \leq P < 0.05$.

tio of second to first month accrual) was also related significantly to the eventual accrual. The more patients enrolled the first 2 months, the greater the absolute enrollment and the proportion of target enrollment eventually achieved.

Looking at the proportion of remaining total enrollment separately in pediatric and adult studies, it is evident that the correlation coefficients with early enrollment parameters tended to be smaller in the pediatric trials (Table 4). The relationship between very early and subsequent enrollment did not differ substantially by trial domain or masking. The mean proportion of target achieved did not differ significantly by age of population ($P = 0.91$), trial domain ($P = 0.12$) or masking ($P = 0.54$).

4. Discussion

This analysis shows that there is a strong relationship between patient enrollment during the first 2 months and the eventual ability of a trial to attain its target sample size. The initial rate of enrollment seemed to determine the subsequent rates of patient recruitment. Inability to reach even half of the target enrollment is not uncommon in RCTs and it may occur in one of six efficacy trials conducted by a very experienced, large trialist group. The data from these HIV trials suggest that the feasibility or futility of a clinical trial project can be gleaned from the early enrollment patterns to a considerable extent.

Enrollment rates in RCTs are determined probably by a cluster of several factors. First, some trials aim to enroll from a prevalent pool of patients, while others have to wait for new incident-eligible cases to accrue. In the presence of a large prevalent pool of patients, enrollment may be rapid. On the other hand, if the patient pool is incident, the enrollment is usually protracted, because new eligible cases have to be identified during the trial conduct. This is the case in perinatal studies where the accrual is dependent on availability of new, incident cases of pregnant HIV-infected women and not on the availability of an existing prevalent pool of patients.

Second, the size of the prevalent patient pool largely depends on how strict eligibility criteria are. For example, ACTG 036 [9] tried to enroll exclusively hemophiliacs and was unable to reach its target sample size. Restrictive entry criteria may hinder the conduct of an RCT. Entry criteria should be realistically selected and should be based on sound clinical judgement, but trialists should avoid being very restrictive.

Third, a critical factor is the attractiveness of the protocol under the circumstances when the study is launched. Patients may be most eager to participate in studies of very promising regimens. The availability of drugs only through clinical research before licensing may further contribute to the popularity of a trial, especially when alternative effective therapies are not available. During the trial's conduct,

Table 4
Spearman correlations of parameters of early accrual with the proportion of remaining target enrollment in various subgroups

Very early accrual parameters	Pediatric $n = 16$	Adult $n = 61$	Complications of HIV $n = 39$	Antiretroviral therapy $n = 38$	Double-blind $n = 48$	Single-blind or unmasked $n = 29$
1st month accrual	0.091	0.539[a]	0.623[a]	0.178	0.384[b]	0.531[b]
2nd month accrual	0.103	0.576[a]	0.454[b]	0.328[b]	0.384[b]	0.689[a]
1st+2nd month accrual	0.155	0.571[a]	0.582[a]	0.276	0.431[b]	0.578[b]
2nd/1st month accrual	0.169	0.274[b]	0.113	0.400[b]	0.166	0.425[b]
1st month/target accrual	0.275	0.410[b]	0.515[b]	0.127	0.339[b]	0.373[b]
1st+2nd month/target accrual	0.418	0.538[a]	0.627[a]	0.266	0.485[a]	0.543[b]

HIV: human immunodefeciency virus
[a] $P < 0.001$.
[b] $0.001 \leq P < 0.05$.

changes in attitude may occur due to external evidence, such as results from another trial, or advances in the development of alternative treatments. This is especially important in rapidly changing fields such as HIV infection. Changing attitudes may affect the popularity of a trial during its conduct. Changes in enrollment may also result from the licensing of hitherto experimental drugs.

Finally, if the network of trialists is not of adequate size, the limited cumulative patient pool can result in problematic enrollment. Usually this is not an issue for large-scale collaborations such as the ACTG, but it may be an issue in single-center trials or trials conducted by smaller networks. Patient availability may become a problem even for large collaborations when the targeted disease or population is rare or uncommon. This was a common issue among trials that were unable to reach half of their target sample size in our series.

The strong association between early and subsequent enrollment that we observed can help in the assessment of a trial's conduct. Strong hints can be obtained as early as the first 2 months. If early enrollment lags seriously behind the expected, recruitment is unlikely to become satisfactory later. Early enrollment may also offer realistic estimates of how long it would take to complete enrollment and whether the target is likely to be reached. Such information would be important in steering the trial. Most of the trials that were characterized as having rapid or very rapid enrollment reached their target sample size. In a few cases early rapid enrollment rates decelerated somewhat over time, but hardly ever was there a trial of slow early enrollment that subsequently accelerated. It is conceivable that exceptions to this rule may occur in other fields of research, beyond HIV infection, especially if there is less time pressure to obtain results and a less rapidly changing therapeutic environment. However, with the currently limited resources, it is likely that slow-starting trials will become increasingly difficult to bring to eventual fruition.

Most of the trials that had slow early enrollment did not reach their target sample size (80%) and more than one-half of them lasted longer than a year and some even several years. One may raise concerns about futility: Is it legitimate to continue a trial when its enrollment pattern predicts it will most likely be unable to reach its target, especially if resources for clinical research are limited [10–13]? Considerations of futility may differ in various RCT settings [14]. In some cases, investigators may expect that even an underpowered trial may offer some useful, even if not conclusive, information. Incomplete information from several small trials may subsequently be subjected to meta-analysis and the pooled results may become decisive [15,16]. In other cases, especially when early enrollment lags seriously behind the expected, early termination due to futility should be seriously considered. Alternatively, one may consider making extensive changes to a protocol, such as relieving restrictions to eligibility criteria. Such changes are often made in HIV-related trials. However, our data suggest that impressive accelerations of enrollment are unlikely to be achieved. Early enrollment data can give strong evidence on the feasibility of an RCT and may help the steering committee glean the eventual fate of a trial.

We found no evidence that the age of the patient population, the trial domain or masking affected the final ability of a trial to accrue its target. There is concern that double-blind placebo controlled studies may be less attractive [17] to patients' participation, but empirical evidence from our database suggests that overall double-masked studies reached as much of their target as unmasked ones.

One disadvantage of our study is that it was limited only to the field of HIV with its own peculiarities of rapidly expanding therapeutics and changes in the course of the epidemic which may affect the available patient pools over time and their heterogeneity [18,19]. It is unknown whether in other diseases with steadier prevalent patient pools, the enrollment patterns may be even more predictable and early enrollment may be even more decisive for the fate of a trial. Although ACTG represents the largest multicenter clinical trials group in the HIV field and it may be difficult to assemble a similar amount of data in other domains, cross-trial analyses of enrollment in other multicenter trial groups should be encouraged. Additionally, further analyses in non-randomized observational prospective studies could complement our insight of enrollment patterns and their significance in other types of prospective research designs.

Acknowledgments

We are grateful to Annice Bergeris for input in data management and to Dr. Robert Schooley and the ACTG leadership for allowing the use of the ACTG database and for helpful comments. Ms. Haidich was supported in part by the General Secretariat for Research and Technology, Greece (grant PENED 99ED27-974).

References

[1] Pocock SJ. Clinical trials: a practical approach. Chichester: John Wiley, 1983.
[2] Piantadosi S. Clinical trials: a methodologic perspective. New York: John Wiley, 1997.
[3] Ioannidis JPA. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998;279:281–6.
[4] Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173–80.
[5] Bozzette SA, Finkelstein DM, Spector SA, Frame P, Powderly WG, He W, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. N Engl J Med 1995;332:693–9.
[6] Kahn JO, Lagakos SW, Richman DD, Cross A, Pettinelli C, Liou S-H, et al. A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. N Engl J Med 1992;327:581–7.
[7] Stiehm ER, Lambert JS, Mofenson LM, Bethel J, Whitehouse J, Nu-

gent R, et al. Efficacy of zidovudine and human immunodeficiency virus (HIV) hyperimmune immunoglobulin for reducing perinatal HIV transmission from HIV-infected women with advanced disease: results of Pediatric AIDS Clinical Trials Group protocol 185. J Infect Dis 1999;179:567–75.

[8] Vorberding PA, Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med 1990;322:941–9.

[9] Merigan TC, Amato DA, Balsley J, Power M, Price WA, Benoit S, et al. Placebo-controlled trial to evaluate zidovudine in treatment of human immunodeficiency virus infection in asymptomatic patients with hemophilia. Blood 1991;78:900–6.

[10] Ware JH, Muller JE, Braunwald E. The futility index. An approach to the cost-effective termination of randomized clinical trials. Am J Med 1985;78:635–43.

[11] Detsky AS. Using economic analysis to determine the resource consequences of choices made in planning clinical trials. J Chronic Dis 1985;38:753–65.

[12] Detsky AS. Are clinical trials a cost-effective investment? JAMA 1989;262:1795–800.

[13] Detsky AS. Using cost-effectiveness analysis to improve the efficiency of allocating funds to clinical trials. Stat Med 1990;9:173–84.

[14] Pocock SJ. When to stop a clinical trial. BMJ 1992;305:235–40.

[15] Chalmers TC, Lau J. Changes in clinical trials mandated by the advent of meta-analysis. Stat Med 1996;15:1263–8.

[16] Lau J, Chalmers TC. The rational use of therapeutic drugs in the 21st century. Important lessons from cumulative meta-analyses of randomized control trials. Int J Technol Assess Health Care 1995;11: 509–22.

[17] Welton AJ, Vickers MR, Cooper JA, Meade TW, Marteau TM. Is recruitment difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. BMJ 1999;318: 1114–7.

[18] Ioannidis JP, Cappelleri JC, Schmid CH, Lau J. Impact of epidemic and individual heterogeneity on the population distribution of disease progression rates: an example from patient populations in trials of human immunodeficiency virus infection. Am J Epidemiol 1996;144: 1074–85.

[19] Ioannidis JP, Lau J. Heterogeneity of the baseline risk within patient populations of clinical trials: a proposed evaluation algorithm. Am J Epidemiol 1998;148:1117–26.