Published OnlineFirst March 8, 2017; DOI: 10.1158/1078-0432.CCR-16-2439

Cancer Therapy: Clinical

Clinical Cancer Research

Clinical Trial Characteristics and Barriers to Participant Accrual: The MD Anderson Cancer Center Experience over 30 years, a Historical Foundation for Trial Improvement

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Abstract

Purpose: Slow-accruing clinical trials delay the translation of basic biomedical research, contribute to increasing health care costs, and may prohibit trials from reaching their original goals.

Experimental Design: We analyzed a prospectively maintained institutional database that tracks all clinical studies at the MD Anderson Cancer Center (Houston, TX). Inclusion criteria were activated phase I–III trials, maximum projected accrual ≥10 participants, and activation prior to March 25, 2011. The primary outcome was slow accrual, defined as <2 participants per year. Correlations of trial characteristics with slow accrual were assessed with logistic regression.

Results: A total of 4,269 clinical trials met inclusion criteria. Trials were activated between January 5, 1981, and March 25, 2011, with a total of 145,214 participants enrolled. Median total enrolment was 16 [interquartile range (IQR), 5–34], with an average enrolment rate of 8.7 participants per year (IQR, 3.3–17.7). There were 755 (18%) trials classified as slow accruing. On multivariable analysis, slow accrual exhibited robust associations with national cooperative group trials (OR = 4.16, $P < 0.0001$ vs. industry sponsored), time from trial activation to first enrolment (OR = 1.13 per month, $P < 0.0001$), and maximum targeted accrual (OR = 0.16 per log10 increase, $P < 0.0001$). Recursive partitioning analysis identified trials requiring more than 70 days (2.3 months) between activation and first participant enrolment as having higher odds of slow accrual (23% vs. 5%, OR = 5.56, $P < 0.0001$).

Conclusions: We identified factors associated with slow trial accrual. Given the lack of data on clinical trials at the institutional level, these data will help build a foundation from which targeted initiatives may be developed to improve the clinical trial enterprise. *Clin Cancer Res; 23(6); 1414–21. ©2017 AACR.*

Introduction

The cancer clinical trial enterprise is increasingly challenged by constrained financial resources, extensive regulatory requirements, protracted drug approval times, and mismatches between available participants and trials (1–3). The past decades have produced an exponential increase in the understanding of cancer biology and a concurrent outcry over rising health care costs and the prolonged times required to translate bench discovery to clinic (4–6). A significant hurdle in advancing the translation of cancer discoveries is slow trial accrual, which may lead to premature trial closures, overutilization of scarce clinical resources, and loss of relevance of the original research question(s) (1, 4, 7–10). A recent article by Stensland and colleagues identified the most frequent reason for a clinical trial to be classified as "failed to complete" was poor patient accrual (11). The need for efficient clinical investigation is illustrated by reports that only a small percentage of major clinical guidelines are supported by prospective evidence (12, 13).

Despite the need to enhance cancer clinical trial development, few studies have identified predictors of slow trial accrual and even fewer still have focused on institutional level analyses. Analyses of accrual to the NCI cooperative group and Cancer Therapy Evaluation Program (CTEP) studies have identified long trial concept review times (median, 1.5–2.5 years) and a high frequency of poor accrual (up to 71%; refs. 7–9, 14). In 2008, the Operational Efficiency Working Group was commissioned to develop guidelines for the NCI trial development processes (14). Despite these efforts on the national level, few data and no guidelines exist at the institutional level.

The goal of this study was to collect enrolment and trial characteristics from phase I–III clinical trials activated in a

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-16-2439

Published OnlineFirst March 8, 2017; DOI: 10.1158/1078-0432.CCR-16-2439

Translational Relevance

Limited resources mandate the careful allocation of assets for clinical research. Given the exponential rise in biomedical discovery, there is an urgent need to streamline the clinical trial process. We analyze a prospectively collected clinical study registry at MD Anderson Cancer Center (Houston, TX) and present our clinical trial experience over a 30-year period. Furthermore, we conduct a detailed analysis of factors that influence slow participant accrual, identifying factors including trial sponsorship and longer development times to be associated with slow accrual. We believe that trends and shortcomings identified in this analysis are applicable to the broader oncologic community. Finally, we present recent institutional initiatives designed to mitigate the factors identified in this analysis.

major academic cancer center and to assess factors associated with slow accrual. On the basis of these results, our institution has initiated clinical research initiatives designed to address identified deficits.

Materials and Methods

The Clinical Oncology Research (CORe) database is a prospectively maintained institutional registry of all clinical studies proposed and conducted at MD Anderson Cancer Center (Houston, TX). Since 1984, all clinical research studies are required to be registered in CORe and longitudinally tracked for milestones of regulatory reviews, approval, participant accrual, and study closure/termination. As of March 25, 2015, a total of 17,632 registered clinical research studies were identified within CORe. Studies were removed because they were non–phase I–III trials, had missing key information, low (<10 participants) or missing information on maximum projected accrual. Clinical trials included in the primary analysis were activated between January 5, 1981, and March 25, 2011, to ensure adequate (at least 3 years) trial follow-up time ($N = 4{,}269$, combined enrolment 145,214). For a sensitivity analysis, we include trials activated up to December 31, 2014 ($n = 5{,}021$; Supplementary Fig. S1). This study was reviewed and deemed Institutional Review Board (IRB) exempt.

Statistical analysis

Achievement of slow accrual was analyzed as the primary outcome. Slow-accruing trials were those that enrolled fewer than 2 participants per year. Univariate and multivariable logistic regressions were utilized. Variables with $P < 0.05$ on univariate analysis were initially entered into a multivariable model and retained only if $P < 0.05$ in the final model after backward elimination. $P < 0.05$ was considered significant. All analysis was conducted with SAS V. 9.4 and JMP Pro V. 11 (both SAS institute Inc.).

Results

Trial characteristics

Trial characteristics are presented in Table 1 as defined by the study investigation team. The median total accrual was 16 participants [interquartile range (IQR), 5–34] with a median accrual rate of 8.7 participants per year (IQR, 3.3–17.7). Among all trials, 755 (18%) accrued fewer than 2 participants per year, including 394 (9%) that accrued 0 participants.

Table 1. Clinical trial characteristics for the primary cohort ($N = 4{,}269$)

Characteristics	All protocols; $N = 4{,}269$	Slow accruing (<2 participants/year); $n = 755$	Not slow accruing (≥2 participants/year); $n = 3{,}514$
Trial source[a]			
Externally peer reviewed	388 (10%)	41 (6%)	347 (11%)
Industry	2,017 (52%)	288 (43%)	1,729 (54%)
Institutional	1,106 (29%)	168 (25%)	938 (29%)
National cooperative group	368 (9%)	178 (26%)	190 (6%)
Trial phase designation			
Phase I	903 (21%)	120 (16%)	783 (22%)
Phase I–II	434 (10%)	46 (6%)	388 (11%)
Phase II	2,040 (48%)	331 (44%)	1,709 (49%)
Phase II–III	46 (1%)	11 (1%)	35 (1%)
Phase III	846 (20%)	247 (33%)	599 (17%)
Trial timing [median time (mo), IQR]			
CORe registration to activation	4.8 (3.1–8.0)	5.2 (3.2–9.0)	4.8 (3.1–7.8)
CORe registration to IRB approval	1.3 (1.0–1.9)	1.4 (1.0–2.3)	1.3 (1.0–1.9)
IRB approval to activation	3.1 (1.5–5.8)	3.2 (1.5–6.2)	3.0 (1.5–5.8)
Activation to first participant[b]	0.8 (0.2–2.1)	3.0 (0.9–7.2)	0.7 (0.2–1.8)
First participant to final "CNPE"[b,c]	23.2 (14.0–37.5)	26.2 (15.6–43.3)	21.0 (11.0–41.0)
Patient enrolment (median, IQR)			
Maximum anticipated accrual	40 (25–75)	30 (15–60)	41 (30–75)
Total participants enrolled per trial[c]	16 (5–34)	0 (0–2)	22 (12–44)
Total participants enrolled all trials	145,214	1,285	143,929
Enrolment rate (participants/year)	8.7 (3.3–17.7)	0 (0–1.2)	11.3 (6.1–20.3)

Abbreviation: CNPE, closed to new patient enrolment.

[a]As defined by study investigator team; externally peer reviewed are those funded from external nonindustry or federal sources (e.g., NIH, Department of Defense, NCI, and CTEP); 390 trials missing study trial source information.

[b]Includes only trials that accrued at least one participant. In the absence of a date for CNPE, the study termination date was used instead.

[c]Includes only trials achieving final termination ($n = 3{,}735$).

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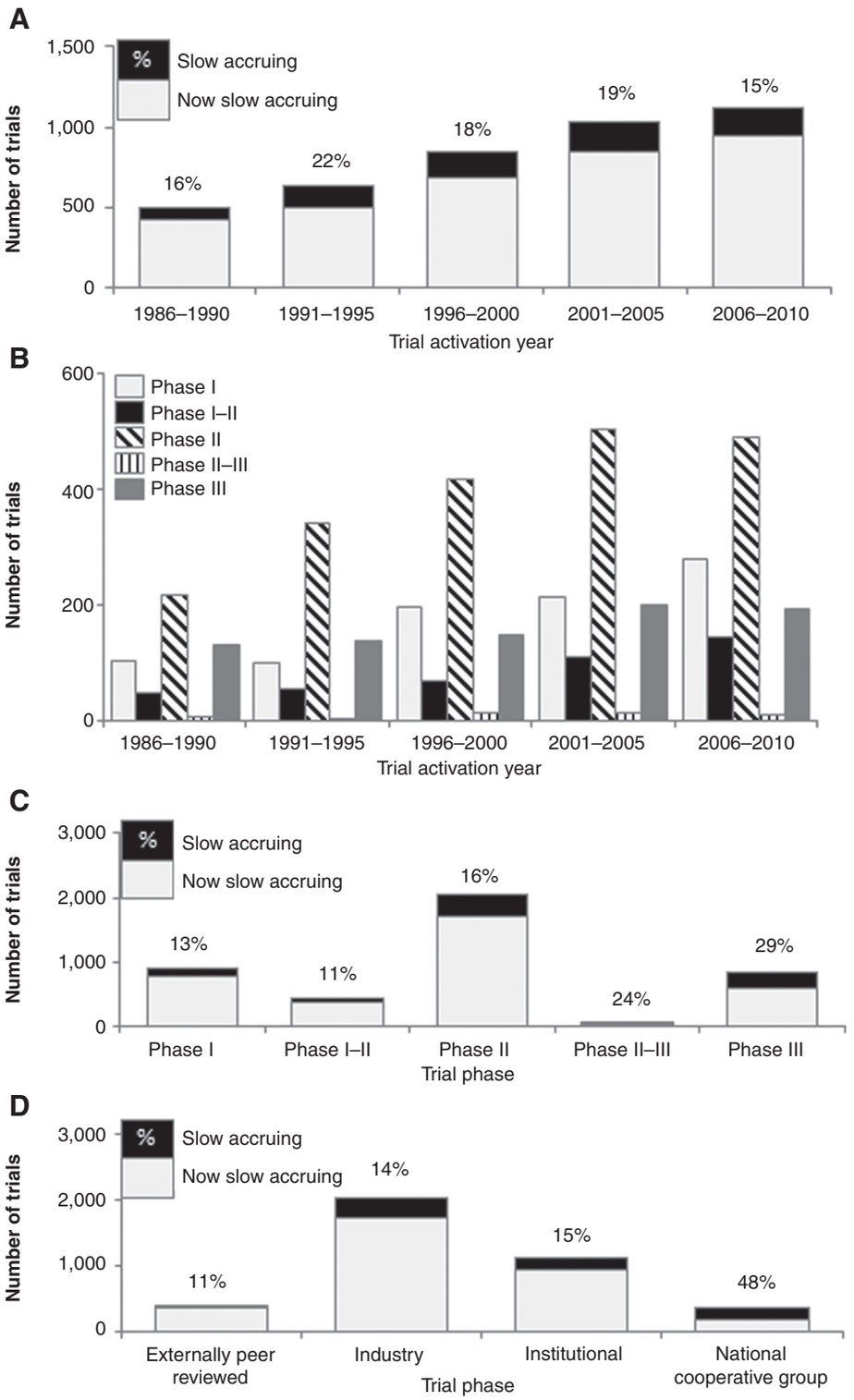

Figure 1.
Frequency distribution of total trials and slow-accruing trials (fewer than 2 participants per year). **A,** Trial activation over time with the proportion of slow-accruing trials displayed. **B,** Frequency of total trials by phase and trial activation year. **C,** Slow-accruing trials by trial phase. **D,** Slow-accruing trials by source of trial support.

Trial activation year

The number of activated trials was observed to increase over time (Fig. 1A). This increase in the number of activated trials was generally reflected in all trial phases (Fig. 1B). The proportion of slow-accruing trials generally decreased over time (OR = 0.95, $P = 0.04$ per every 5 years; Table 2; Fig. 1A). However, the magnitude of this association was relatively weak, with variations in the frequency of slow-accruing trials across time periods:

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Table 2. Univariate and multivariable logistic regression for a slow-accruing trial (less than 2 patients/year) for the primary cohort ($N = 4,269$)

	Univariate analysis		Multivariable analysis	
Characteristics	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Trial activation year (per 5 years)	0.95 (0.90–1.00)	0.04	NI	
Trial activated 2000 or later (vs. prior to 2000)	0.83 (0.71–0.98)	0.02	NI	
Max anticipated accrual (per log10)	0.48 (0.38–0.59)	<0.0001	0.19 (0.13–0.27)	<0.0001
Trial phase[a]				
Phase I	1 (reference)		1 (reference)	
Phase I–II	0.77 (0.54–1.11)	0.16	0.98 (0.58–1.67)	0.95
Phase II	1.26 (1.01–1.58)	0.04	1.40 (0.99–1.98)	0.06
Phase II–III	2.05 (1.01–4.15)	0.05	3.10 (1.18–8.12)	0.02
Phase III	2.69 (2.11–3.43)	<0.0001	1.98 (1.31–2.98)	0.001
Trial source[a]				
Industry	1 (reference)		1 (reference)	
Externally peer reviewed	0.71 (0.50–1.00)	0.046	0.72 (0.43–1.22)	0.22
Institutional	1.08 (0.88–1.32)	0.49	1.30 (0.96–1.75)	0.09
National cooperative group	5.63 (4.43–7.15)	<0.0001	4.59 (3.22–6.54)	<0.0001
Trial timing (per month)				
CORe registration to IRB approval	1.11 (1.05–1.17)	0.0004	NI	
IRB approval to study activation	1.01 (1.00–1.02)	0.13	NI	
Activation to first patient	1.09 (1.07–1.11)	<0.0001	1.08 (1.06–1.10)	<0.0001
Total number of trials within a clinical department during the study period (department total trial activation)[a]				
High (251+ trials)	1 (reference)		1 (reference)	
Moderate (80–250 trials)	2.73 (2.28–3.27)	<0.0001	1.32 (1.00–1.73)	0.048
Low (1–79 trials)	2.49 (1.96–3.17)	<0.0001	1.42 (0.97–2.08)	0.07
Number of trials activated within the same year in a clinical department (department annual trial activation rate)[a]				
High (17+ trials in a year)	1 (reference)		NI	
Moderate (7–16 trials in a year)	2.25 (1.77–2.86)	<0.0001	NI	
Low (0–6 trials in a year)	1.62 (1.29–2.04)	<0.0001	NI	

Abbreviations: 95% CI, 95% confidence interval; NI, not included.

[a]Included into the multivariable analysis if the variable as an overall class met a significance threshold of $P < 0.05$.

1986–1990 (16%), 1991–1996 (22%), 1996–2000 (18%), 2001–2005 (19%), and 2006–2010 (15%; Fig. 1A).

Trial phases and sources

The highest frequencies of slow-accruing trials were in phase III (29%) and II–III (24%) trials, whereas the lowest frequencies were among phase I (13%) and I–II (11%) trials (Fig. 1C). When compared with phase I trials, both phase II (OR = 1.26, $P = 0.04$ vs. phase I), II–III (OR = 2.05, $P = 0.05$), and III (OR = 2.69, $P < 0.0001$) trials exhibited a significantly higher odds of slow accrual on univariate analysis. On multivariable analysis, a significant association was observed for phase II–III (OR = 3.10, $P = 0.02$) and III (OR = 1.98, $P = 0.001$) with slow accrual (Table 2).

Among trial sources, the highest frequency of slow accrual was observed among national cooperative group trials (48%), whereas the lowest frequency was among externally peer-reviewed trials (11%). Trials designated as externally peer reviewed are those funded from external nonindustry or federal sources [e.g., NIH (Bethesda, MD), NCI (Rockville, MD), and CTEP]. National cooperative group trials (OR = 5.63, $P < 0.0001$ vs. industry) were significantly associated with slow accrual, whereas externally peer-reviewed trials (OR = 0.71, $P = 0.046$) were inversely associated with slow accrual. On multivariable analysis, only national cooperative group trials maintained significance (OR = 4.59, $P < 0.0001$; Table 2).

Timelines for trial activation and early participant enrolment

After a protocol has been written, the regulatory and scientific review and approval process is initiated by protocol submission for review and approval sequentially by a Clinical Research Committee, followed by the IRB (Fig. 2A). The median time from protocol submission to IRB approval was 1.3 months (IQR, 1.0–1.9) and from IRB approval to study activation was 3.1 months (IQR, 1.5–5.8). The median time from study activation to first participant enrolled was 0.8 months (IQR, 0.2–2.1; Table 1). Slow-accruing trials exhibited longer times from study registration in CORe to activation (median, 5.2 vs. 4.8 months; $P = 0.006$), study activation to first participant enrolment (median, 3.0 vs. 0.7 months; $P < 0.0001$), and first participant registration to final closure to new participant entry (median, 26.2 vs. 21.0 months, $P = 0.005$; Fig. 2B–D).

Time between protocol submission to IRB approval (OR = 1.11 per month, $P = 0.0004$) and between study activation and first participant enrolment (OR = 1.09, $P < 0.0001$) was significantly associated with slow accrual (Table 2), whereas the time between IRB approval and study activation was not ($P = 0.13$). On multivariable analysis, only longer time between study activation and first participant enrolment was significantly associated with slow accrual (OR = 1.08, $P < 0.0001$). A recursive partitioning analysis determined 70 days (2.3 months) to be an optimal cut-off point for first patient accrual (OR = 5.56, $P < 0.0001$). Trials with first patient enrolled beyond 70 days were significantly associated with slow accrual.

Department-specific trial activity

To assess differences in accrual rates across clinical departments, we stratified on the basis of the total number of trials activated within a department. A total of 59 departments had activated trials during the study period, with a median of 19 trials (range, 1–646) per department. Examination of the distribution of trial activation identified three groupings: low (1–79 trials, 43 departments), moderate (80–250 trials, 10 departments), and

Published OnlineFirst March 8, 2017; DOI: 10.1158/1078-0432.CCR-16-2439

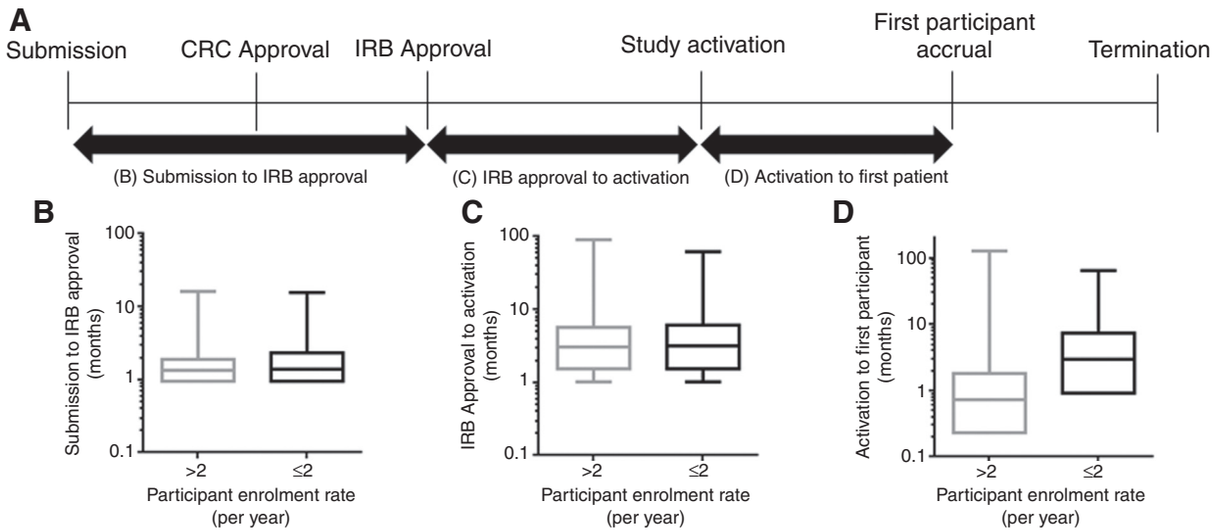

Figure 2.

A, Schematic of the trial approval process at MD Anderson Cancer Center. CRC, Clinical Research Committee. **B–D,** Time from protocol submission to IRB approval (**B**), time from IRB approval to study activation (**C**), and time from trial activation to first participant enrolled stratified by participant enrolment rate (**D**).

high (>250 trials, 6 departments) total trial activations. Trials from departments with moderate or low total trial activations had significantly higher odds of slow accrual rates compared with trials from departments with high total trial activations (OR = 2.73, $P < 0.0001$; and OR = 2.49, $P < 0.0001$, respectively; Table 2; Fig. 3A).

As total department trial activation is a function of the yearly rate of trial activation and number of years that department has been active, we assessed the impact of annual trial activation rates. For each trial, we calculated the total number of additional trials activated within the same department in the same year. The median annual activation rate was 3 additional trials per year (range, 1–60). Analyzing by tertiles revealed that trials in departments with moderate (second tertile: 7–16 trials/year; OR = 2.25, $P < 0.0001$ vs. third tertile) or low (first tertile: 0–6 trials/year, OR = 1.62, $P < 0.0001$ vs. third tertile) annual activation rates exhibited a significantly higher odds of being slow accruing compared with trials in departments with high total annual activation rates (third tertile: >16 trials/year). Significance was not maintained on multivariable analysis (all $P > 0.05$; Table 2; Fig. 3B).

Over the course of the analysis, 616 principle investigators activated clinical trials (median of 3 trials per investigator). We stratified trials by the number of total trials opened by that principle investigator as follows: high volume (activated >3 clinical trials; $n = 278$), moderate volume (activated 2–3 clinical trials; $n = 139$), and low volume (activated 1 clinical trial; $n = 199$). This analysis identified lower accrual rates among low-volume principle investigators (median accrual: high-volume, 8.8 participants/year; moderate volume, 8.0; and low volume, 6.9; ANOVA $P = 0.002$). In a subset of trials with available data ($n = 630$), the association of Investigational New

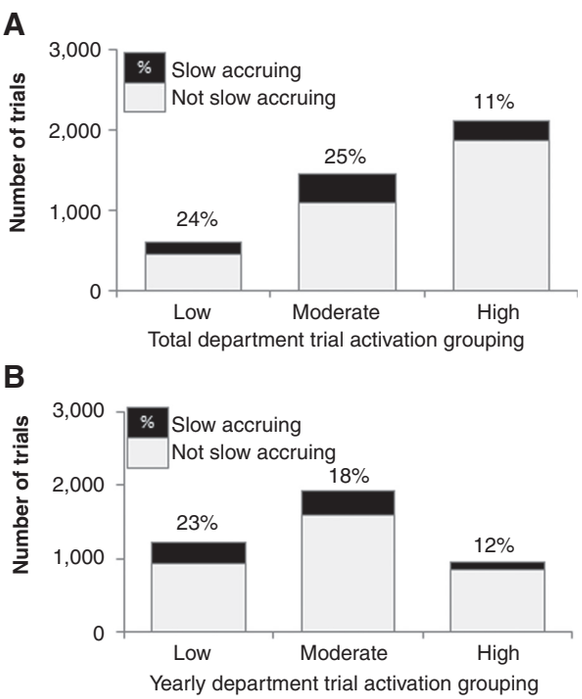

Figure 3.

A and **B,** Frequency of slow-accruing trials (fewer than 2 participants per year) with respect to the total number of trials activated in that department (**A**) or number of trials activated within the same year in the same department (**B**). Proportion of slow-accruing trials is shown at the top of each bar.

Published OnlineFirst March 8, 2017; DOI: 10.1158/1078-0432.CCR-16-2439

Drug (IND) status with accrual rate was analyzed. This analysis revealed similar accrual rates in trials in which IND status was exempt versus nonexempt (median accrual rate: 12.2 vs. 12.1 participants/year; $P = 0.46$).

Sensitivity analysis: slow trial accrual

We conducted a sensitivity analysis defining slow trial accrual at <6 participants (38% of total trials) per year (Supplementary Table S1); univariate and multivariable analyses revealed similar results to those observed with the prior multivariable analysis (Table 2). When analyzing with a cut-off point of <6 participants per year, recursive partitioning analysis identified an optimal cut-off point for time to first participant enrolment to be 60 days (OR = 4.29, $P < 0.0001$). Similarly, modifying trial inclusion criteria to include trials activated up to December 31, 2014 ($n = 5{,}021$; Supplementary Table S2), revealed similar results. Of 809 trials activated between 2011 and 2014, 86 (11%) were slow accruing, which was lower than the 18% rate of slow-accruing trials observed among trials activated between 1981 and 2011.

Trial publications as a surrogate measure of trial success

We assessed the association of accrual rates with frequency of produced peer-reviewed publications, as both metrics may be viewed as indicators of trial "success." Peer-reviewed publications resulting from a subset of 100 randomly selected protocols that accrued fewer than 2 participants per year as well as a set of 100 protocols that accrued at least 2 participants per year, matched by trial source, phase, year of activation, and maximum accrual size, were identified via searches in PubMed and Google Scholar using the related ClinicalTrials.gov number (when available), trial title, and names of principal investigators. Among slow-accruing trials, 14 (14%) produced at least one publication (range, 1–3), with a total of 18 publications. In contrast, among trials accruing at least 2 participants per year, 69 (69%) produced at least one associated publication (range, 1–16), with a total of 147 publications.

Institutional initiatives to improve trial accrual

As noted in our analysis, national cooperative group trials are associated with slow participant accrual, a finding noted in other analyses (15). We speculate that the lack of incentives for local investigators may have contributed to slow accrual, as authorship on the resulting article is often not guaranteed, and capitated funding rarely supports the total trial costs. To enhance accrual, MD Anderson Cancer Center has provided subsidized funding for these trials since 2010, providing an additional $2,000 per participant toward support of clinical research personnel within the enrolling department. To evaluate the impact of this program, a preliminary analysis noted a decrease in slow-accruing trials after 2010 (Supplementary Fig. S2).

In addition to supplementary funding for national cooperative group trials, other institutional funding sources have been created to defray trial costs. Since 2013, underfunded novel, IRB-approved, investigator-initiated trials may apply to the High-Impact Clinical Research Support Program (HI-CRSP) program, which funds 3 to 5 applications per year for up to $100,000 per year for 1 to 2 years. Twelve HI-CRSP trials have enrolled patients after obtaining this funding, of which only 1 trial (8%) exhibited an accrual rate of fewer than 2 participants per year.

Finally, since 1999, MD Anderson Cancer Center has conducted a semiannual institutional review by the electronic Protocol Accrual Auditing Committee (ePAAC) to flag protocols meeting the following criteria: has previously enrolled participants but accrued fewer than 3 during the past 6 months, IRB approval for at least 6 months but not yet activated, and activation for at least 6 months with zero participants accrued. Flagged trials are reviewed, and the investigators are required to provide efforts for increasing accrual. Upon two or more reviews, if the trial is judged unlikely to meet accrual goals by the committee, these trials are closed. From 2007 to 2014, 6,562 clinical studies have been reviewed by ePAAC, resulting in 939 studies (14%) temporarily or permanently closed.

Discussion

This study provides an overview of phase I–III clinical trial characteristics and an analysis of the predictors of slow trial accrual at a large tertiary cancer center. We believe that this analysis is representative of national trends and provides insight into the clinical trial enrolment given the concordance with similar analyses (16–18). It should be emphasized that trials activated after 2011 were not analyzed in the primary analysis. However, a sensitivity analysis was performed extending to the trials enrolled until 2014. Nevertheless, the presented data may not reflect the full spectrum of most contemporary trials.

We found that the majority of protocols conducted at MD Anderson Cancer Center were phase II (48%) and industry sponsored (52%), similar to other tertiary cancer referral centers. An analysis of 83 lung cancer trials from Washington University School of Medicine (WUSM, St. Louis. MO) and 218 oncology trials from Vanderbilt-Ingram Cancer Center (VICC; Nashville, TN) and its affiliated network sites (VICC/VICCAN) also identified the majority of trials to be phase II (WUSM, 72%; VICC/VICCAN, 43%) and industry sponsored (WUSM, 53%; VICC/VICCAN, 62%; refs. 16, 17). In addition, our study identified a median accrual of 16 participants across all trials, which is higher than the medians identified at VICC/VICCAN (8.7) and WUSM (7.4; ref. 16, 17). However, our analysis did not consider 188 studies with maximum projected accrual of <10 participants.

Analyses of CTEP-sponsored trials by Cheng and colleagues identified trial development time of <12 months (9) and time from activation to first participant enrolment of fewer than 2 months (7) to be predictive of attaining accrual goals. We analyzed multiple steps of the trial activation process at MD Anderson Cancer Center and found that the timeframes identified here were similar to those reported from other large academic institutions (Table 1). For example, median time from protocol submission to trial activation was 146 days (4.8 months) at MD Anderson Cancer Center, compared with 172 days reported for VICC/VICCAN, 163 days for WUSM, and 112.5 days for the University of Torino (Turin, Italy; refs. 16, 17). However, it should be noted that over time, regulatory hurdles have generally increased (1, 19) and that many of the trials analyzed here were activated prior to those in other analyses. With regard to trial development, on multivariable analysis only time from activation to first participant enrolment maintained a significance association with slow accrual (Table 2). Furthermore, our identified cut-off points for first participant enrolment of 60 or 70 days are

Published OnlineFirst March 8, 2017; DOI: 10.1158/1078-0432.CCR-16-2439

similar to the 2-month cut-off point identified by Cheng and colleagues (7). A recent analysis by Bennette and colleagues presented a multivariable model associating trial characteristics with low accrual in cooperative group–sponsored phase II and III trials (18). This group identified phase III trials, rarity of the condition treated, and specific therapeutic modalities to be associated with low accrual. The analysis presented notes a similar association between phase III studies and slow accrual, but generally presents a group of trial characteristics that are nonoverlapping and thus complementary to those presented by Bennette and colleagues. A final model to identify trials at risk for slow accrual will likely require parameters presented in both analyses. Factors of potential importance that could not be analyzed included protocol design (e.g., precision medicine/biomarker-driven protocols), protected time of principle investigators, drug accessibility outside of a protocol, protocol staffing, patient population characteristics, and FDA approval status of the investigational agent.

With regards to protocol design, biomarker-driven studies are of particular contemporary relevance given the rise in molecular testing. We have assessed accrual rates in four biomarker-driven trials: Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE; accrual rate, 107 participants/year; ref. 20), BATTLE-2 (accrual rate, 88 participants/year), BATTLE-front line (BATTLE-FL; accrual rate, 19 participants/year), and the Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 (I-SPY 2; accrual rate, 88 participants/year; refs. 21, 22). Although a more thorough analysis is warranted, despite a general increase in trial complexity for biomarker-driven trials and more stringent eligibility criteria, an analysis of this limited sampling showed that accrual rates are not adversely affected. In fact, these trials accrued better than comparable trials, which could contribute by cutting-edge science, novel trial designs, and potentially better treatments.

In addition to providing additional funding for national cooperative group trials and inadequately funded novel trials via HI-CRSP, a number of institutional initiatives have also been designed to improve the trial development process. These include an annual 3-day intensive clinical trial method and design workshop for junior faculty initiated in 2014 that seeks to enhance the quality of clinical trials conducted at MD Anderson Cancer Center. MD Anderson Cancer Center is now negotiating large strategic agreements with pharmaceutical companies for the development of multiple trials within a single contract to facilitate more rapid trial activation and robust accrual. Finally, our institution has opened a number of regional care centers throughout the Houston metropolitan area. Participants from these centers generally reflect a less treatment-refractory population that may be more suitable for enrolment into phase III and national cooperative group trials. In addition to institutional initiatives, trial participant engagement can also be promoted through multiple diverse channels (10). These include web-based educational platforms to enhance participant knowledge, attitudes, and preparation for trial enrolment (23, 24). Most recently, there has been interest in leveraging social media tools to promote self-referral (25–27). Furthermore, individual departments within our institution have evolved research-focused infrastructures worth further discussion. The Investigational Cancer Therapeutics department is a department that has been tasked with conducting all-comers early-phase clinical trials. The impact of such infrastructure elements has been outlined in a recent publication by our group (28).

Various weaknesses of our analysis deserve mention. In analyzing factors predictive of slow accrual, we focused our primary outcome on slow accrual defined as fewer than 2 participants per year. We removed very small trials (maximum projected accrual <10) as low accrual rates might have been acceptable for such trials. As a cut-off point of fewer than 2 participants per year could be considered arbitrary, we conducted a sensitivity analysis at fewer than 6 participants per year. We also evaluated another potential "marker" for trial impact or success, the rate of associated publications, in matched samples of 100 slow-accruing and non–slow-accruing trials. This analysis identified almost a 5-fold difference in the rate of peer-reviewed publications from slow-accruing and non–slow-accruing trials (14% vs. 69% of trials producing at least one publication, respectively). Other weaknesses of the current analysis include the possibility of selection biases in excluded trials as trials exclusion for missing data may have occurred in a nonrandom way. The large sample size utilized in this study has the potential to highlight clinically insignificant differences with statistically significant P values. Finally, the presented analysis represents a single institution experience and thus must be validated in an external dataset. These results may be indicative of our patient population, which is enriched with patients who are motivated to seek newer targeted agents and thus preferentially enroll on early-phase trials and not on phase III or national cooperative group trials that test more established therapeutics.

In conclusion, we have reported our clinical trial characteristics and conducted an analysis associating trial factors with slow participant accrual. Analysis of clinical trial performance on the institutional level is lacking and sorely needed. Prior to the current report, we only identified two prior publications focusing on this topic (16, 17). Thus, the goals of the current analyses are to build the foundation to assess the current clinical trial landscape, generate evidence-based guidelines for trial design and monitoring, and identify weaknesses in the clinical trial enterprise. On the basis of our analysis, we believe that common themes of fast-accruing trials include the following: momentum, quick identification of the first trial participants sets the pace for continued robust accrual and investigator incentives, the potential for greater academic credit for the institutional principle investigator likely facilitates faster participant accrual (e.g., institutional or industry trials and phase I or phase II trials).

Disclosure of Potential Conflicts of Interest

S.I. Sherman reports receiving speakers bureau honoraria from Genzyme and is a consultant/advisory board member for Bristol-Myers Squibb, Eisai, Eli Lilly, Exelixis, LOXO, NovoNordisk, and Veracyte. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Tang, S.I. Sherman, D.S. Hong, J.C. Yao, A. Buzdar, G. Wilding, J.J. Lee
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Published OnlineFirst March 8, 2017; DOI: 10.1158/1078-0432.CCR-16-2439

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Acknowledgments

The authors would like to acknowledge Maria Mercado and Alberto Renteria for their assistance in compiling the analyzed data, Christine Wogan for assistance in manuscript preparation, and Jiaomin Ouyang for figure preparation.

Grant Support

The research was supported in part by grant from the NCI (CA016672).

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Received October 1, 2016; revised December 15, 2016; accepted December 19, 2016; published OnlineFirst March 8, 2017.

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Published OnlineFirst March 8, 2017; DOI: 10.1158/1078-0432.CCR-16-2439

Clinical Cancer Research

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Clin Cancer Res 2017;23:1414-1421. Published OnlineFirst March 8, 2017.