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The Prevalence and Economic Impact of Low-Enrolling Clinical Studies at an Academic Medical Center

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Abstract

Purpose—The authors sought to assess the prevalence and associated economic impact of low-enrolling clinical studies at a single academic medical center.

Method—The authors examined all clinical studies receiving institutional review board (IRB) review between FY2006-FY2009 at Oregon Health & Science University (OHSU) for recruitment performance and analyzed them by type of IRB review (full-board, exempt, expedited), funding mechanism, and academic unit. A low-enrolling study included those with zero or one participant at the time of study termination. The authors calculated the costs associated with IRB review, financial set-up, contract negotiation, and department study start-up activities and the total economic impact on OHSU of low-enrolling studies for FY2009.

Results—A total of 837 clinical studies were terminated during the study period, 260 (31.1%) of which were low-enrolling. A greater proportion of low-enrolling studies were government-funded than industry-funded ($P=.006$). The authors found significant differences among the various academic units with respect to percentages of low-enrolling studies (from 10% to 67%). The uncompensated economic impact of low-enrolling studies was conservatively estimated to be nearly \$1 million for FY2009.

Conclusions—A substantial proportion of clinical studies incurred high institutional and departmental expense but resulted in little scientific benefit. While a certain percentage of low-

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enrolling studies can be expected in any research organization, the overall number of such studies must be managed to reduce the aggregate costs of conducting research and to maximize research opportunities. Effective, proactive interventions are needed to address the prevalence and impact of low enrollment.

Academic medical centers (AMCs), or institutions with the core mission of conducting clinical research, play a vital role in the discovery of new knowledge, the evaluation of current therapies, and the education of the medical and local communities.¹ One critical role of an AMC is to conduct research that advances basic scientific observations to applications in medical practice. The National Institutes of Health (NIH) has made translational research a priority, in part through the formation in 2006 of the Clinical and Translational Science Awards (CTSA) program. In that effort to improve bidirectional translational science, four strategic goals were formulated—the first of which is to enhance the national capability for clinical and translational research.² This goal includes increasing efficiency, quality, and safety in the conduct of research.³ As one of the first CTSA-funded sites, Oregon Health & Science University (OHSU) has undertaken efforts to enhance translational science by identifying and overcoming local barriers to clinical research. One such important barrier is enrolling sufficient numbers of participants in clinical studies to support their stated scientific objectives.

The recognition of barriers to successful participant enrollment in clinical studies is not new—a study over 25 years ago found that one third of a cohort of 41 randomized clinical studies at the NIH recruited less than 75% of their planned enrollment goals.⁴ A sampling of 13 studies sponsored by the National Heart, Lung, and Blood Institute found that planned enrollment was completed for only two of the studies (15.4%),⁵ and more recent investigations of federally-sponsored oncology trials show that the proportion of studies that failed to achieve minimum recruitment goals ranged from over 25% to nearly 40%.⁶⁻⁸ Furthermore, specific milestones can be used early in the enrollment period to predict eventual enrollment success for oncology studies.⁹ Studies that do not achieve planned enrollments are unable to support their intended scientific hypotheses, thus reducing their scientific relevance and the efficiency of the entire clinical research enterprise.

To determine the institutional scope of this problem, to understand its impact on resource utilization, and to set the stage for effective remediation, we analyzed the prevalence of studies that were unsuccessful in enrolling participants and their associated administrative costs at a single AMC during a four-year period. We discuss the economic implications of such studies and present strategies for addressing this issue.

Method

Categorizing low-enrolling studies

We included all clinical studies at OHSU terminated between July 1, 2005 and June 30, 2009 (FY2006 – FY2009) in this analysis. We defined *terminated studies* as those in which participant recruitment and all research activities, including participant follow-up or data analysis, were completed during the study period. We collected data from electronic records maintained by the OHSU institutional review board (IRB). This database includes all OHSU human studies and study enrollment information at the time of each continuing review and at study termination. We defined *low-enrolling studies* as those with zero or one participant enrolled at the time of study termination. We chose this definition of low enrollment based on a threshold that would be considered a failure to meet scientific endpoint objects in almost every context. We included only terminated studies in the analysis, so we analyzed only confirmed final enrollment results. To better understand potential identifying

characteristics of these studies, we examined low enrollment by (1) IRB review type, (2) academic unit conducting the research, and (3) funding mechanism.

IRB review type

We categorized clinical studies by IRB review type: full-board, expedited, and exempt. Studies requiring full-board review, as defined within the Code of Federal Regulations on IRB functions and operations,¹⁰ were approved at a convened meeting with a committee quorum. Expedited or exempt studies were reviewed and approved by the IRB chair or other qualified reviewers without involvement of the board. For the purpose of this analysis, we compared the prevalence of low-enrolling studies with full-board review to those with expedited/exempt review. We calculated the economic resources attributable to low-enrolling studies involving full-board review.

Academic unit conducting the research

We also assessed the prevalence of low-enrolling studies across academic units, including departments, divisions, or other organized research units. We limited analyses of academic units to those with more than 20 terminated studies between FY2006 to FY2009, which was the minimum sample size required to calculate median costs and avoid aberrant results.

Funding mechanism

Funding sources for clinical research include industry, government, and other sources. Industry-funded studies receive primary financial support from private corporations and include both those designed by industry and those developed by investigators at OHSU but supported by industry; the latter studies are typically termed *investigator-initiated*. Government funding includes federal- and state-supported studies. The other sources category includes those studies sponsored by agencies, such as foundations, or other institutions, those supported by multiple sources of funding, and those conducted without any extra-institutional financial support.

Calculating uncompensated costs due to low enrollment

We estimated uncompensated costs associated with low-enrolling, full-board reviewed studies for FY2009 across four primary sources of administrative support for the development and conduct of clinical research: (1) the principal investigators (PIs) and their academic units, (2) the Clinical Trials Office (CTO) contracting unit, (3) the OHSU IRB, and (4) the Sponsored Projects Administration (SPA).

PIs and their academic units—This source of administrative support provides substantial upfront investment in the development of a clinical study. Each academic unit requires specific and, to some extent, unique, processes and reviews. For example, the OHSU Knight Cancer Institute, a National Cancer Institute-designated cancer center, provides a separate scientific review of all oncology clinical studies. The PI and his or her staff must also prepare submissions to the IRB, negotiate and prepare study budgets, and implement the study, including collecting regulatory documents, interfacing with infrastructure units such as pharmacy and nursing, participating in investigator meetings and monitor visits, and creating recruitment plans.

CTO contracting unit—The CTO contracting unit is responsible for coordinating and negotiating contracts for industry-sponsored clinical studies. This negotiation process includes the review of confidential disclosure agreements (CDAs), clinical trial agreements (CTAs), subcontracts, and amendments.

OHSU IRB—The OHSU IRB reviews all research involving human subjects performed by OHSU faculty, research staff, and students. All open, non-exempt clinical studies are reviewed by the IRB at least annually, and any study design modifications or unanticipated problems are reviewed as necessary.

SPA—The SPA manages the financial aspects of all OHSU-sponsored projects. For each research award received by OHSU, the award account must be initiated, managed, and closed. Expenditures related to the conduct of clinical studies are managed through this office.

Calculating the cost of administrative support

We separated the cost of administrative support for study development into three types: (1) start-up, (2) maintenance, and (3) close-out costs (see Table 1). We included only full-board review studies in the cost analysis, as these types of studies are the most resource intensive. We also included only costs not directly reimbursable for efforts attributed to support low-enrolling studies.

Start-up costs—Start-up costs are associated with activities required to prepare a clinical study for enrollment. Start-up costs include preparation of study materials, IRB initial review, preparation of study budgets, contract negotiation, awards set-up, and study planning meetings. Costs associated with study team preparation at the academic unit level for new studies presented to the IRB in FY2009 are based upon estimates of the average salary with fringe benefits for a study coordinator as well as previous estimations used by Dirvage and Bridges¹¹ and C-Change.¹² The salary for study coordinators, including fringe benefits, is estimated to be \$60/hour. These costs are an underestimation of the total start-up costs, as they do not include the time and effort consumed by the study PI(s), biostatistician, or other study team members, such as co-investigators and collaborators, pharmacists, nursing staff, clinical department staff, and/or academic unit administrative staff. Some academic units have centralized resources to negotiate budgets and prepare studies for IRB review, and OHSU runs a centralized office that all academic units can utilize for these activities. These centralized resources recoup their costs through a non-refundable start-up fee payable upon completion of the activities. However, many studies at our institution do not utilize these central offices and do not recover their start-up costs unless they enroll participants.

To estimate IRB personnel effort, we included the anticipated time required to support a full-board review and approval process. In calculating IRB cost estimates, we excluded industry-designed studies, as the IRB charges review fees at initiation of those studies to recoup the cost of the review.

Industry sponsors often require CDAs prior to providing clinical trial documents. CDAs are reviewed by the CTO contracting unit to ensure the terms and conditions are in accordance with OHSU policies. Prior to the initiation of industry-sponsored clinical studies, the CTO contracting unit negotiates the terms and conditions of the CTA with the industry sponsor. The costs associated with low-enrolling studies reflect the estimated percentage of low-enrolling studies across the total number of CTAs and CDAs negotiated. Additionally, award set-up by SPA is required for all sponsored studies, and so the effort associated with setting up studies financially is attributed to all studies.

Maintenance costs—Maintenance costs are associated with the ongoing activities required to keep a study open regardless of whether participants are enrolled. For example, amendments to CTAs require review and negotiation by the CTO contracting unit, so costs

are based upon estimated efforts. Also, the IRB must review non-exempt studies annually, as well as any modifications to the study. In our analysis, we used the number of IRB modifications and annual continuing reviews reported by the IRB during FY2009 and determined uncompensated costs for conducting these reviews accordingly.

Close-out costs—Close-out costs are generated when studies are terminated. Study termination must be reported to and reviewed by the IRB. In addition, the SPA must close the study account, involving review and reconciliation of all study charges.

Statistical analysis

We summarized categorical and ordinal groups using univariate and cross-tabulated frequency distributions. We compared low-enrolling studies for each identified characteristic using the Kruskal-Wallis test. We calculated post-hoc comparisons of statistically significant observations using the Mann-Whitney tests. We maintained a maximum two-tailed alpha of 0.05 for determining statistical significance. We performed all statistical analyses with SPSS (version 17.0, Chicago, IL, www.spss.com).

The OHSU IRB determined that this study did not require approval, as the data provided by the IRB did not include any identifiable information and were not obtained through interaction with human subjects.

Results

In our analysis, we found a total of 837 terminated studies conducted by 57 academic units between FY2006 and FY 2009, and we identified 260 (31.1%) as low-enrolling (see Table 2). This cohort of total terminated studies constituted 24.1% of all 3,470 clinical studies conducted at OHSU during the study period. Of the total sample of terminated studies, 383 (45.8%) required IRB full-board review, and, of these, 173 (45.2%) were low-enrolling studies. Of the 454 exempt or expedited studies (54.2% of all terminated studies), 87 (19.2%) resulted in low enrollment; significantly less than the 45.2% of full-board reviewed studies ($P \leq .001$). Full-board studies included those involving therapeutic interventions and were generally more complex than expedited or exempt studies.

Comparison by funding mechanism

Table 3 summarizes the low enrollment rates by funding mechanism (industry, government, or other sources). The other sources category (such as internal, foundation, and multiple sources of funding) was the most common source of financial support for the studies that we examined (416 of 837 studies, 49.7%). Studies supported by other funding mechanisms had the smallest proportion of low enrollment (85 of 416, 20.4%; $P \leq .001$). Clinical studies that received funding from government sources (97 of 837, 11.6%) had the highest incidence of low enrollment (52 of 97, 53.6%). Across all review types, government-funded studies had a greater proportion of low-enrolling studies compared to industry-funded studies ($P = .006$). Of those studies requiring full-board review, government-funded studies also had the greatest incidence of low enrollment (36 of 48, 75.0%) compared to studies supported by industry (110 of 271, 40.6%) and other sources (27 of 64, 42.2%) (government vs. industry: $P > .001$; government vs. other: $P = .001$). When comparing exempt/expedited studies by funding mechanisms, differences were observed between government (16 of 49, 32.7%) and other funding (58 of 352, 16.5%) ($P = .006$).

Comparison across academic units

We identified 16 of the 57 (28.1%) academic units in the sample with more than 20 studies. These academic units accounted for 603 studies (72.0% of the total terminated studies). The

number of low-enrolling studies within these academic units ranged from 29 studies (10%) to 46 studies (67%).

Economic impact of low-enrolling studies

To understand the economic implications (uncompensated costs), we calculated the estimated unit and administrative costs attributable to the low-enrolling studies. We estimated the uncompensated costs associated with studies terminated with low enrollments for study start-up, maintenance, and close-out activities across the involved infrastructure (IRB, CTO contracting unit, and SPA). A complete list of identified costs and the variables used for the cost estimations are found in Table 1. Our estimated financial impact of low enrollment is conservative, as it includes neither exempt nor expedited studies (454 of 837, 54.2%) nor PI time.

The total institutional uncompensated cost of studies that enrolled zero or one participant was approximately \$990,000 in FY2009. Start-up and maintenance costs represented approximately \$637,000 (64.4% of the total cost) and \$350,000 (35.4% of the total cost), respectively (see Table 4). Of the start-up costs, the largest proportion was associated with study preparation (about \$466,000 or 47.1% of the total cost), including developing study tools, and pre-initiation and initiation meetings.¹² We estimated the average cost to initiate one study to be \$4,800. The largest sub-component of maintenance costs was associated with study modifications (about \$315,000 or 31.8% of the total cost). We estimated the resources allocated to IRB review of modifications and continuing reviews of low enrolling studies to be \$30,000 (3.1% of the total cost). We found close-out costs linked with low-enrolling studies (about \$2,000 or .2% of the total cost) to be relatively small in proportion to both study start-up and annual maintenance costs.

Discussion

Clinical and translational research in the United States has been characterized as fragmented, poorly coordinated, slow, and expensive.¹³⁻¹⁵ An important component of clinical research occurs at AMCs, but there are few objective assessments of its cost or effectiveness. Our findings focus on one major problem within the ailing system of clinical research: low-enrolling studies. Almost one out of every three terminated clinical studies at OSHU enrolled zero or one participant during the period of our research. Although our research was limited to a single AMC, it is highly likely that enrollment efforts and their costs are similar at other institutions; for example, research in oncology has shown a great deal of similarity in low-enrolling studies among different cancer centers.¹¹ The costs of such low-enrolling studies are extensive and represent an important drain on research resources both locally and nationally, a particularly important issue in a constrained economic environment.

The financial implications of clinical studies that do not enroll enough participants are often overlooked and, while being relatively opaque to individual researchers, such costs can quickly accumulate to represent a significant amount of an institution's resources. At our institution, the annual administrative cost for low-enrolling, full-board review studies was found to be almost \$1 million for FY2009. Importantly, the consumption of these valuable resources presumably resulted in minimal scientific benefit. More worrisome, such studies indirectly may have prevented the conduct of other research that would have been more likely to achieve its primary endpoints through successful recruitment.

The scientific and financial implications of low enrollment warrant substantial efforts to foster awareness of their effects and to develop methods for prevention and mitigation. The largest proportion of cost was attributed to study start-up. Approaches to avoid this significant effort should include routine and objective feasibility assessments prior to

supporting the initiation of a study. Ongoing maintenance costs were also substantial, suggesting a need for strategies to proactively recognize and close low-enrolling studies. Our research highlights three characteristics that might focus these efforts: (1) the type of IRB review required, (2) the funding mechanism, and (3) the type of academic unit conducting the research. Studies requiring full-board review and those funded by government sources more frequently involved low enrollment, hence an earlier review of such potential studies at the concept level could be helpful. Preemptively preventing studies that may present potential barriers to feasibility will avoid the allocation of the critical and significant resources necessary to start and maintain a study to research that is at-risk for low enrollment. As our data shows, interventions to close studies once they exhibit symptoms of low enrollment are suboptimal, as resources have already been spent and cannot be recovered. Finally, understanding and reducing the variation in study design and conduct among academic units could identify potential strategies directed to addressing low-enrolling studies. Our research highlights the overarching argument that implementation of improvements to clinical research cannot be done in isolation by any one group or one particular area of implementation; rather, there is a need to address barriers to clinical research from a concurrent and collaborative approach across all parties to create a more efficient and effective clinical research system, i.e., taking more of a systems approach.¹⁶

In addition, two specific cultural issues must be addressed to reduce the proportion of low-enrolling studies: the paradox of abundance and sunk-cost bias. The paradox of abundance is the overestimation of institutional resources potentially available to support the nearly infinite number of possible clinical studies. Management literature shows that, with such a misperception, there is an increased time to market (in our case, achievement of recruitment goals), an increased number of unexciting products (or studies), and an increased number of failures.¹⁷ There must be a widespread understanding that all groups operate within the boundaries of constrained resources and that the commitment of those resources must be carefully undertaken early in the process of study inception. The other cultural issue, sunk-cost bias, in which the irrecoverable costs incurred in building the study hinder rational decision-making in later phases, must be appreciated.¹⁸ It is well known that the level of effort and resources necessary to initiate clinical research is substantial; yet inappropriately continuing to pursue those studies that have a high likelihood of low enrollment incurs additional financial and resource costs. Recognizing the point at which low enrollment will not be reversed, and discontinuing efforts on the study, would restrain cost accumulation.

Our study has a few limitations. First, our research underestimated the true costs of low enrollment. We included only studies involving full-board IRB review and used a conservative estimate that incorporated only the standard institutional costs common across all clinical research. We also chose to include only terminated studies in our analysis and did not account for those studies that are ongoing yet continue not to enroll participants. In considering the total level of effort and financial implications of low enrollment, it must be recognized that each academic unit has unique approaches to the development and conduct of clinical research that will variably affect study costs, which we did not take into consideration. Moreover, our assessment of economic implications of low enrollment did not consider activities such as preparing and writing study protocols by the PI, completing study-specific training, and conducting recruitment activities. Clinical and administrative activities, including drug dispensing and maintenance, nursing support, regulatory reporting, and screening of participants, were also not included in our analysis. Finally, our analysis did not account for intangible costs, including the detrimental impact of low-enrolling clinical studies to the reputation of the university and PI, and relationships built across the research community.

Conclusions

Improving the productivity of research is one of the fundamental challenges to transforming clinical and translational science and cultivating a culture of excellence across all academic medical centers. The etiology of low-enrolling studies must be further examined to determine the underlying causes and thus enable prevention and mitigation. As part of a comprehensive effort to reform clinical research on an institutional level, we are developing an objective understanding of the characteristics and impact of low-enrolling studies. Our findings set the stage for undertaking targeted approaches to reduce the problem and increase clinical research effectiveness.

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Ethical approval: The OSHU Institutional Review Board determined that this study did not require approval.

Table 1

Categories of Unreimbursed Costs Due to Low Enrollment of Clinical Studies, Oregon Health & Science University, FY2009

Categories of cost	Explanation	Calculations included
Start-up costs		
Clinical study preparation by study team	Costs associated with study team (excluding the principal investigator) in preparing industry-sponsored trials, including study tools, pre-initiation, and initiation meetings	<ul style="list-style-type: none"> • Number of full-board studies • Estimated hours of coordination and review • Estimated hourly wage for a study coordinator • % low-enrolling industry-sponsored trials
Uncompensated industry clinical study start-up, budget, and institutional review board (IRB) preparation	Costs not associated with Clinical Trials Office (CTO) support or other centralized unit	<ul style="list-style-type: none"> • Number of studies that request CTO support • Fixed cost per study required by CTO
Non-industry study IRB full-board review	IRB costs associated with IRB reviewer's efforts to conduct an IRB review and costs to support the review of a study	<ul style="list-style-type: none"> • Number of non-industry studies requiring full-board reviews • % non-industry low-enrolling full-board review studies • Cost of an IRB review
Confidential disclosure agreement (CDA) negotiation	Costs to conduct negotiations with the sponsor for industry-sponsored clinical studies	<ul style="list-style-type: none"> • Number of CDA negotiations • Estimated number of hours for negotiations • Estimated hourly wage for CTO contracting unit personnel
Clinical trial agreement (CTA) negotiation	Costs to conduct negotiations with the sponsor for industry-sponsored clinical studies	<ul style="list-style-type: none"> • Number of CTA negotiations • Estimated number of hours for negotiations • Estimated hourly wage for CTO contracting unit personnel
Award set-up	Costs require to set up study accounts	<ul style="list-style-type: none"> • Number of new studies • Estimated number of hours to set up a new account • Estimated hourly wage for Sponsored Projects Administration (SPA) personnel
Maintenance costs		
Continuing IRB reviews	Costs associated with preparation of continuing reviews mandated by regulations	<ul style="list-style-type: none"> • Number of continuing reviews • Number of hours to prepare continuing reviews per study • Estimated hourly wage for a study coordinator • % low-enrolling full-board review studies
Study modifications	Costs associated with study staff submission of modifications to a study during the enrollment period	<ul style="list-style-type: none"> • Number of modifications • Estimated hours to prepare and review modifications per study • Estimated hourly wage for a study coordinator
CTA amendments negotiation	Number of amendments of existing agreements that	<ul style="list-style-type: none"> • Number of CTA amendments

Categories of cost	Explanation	Calculations included
	are processed annually	<ul style="list-style-type: none"> Estimated number of hours to negotiate an amendment Estimated hourly wage for CTO contracting unit personnel
Close-out costs		
Award close-out	Costs required to close an account at the end of the study	<ul style="list-style-type: none"> Number of studies closed Estimated number of hours to close an account Estimated hourly wage for SPA personnel

Terminated Clinical Studies by Enrollment and Institutional Review Board (IRB) Review Type, Oregon Health & Science University, FY2006-FY2009

Table 2

	No. of studies (% of 837)		No. of studies (% of review type total)	
	≤ 1 participant enrolled at termination	> 1 participant enrolled at termination	Total no. of studies (%)	> 1 participant enrolled at termination
IRB Review Type				
Full-board	173 (20.7)	210 (25.1)	383 (45.8)	210 (54.8)
Exempt/Expedited	87 (10.4)	367 (43.8)	454 (54.2)	367 (80.8)
Total	260 (31.1)	577 (68.9)	837 (100)	-

Table 3

Terminated Low-Enrolling Clinical Studies by Funding Mechanism and Institutional Review Board Review Type, Oregon Health & Science University, FY2006-FY2009

Funding mechanism	Full-board			Exempt / Expedited			All studies		
	Total studies	Studies with low enrollment	% with low enrollment	Total Studies	Studies with low enrollment	% with low enrollment	Total studies	Studies with low enrollment	% with low enrollment
Industry	271	110	40.6	53	13	24.5	324	123	38.0
Government	48	36	75.0	49	16	32.7	97	52	53.6
Other	64	27	45.2	352	58	16.5	416	85	20.4
Total	383	173	45.2	454	87	19.2	837	260	31.1

Table 4

Estimated Annual Economic Impact of Terminated Low-Enrolling Studies, Oregon Health & Science University, FY2009

Activity	No. of low-enrolling studies requiring each activity	Cost of activity (\$)	Cost of activity for all low-enrolling studies (\$)	Total cost (\$) (FY2009)
Start-up costs				637,080
Clinical study preparation by study team	97	4,800	465,600	
Uncompensated industry clinical study start-up, budget, and institutional review board (IRB) preparation	20*	3,250	65,000	
Non-industry study IRB full-board review	70	1,023	71,610	
Confidential disclosure agreement (CDA) negotiation	50	125	6,250	
Clinical trial agreement (CTA) negotiation	57	400	22,800	
Award set-up	97	60	5,820	
Maintenance costs				349,875
Continuing IRB reviews	229	130	29,770	
Study modifications	1614	195	314,730	
CTA amendment negotiation	43	125	5,375	
Close-out costs				1,940
Award close-out	97	20	1,940	
				Total: 988,895

* A total of 45 full-board studies in FY2009 used central resources for start-up, budget, and/or IRB preparation and therefore charged non-refundable start-up fees to recoup the costs of these activities regardless of subsequent enrollment.