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Outcomes Research

Temporal Trends and Predictors for Cancer Clinical Trial Availability for Medically Underserved Populations

David E. Gerber,[a,d,e] Ashley M. Lakoduk,[b] Laurin L. Priddy,[d] Jingsheng Yan,[d] Xian-Jin Xie[c,d]

[a]Division of Hematology-Oncology, Department of Internal Medicine, [b]Department of Cell Biology, [c]Division of Biostatistics, Department of Clinical Sciences, and [d]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [e]Oncology Clinic, Parkland Health and Hospital System, Dallas, Texas, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cancer • Clinical trials • Underserved populations • Underrepresented minorities • Accrual

Abstract

Background. Lack of access to available cancer clinical trials has been cited as a key factor limiting trial accrual, particularly among medically underserved populations. We examined the trends and factors in clinical trial availability within a major U.S. safety-net hospital system.

Materials and Methods. We identified cancer clinical trials activated at the Harold C. Simmons Cancer from 1991 to 2014 and recorded the characteristics of the trials that were and were not activated at the Parkland Health and Hospital System satellite site. We used univariate and multivariate logistic regression to determine the association between trial characteristics and nonactivation status, and chi-square analysis to determine the association between the trial characteristics and the reasons for nonactivation.

Results. A total of 773 trials were identified, of which 152 (20%) were not activated at Parkland. In multivariable analysis, nonactivation at Parkland was associated with trial year, sponsor, and phase. Compared with the 1991–2006 period, clinical trials in the 2007–2014 period were almost eightfold more likely not to be activated at Parkland. The most common reasons for nonactivation at Parkland were an inability to perform the study procedures (27%) and the startup costs (15%).

Conclusion. Over time, in this single-center setting, a decreasing proportion of cancer clinical trials were available to underserved populations. Trial complexity and costs appeared to account for much of this trend. Efforts to overcome these barriers will be key to equitable access to clinical trials, efficient accrual, and the generalizability of the results. ***The Oncologist*** 2015;20:674–682

Implications for Practice: Despite numerous calls to increase and diversify cancer clinical trial accrual, the present study found that cancer clinical trial activation rates in a safety-net setting for medically underserved populations have decreased substantially in recent years. The principal reasons for study nonactivation were expenses and an inability to perform the study-related procedures, reflecting the increasing costs and complexity of cancer clinical trials. Future efforts need to focus on strategies to mitigate the increasing disparity in access to clinical research and cutting-edge therapies, which also threatens to hinder study accrual, completion rates, and generalizability.

Introduction

Accrual to cancer clinical trials remains a major challenge [1–3]. Currently, fewer than 5% of U.S. adult cancer patients enroll in clinical trials. Poor study accrual hinders study completion, wastes resources, and limits the generalizability of the results. Multiple factors limiting study enrollment have been identified. These include intrinsic patient characteristics, such as age [3–5], sex [3], race [3, 6–8], and socioeconomic status [6, 9]. Physician characteristics, attitudes toward patients [10], and communication skills [10–14] have also been associated with study accrual. Additionally, factors related to the consent process itself, such as its timing in relation to the cancer diagnosis and consenter experience, appear to influence patient interest in clinical research [15, 16]. Finally, increasingly numerous and stringent eligibility criteria have limited study enrollment [17–22].

Historically, cancer clinical trial accrual rates have been particularly low among underserved populations [3]. The reasons for these trends are multifactorial. Patient mistrust and a poor understanding of the protocols has been associated with decreased enrollment [23, 24]. A greater comorbidity burden could also limit eligibility of such patients disproportionately [25]. Finally, underserved populations might have

Correspondence: David E. Gerber, M.D., Division of Hematology-Oncology, Harold C. Simmons Comprehensive Cancer Center, 5323 Harry Hines Boulevard, Mail Code 8852, Dallas, Texas 75390-8852, USA. Telephone: 214-648-4180; E-Mail: david.gerber@utsouthwestern.edu Received March 4, 2015; accepted for publication April 1, 2015; published Online First on May 27, 2015. ©AlphaMed Press 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2015-0083

less access to clinical trials [26]. Addressing these barriers to include these populations in clinical trials has emerged as a major focus for cancer physicians and researchers nationwide [27, 28].

Clinical trial availability represents an initial and essential step in the accrual process. Therefore, to determine the potential effect of cancer clinical trial availability in a medically underserved population, we examined the proportion of clinical trials within a National Cancer Institute (NCI)-designated cancer center that were activated in a major urban safety-net satellite site that provides care to low-income, uninsured, and vulnerable populations. Owing to the perceived increases in the cost and complexity of oncology clinical research over time—factors that can threaten trial activation and conduct in underserved settings—we focused, in particular, on the temporal trends.

Materials and Methods

Study Setting

The Harold C. Simmons Comprehensive Cancer Center is an NCI-designated cancer center within the University of Texas (UT) Southwestern Medical Center, located in Dallas, Texas. In 2013, Dallas County had a population of 2.48 million, of which 39% were Hispanic, 32% were non-Hispanic white, and 23% were African American [29]. The Parkland Health and Hospital System (Parkland) is the sole safety-net medical provider for all cancer treatment in Dallas County. As the Dallas County integrated safety-net health system, Parkland consists of a 900-bed tertiary care hospital and 12 community-oriented primary care clinics throughout Dallas County. Parkland is responsible for the medical care of all uninsured residents in Dallas County. The principal community oncology practice in Dallas County (Texas Oncology) does not accept Medicaid and does not have a charity plan. Thus, uninsured and underinsured individuals are referred to Parkland for cancer care at diagnosis. The inpatient facility and an outpatient primary care and specialty clinic building are located directly adjacent to the UT Southwestern campus. Annually, the Parkland system treats more than 1.5 million patients. Disease-specific oncology clinics are held 5 days per week in a designated oncology space, which includes a 24-chair infusion area.

The Parkland cancer program is accredited by the American College of Surgeons Commission on Cancer. Oncology clinic staff and administrators are full-time Parkland employees. As previously described [30], the oncology clinics are staffed entirely by UT Southwestern medical oncology faculty and fellows. Additionally, there are three full-time clinical research staff (one research manager and two research coordinators) in the Parkland oncology clinic, all of whom are Simmons Cancer Center Clinical Research Office employees.

A single scientific and safety review process for cancer clinical trials covers both UT Southwestern and Parkland. This includes approval and endorsement by a disease-oriented team, review and approval by the Simmons Cancer Center protocol review and monitoring committee, and review and approval by the UT Southwestern institutional review board (IRB). Additionally, a number of Parkland-specific steps are required, including submission of a study intake form that is distributed to all departments involved in the study (e.g., pathology, radiology, pharmacy). Once a study has IRB approval and all Parkland department approvals, it undergoes a final review and approval by the hospital research manager. At that point, it will be opened to accrual.

Data Sources and Variables

We identified clinical trials activated in the Simmons Cancer Center from the Velos database from 1991 (the first year for which data were available) through May 2014. Velos eResearch (Velos, Fremont, CA, http://www.velos.com) is a study management tool used to help investigators manage the set up and day-to-day activities of human research studies. We excluded the following study types from our analysis: pediatric clinical trials (because these are activated exclusively at the Children's Medical Center), studies categorized as retrospective medical records reviews, single-patient investigational new drug (IND) applications, and trials opened exclusively at remote satellite sites (e.g., the Veterans Affairs North Texas Health Care System). We categorized trials according to the activation year, type (ancillary, correlative, prevention, screening, supportive, diagnostic, epidemiologic, observational, registry, interventional, therapeutic), phase (not applicable, pilot/feasibility, I, II, III), primary management group (breast, ear, nose and throat [ENT], gastrointestinal [GI], genitourinary [GU], gynecology, lung, malignant hematology, radiation oncology, other), investigator-initiated, rare disease (defined as tumor types with an incidence rate of $\leq$6 per 100,000, or fewer than 10 cases seen in a given year), and sponsor (external peer reviewed, industry, institutional, national cooperative group, not defined). Trials designated as having no phase were generally nontherapeutic studies. The "other" management group included the phase I program and developing programs (e.g., melanoma, sarcoma). The primary management categories were grouped according to clinical structure at Parkland: for example, lung-ENT are combined at a single clinic, just as are GI-GU. For these analyses, radiation oncology was selected as the reference group, because a single radiation oncology clinical operation provides care to both Parkland and Simmons Cancer Center patient populations. All the other groups have separate Parkland and Simmons clinical operations. We recorded whether the trial was activated at Parkland. We then grouped the trial characteristics into larger categories for statistical analysis. We grouped the activation year as 1991–2006 and 2007–2014, because 2007 marked a key point in restructuring and expanding the clinical research office at the Simmons Cancer Center. We selected this cutpoint a priori before reviewing the results of our analysis. For instances in which clinical trials spanned multiple phases (e.g., phase I/II trials), the categorization was assigned according to the earlier phase, because the earlier phase trials were more likely to have features affecting the activation process, such as complex study procedures.

We obtained the dominant reason for trial nonactivation at Parkland from the clinical research managers and coordinators and, in some instances, from the principal investigators. A senior clinical research manager (L.L.P.) conducted the interviews and recorded the reasons provided. This information was reviewed by an experienced clinical investigator (D.E.G.), who provided guidance on categorization and grouping. To limit the possibility of influencing and biasing the interviewed individuals, we did not provide the interviewees with a list of categories

from which to choose. Instead, we recorded their feedback as raw data and subsequently assigned the categories. In some instances, the clinical research personnel had archived correspondence (typically electronic mail) that they referenced to provide the requested information. In cases in which individuals no longer held the clinical research position relevant to the trials in question but who still were employed at our medical center, they were contacted and interviewed. We did not contact former clinical research staff who had left our institution. Ultimately, the reasons for nonactivation at Parkland were categorized as follows: startup costs; startup timelines/approval process; intervention not available (e.g., hematopoietic stem cell transplants are not performed at Parkland; thus, clinical trials related to stem cell transplants are not feasible at Parkland); study population not seen (e.g., patients with graft-vs.-host disease are not routinely seen at Parkland owing to the lack of stem cell transplants); standard of care therapies not on formulary (which usually occurred with new treatments or combinations, such as nab-paclitaxel for lung cancer [although on the formulary for pancreatic cancer at Parkland]); the required oversight committee was not available (i.e., the lack of an institutional biosafety committee, precluding the activation of trials using agents considered potential biohazards, such as human and animal pathogens, recombinant DNA, viral vectors, pest insects); clinic scheduling; research staffing; clinician availability (faculty-level physician expertise for certain [typically rarer] malignancies might not be present at Parkland); and study procedures (e.g., frequent electrocardiograms [ECGs] or pharmacokinetics [PK] blood sampling). We grouped the reasons as site-related if it appeared unlikely that sponsor actions could have addressed them (e.g., study intervention not available) and as sponsor-related if it appeared likely that sponsor actions could have addressed them (e.g., study startup costs).

Statistical Analysis

Summary statistics, including the mean, median, and frequency, were recorded. We used univariate and multivariate logistic regression to determine the association between the trial characteristics and activation at Parkland. For the initial multivariate model, we entered all variables with $p < .2$ on univariate analysis. We then performed backward selection, removing the variables with the largest p value $> .05$ one by one to generate the final model. We used chi-square analysis to determine the association between the trial characteristics and the reasons for not activating the trial at Parkland. To compare trends in safety-net site activation by trial characteristics across time periods, we generated three-way tables analyzed by Cochran-Mantel-Haenszel p values. All statistical calculations were performed using SAS for Windows, version 9.3 (SAS Institute, Inc., Cary, NC, http://www.sas.com).

Results

Through the initial Velos report, we identified 1,175 clinical trials. The following trials were removed: 345 pediatric studies, 28 retrospective medical record reviews, 6 single-patient INDs, 2 duplicates, 19 that had only opened at satellite sites, and 2 that had never been intended for activation. Thus, 773 trials remained in the final study cohort. Of these, 77% were interventional/therapeutic trials, 36% were industry-sponsored, and 64% were phase II or phase III trials. Additional characteristics of these trials are listed in Table 1.

Table 1. Baseline trial characteristics

Characteristic	*n* (%)
Activation year	
1991–2006	259 (33)
2007–2014	515 (67)
Primary management group	
Lung/ENT	103 (13)
Malignant hematology	107 (14)
Radiation oncology	109 (14)
GI/GU	125 (16)
Breast/gynecology	237 (31)
Other	92 (12)
Phase	
Not applicable	176 (23)
Pilot/feasibility, I	103 (13)
II	254 (33)
III	240 (31)
Type	
Interventional/therapeutic	592 (77)
Other	181 (23)
Sponsor type	
Industry	275 (36)
Other	498 (64)
Investigator initiated	
Yes	203 (26)
No	570 (74)
Rare disease	
Yes	38 (5)
No	174 (22)
Not reported	561 (73)

Abbreviations: ENT, ear, nose, and throat; GI, gastrointestinal; GU, genitourinary.

The overall Simmons clinical trial portfolio differed in a number of characteristics between the early (1991–2006) and late (2007–2014) time periods. First, although the late time period (7-year duration) represents less than one half the time represented in the early time period (15-year duration), two thirds of the trials in our study cohort were activated during the later time period. In general, trials activated during the late time period were more likely to be an earlier phase. For 1991–2006 and 2007–2014, respectively, the trial phases were as follows: not applicable (27% vs. 21%), pilot/feasibility/phase I (9% vs. 16%), phase II (32% vs. 33%), and phase III (32% vs. 30%). They were also slightly more likely to be interventional/therapeutic (72% vs. 79%) and to be industry-sponsored (28% vs. 40%).

A total of 152 clinical trials (20%) were not activated at the safety-net site (Parkland). The principal reasons for nonactivation are listed in Table 2. The reason was considered sponsor-related in 34% of the cases, site-related in 49%, and unknown in 17%. Among the sponsor-related reasons, the startup costs were the most common. Among the site-related

Table 2. Reasons for trials not being activated at safety-net site

Reason	*n* (%)
Sponsor-related	
Startup costs	22 (15)
Startup timelines, approval process	7 (5)
Satellite sites not desired	11 (7)
Perceived inconvenience	9 (6)
Site-related	
Intervention not available	12 (8)
Study population not seen	2 (1)
Standard of care therapies not on formulary	5 (3)
Required oversight committee not available	5 (3)
Clinic scheduling	2 (1)
Research staffing	5 (3)
Clinician availability	5 (3)
Study procedures (e.g., ECGs, PK)	41 (27)
Unknown	26 (17)

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetics.

reasons, study procedures (e.g., ECGs and PK blood sampling) were the most common.

The association between the trial characteristics and nonactivation at the safety-net site is shown in Table 3 (univariate analysis) and Table 4 (multivariate analysis). We noted a clear increase in the likelihood of nonactivation over time (odds ratio, 7.94 for 2007–2014 compared with 1991–2006). Nonactivation rates by specific year are shown in Figure 1A for all trials, Figure 1B for interventional/therapeutic trials, and Figure 1C for noninterventional/therapeutic trials. Similar differences were observed when using other temporal cut-points. For instance, the nonactivation rate in 1991–2003 was 3% versus 23% in 2004–2014 ($p < .001$). The nonactivation rate in 1991–2009 was 13% versus 27% in 2010–2014 ($p < .001$). Regarding the primary management group, the highest rates of safety-net nonactivation were among the hematologic malignancy and other (including phase I trials) categories. For the trial phase, the lowest rate of safety-net site activation occurred among the feasibility/pilot/phase I studies, with a progressive increase noted for each phase increase. Industry-sponsored trials were less likely to be activated at the safety-net site. Despite changes in the distribution of the trial phase and sponsor over time at our center, the trial activation year, management group, and phase remained strongly associated with activation status in a multivariable model incorporating each of these variables. Because interventional/therapeutic trials are often the principal focus of clinical trial accrual efforts, we analyzed the predictors of safety-net site activation for this subset (which represented 77% of the total trials in our study) in separate univariate and multivariate analyses (supplemental online Tables 1, 2), which yielded similar results.

We also examined the association between trial characteristics and the reasons for the trial not being activated at the safety-net site (Fig. 2). A nonsignificant association was found for trial activation year, with site-related reasons accounting for all nonactivations in 1991–2006 and 60% of the reasons for nonactivation in 2007–2014 ($p = .16$). Site-related reasons accounted for 78% of the nonactivations for phase I trials, 60% for phase II, and 55% for phase III ($p = .10$). Site-related reasons accounted for 65% of nonactivations for interventional/therapeutic trials compared with 40% of nonactivations for noninterventional/therapeutic trials ($p = .04$). Also, a significant association was found with management group ($p = .03$). For 17% of the nonactivations, the reasons were not available. In general, these trials were older (median year, 2008) than the trials for which reasons were available (median year, 2012).

Finally, we found that the association between certain trial characteristics and nonactivation at the safety-net site differed over time. For instance, in 1991–2006, sponsor type was not associated with safety-net activation: only 4% of industry-sponsored and 4% of other sponsor trials were not activated at the safety-net site ($p = 1.00$). However, during the 2007–2014 time period, 39% of industry-sponsored trials were not activated at the safety-net site compared with 20% of other trials ($p < .001$; Cochran-Mantel-Haenszel for time trend $p < .001$). Similarly, the trial phase was associated with nonactivation at the safety-net site only during the more recent time period (Cochran-Mantel-Haenszel for time trend $p = .005$). In 1991–2006, the nonactivation rate was 4% for all study phases ($p = 1.00$). In 2007–2014, the nonactivation rates were 19% for no phase, 39% for pilot/feasibility/phase I, 33% for phase II, and 22% for phase III ($p = .003$).

Discussion

It has long been recognized that the lack of available trials is a major factor limiting accrual to adult cancer clinical trials [26, 31]. A number of potential underlying reasons exist for this lack of research opportunities. Recent years have seen trial eligibility criteria become increasingly numerous and stringent, resulting in the exclusion of a greater proportion of potential participants [17, 21, 32]. Transportation and scheduling issues could also limit study access [33]. Nowhere has this been a greater issue than for medically underserved populations and underrepresented minorities, which have particularly low clinical trial participation rates [3]. Among other cited reasons, a greater comorbidity burden and mistrust of the medical establishment could render these populations less eligible for, or interested in, clinical research opportunities [23–25]. Additionally, such individuals might have less access to available clinical trials [26].

To our knowledge, ours is the first study that systematically examines institutional availability of cancer clinical trials for these historically underrepresented populations. Specifically, we examined the trends and factors related to study activation in an urban safety-net healthcare system associated with a major academic medical center. To conduct the present analysis, we compared these study activation rates with those of the affiliated NCI-designated cancer center, which is staffed by the same academic medical oncology faculty and served by the same clinical research office. Most importantly, we found that, even when controlling for multiple clinical trial characteristics, a near eightfold increase has occurred in the proportion of cancer clinical trials that are not activated within the safety-net setting. Additionally, certain disease types (including lung cancer, head-and-neck cancer, and hematologic malignancies) and trial phases (specifically phase I) were associated with nonactivation. This distribution could exacerbate the access

Table 3. Predictors of clinical trials not opening at safety-net site (all trials)—univariate analysis

Characteristic	Not activated at safety-net site	OR (95% CI)	*p* value	Overall *p* value
Activation year				
1991–2006	10/258 (4)	Reference		<.001
2007–2014	142/515 (28)	9.44 (4.87–18.28)	<.001	
Primary management group				
Lung/ENT	27/103 (26)	5.18 (2.14–12.52)	<.001	
Malignant hematology	41/107 (38)	9.05 (3.83–21.38)	<.001	<.001
Radiation oncology	7/109 (6)	Reference		
GI/GU	19/125 (15)	2.61 (1.05–6.48)	.04	
Breast/gynecology	17/237 (7)	1.13 (0.45–2.80)	.80	
Other	41/92 (45)	11.71 (4.91–27.94)	<.001	
Phase				
Not applicable	23/176 (13)	Reference		
Pilot/feasibility, I	32/103 (31)	3.00 (1.64–5.49)	<.001	<.001
II	59/254 (23)	2.01 (1.19–3.41)	.009	
III	38/240 (16)	1.25 (0.72–2.19)	.43	
Sponsor type				
Industrial	82/275 (30)	2.60 (1.81–3.73)	<.001	<.001
Other	70/498 (14)	Reference		
Type				
Interventional/therapeutic	125/592 (21)	Reference		.068
Other	27/181 (15)	0.66 (0.42–1.03)	.068	
Investigator initiated				
Yes	35/203 (17)	0.81 (0.53–1.22)	.31	.31
No	117/570 (21)	Reference		
Rare disease				
Yes	12/38 (32)	1.03 (0.48–2.18)	.95	.95
No	54/174 (31)	Reference		

Data presented as *n* (%), unless otherwise noted. OR >1 indicates trial less likely to be activated at safety-net site.
Abbreviations: CI, confidence interval; ENT, ear, nose, and throat; GI, gastrointestinal; GU, genitourinary; OR, odds ratio.

disparities because the burdens of smoking and smoking-related diseases are greatest in underserved populations [34, 35]. The variety of tumor types and multiple lines of previous therapy allowed on many phase I trials could also be particularly relevant to a safety-net setting.

We identified numerous reasons for trial nonactivation, including sponsor-related (most commonly, study cost) and site-related (most commonly, the inability to perform the study-related procedures such as frequent ECGs or PK blood sampling). How these can be addressed is a complex undertaking that will require input from all parties. With the goal of optimizing the clinical and biologic information gleaned from each research subject, clinical trials have become increasingly complicated and regularly feature requirements for archival tumor tissue, frequent phlebotomy for pharmacokinetic and pharmacodynamic assessments, frequent quality-of-life and patient-centered outcome determinations, and additional safety considerations such as regular cardiac monitoring [36]. Safety-net medical facilities, which might already be stretching resources to provide routine clinical care, will face disproportionate challenges to meeting these requirements. Issues related to trial startup costs could be multifactorial, potentially reflecting increasing charges from the study site or—in particular, since the recent economic downturn—less willingness to pay pre-existing charges on the part of the sponsor.

Some key reasons for the lack of trial activation at our safety-net clinical site are clearly defined, although not necessarily readily addressed. The lack of a hematopoietic stem cell transplant program at the site precludes activation of any clinical trial using that modality or studying a related medical condition (e.g., graft-vs.-host disease). Creation of an institutional biosafety committee or establishing an oversight agreement with the existing UT System institutional biosafety committee would permit consideration of perceived high-risk therapeutic agents, such as viral vectors and their byproducts. However, this limitation accounted for only 3% of the trials not activated at the safety-net site. The substantial increase in early-phase and industry-sponsored trials noted in our series might reflect our center's maturation and growth as a regional cancer center. Separately, the trend could also be an indication of a general decline in the number of national cooperative trials because of financial constraints and restructuring. Regardless of the explanation, securing the interest and participation of industry partners is essential. This will require negotiation of study terms and conveyance of the potential benefits of safety-net site activation, such as increased and diversified accrual. Streamlining the startup processes and timelines could also

Table 4. Predictors of clinical trials not opening at safety-net site (all trials)—multivariate analysis

Characteristic	OR (95% CI)	*p* value	Overall *p* value
Activation year			
1991–2006	Reference		<.001
2007–2014	7.94 (3.99–15.80)	<.001	
Primary management group			
Lung/ENT	4.58 (1.81–11.61)	.001	
Malignant hematology	10.15 (3.92–26.28)	<.001	<.001
Radiation oncology	Reference		
GI/GU	2.91 (1.11–7.61)	.03	
Breast/gynecology	1.72 (0.67–4.46)	.26	
Other	13.21 (5.24–33.31)	<.001	
Phase			
Not applicable	Reference		
Pilot/feasibility, I	3.15 (1.55–6.40)	.001	.004
II	2.38 (1.27–4.46)	.007	
III	1.52 (0.78–2.97)	.22	
Sponsor type			
Industrial	1.60 (1.01–2.52)	.04	.04
Other	Reference		

Abbreviations: CI, confidence interval; ENT, ear, nose, and throat; GI, gastrointestinal; GU, genitourinary; OR, odds ratio.

increase sponsor interest in the site. Conducting phase I clinical trials at the safety-net site will require considerable effort and infrastructure development, unless a method exists to treat the patients within the existing phase I program at our university site. This is the clinical model used by our radiation oncology department (in which all patients are treated within a single clinical operation), which had the highest proportion of safety-net trial activation (94%) of any management group in our study. Even more broadly, perhaps the health plans newly available through the Affordable Care Act will expand the treatment options for underserved populations in Dallas and nationwide, providing patients with increased access to cancer clinical trials.

Additional areas that could be targeted to expand access to clinical trials among underserved populations include factors related to trial design and financing. The increased complexity of clinical trials in recent years reflects the heightened sophistication of scientific analyses in clinical research (e.g., predictive and pharmacodynamic biomarkers) and increased safety and regulatory requirements (e.g., extensive ECG analyses). These complexities affect not only the study costs and procedures but also the length of the protocol documents and number of eligibility criteria. Addressing these issues requires a careful balance between maximizing the yield of efficacy and biomarker data in a trial and providing real-world effectiveness readouts. Clinical trial financing requires consideration of multiple ethical principles. Coverage analyses determining which costs are assigned to study sponsors (i.e., research components) and which to the patient and/or third-party payor (i.e., standard of care components) are performed in a unified fashion, regardless of patients' financial and insurance status. Any financial assistance provided to clinical trial participants must be provided equally to all participants and must not be considered potentially coercive to the potential study subjects.

The present study had a number of limitations. First, as suggested by the factors detailed in the present report, the present single-center experience might not be broadly generalizable. Nevertheless, our analysis had features that suggest our findings are unlikely to be unique. Although academic medical centers represent only 5% of all hospitals, they provide 37% of all charity care and 26% of all Medicaid hospitalizations [37]. Additionally, some observed trends seem unlikely to reflect site-specific considerations. For instance, although the capacity to perform clinical procedures at the safety-net site did not diminish during our study periods (and, indeed, likely increased), an increasing proportion of clinical trials were not activated there because of the inability to perform study-related procedures. This suggests that, over time, clinical trial protocols are becoming increasingly complex to implement and conduct [38]. Another limitation was that our analysis did not capture the possibility of clinical trials that were never activated at any site within our system because they could not be activated at the safety-net site. Unmeasured variables, such as changes in regulatory requirements, investigator mix, and clinical trial office personnel, could also affect trial activation. The possibility also exists of a misclassification of the reasons for nonactivation, which might have been lessened by having multiple clinical investigators assign categories and then measure concordance. Additionally, the reasons for trial nonactivation at the safety-net site were missing for 17% of cases, reflecting the inherent challenges of obtaining information on previous clinical trials that was not captured prospectively. That this proportion was not greater reflects the time distribution of the nonactivated trials: only 3% were from before 2004. In collecting this information, recall bias could also have been present among the personnel interviewed. We sought to minimize this effect

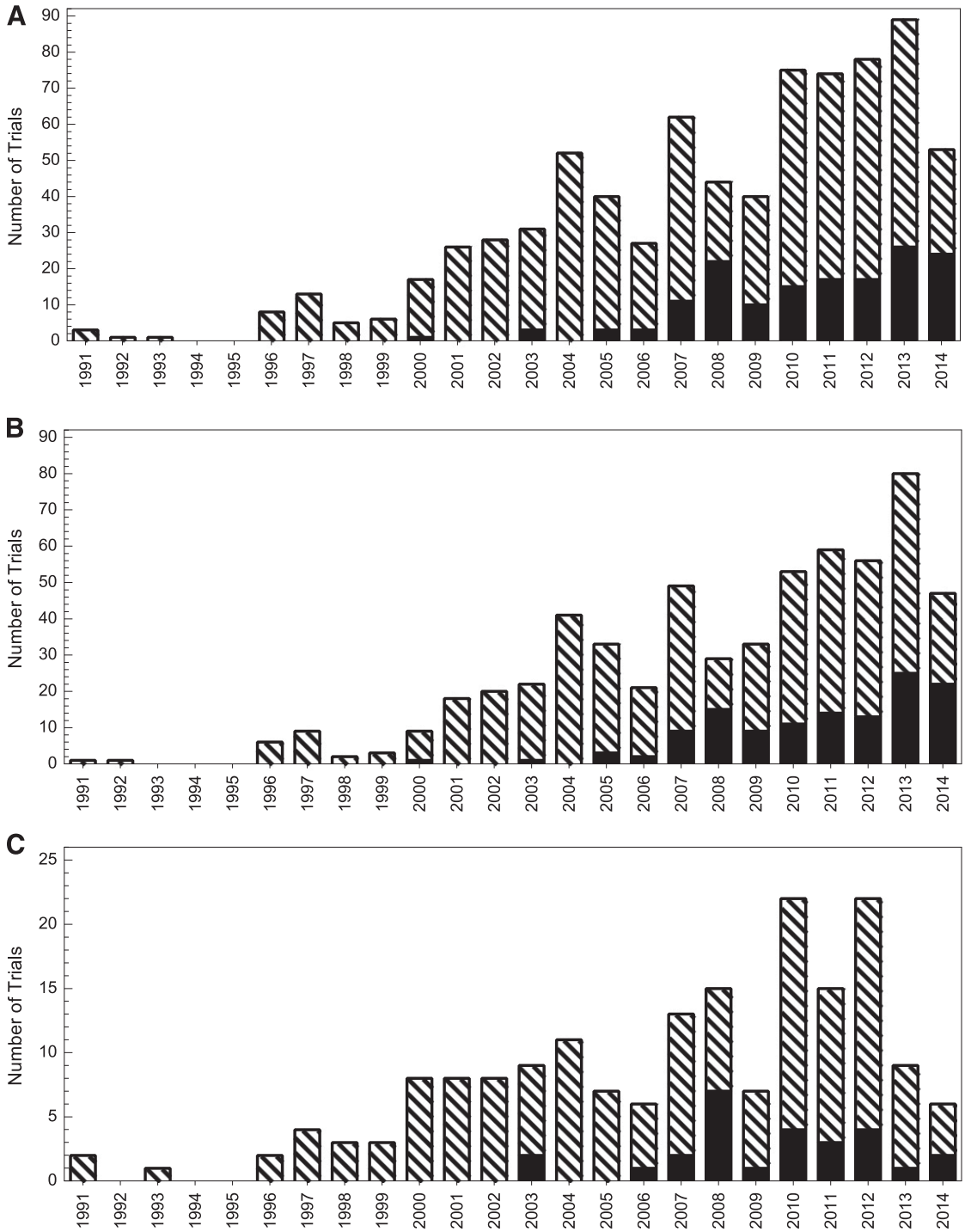

Figure 1. Number and proportion of clinical trials not activated at safety-net site. **(A):** All trials. **(B):** Therapeutic/interventional trials. **(C)**: Nontherapeutic/noninterventional trials. Black bars indicate not activated at safety-net site; hatched bars, activated at safety-net site. Data for 2014 represent January 1, 2014, through May 30, 2014.

by recording the interviewees' responses as raw data and then assigning the categorization, rather than providing a list of reasons from which to choose.

Conclusion

In the present single-center setting, over time, an increasing proportion of cancer clinical trials were not accessible to the underrepresented minorities and medically underserved populations. This trend was not explained by changes in the types of clinical trials under consideration. Several sponsor- and site-related reasons underlie this phenomenon, most commonly concerns regarding startup costs and a limited ability to perform increasingly complex study procedures. These initial findings merit additional investigation. If confirmed, future discussion will need to focus on strategies to mitigate an increasing disparity in access to clinical research

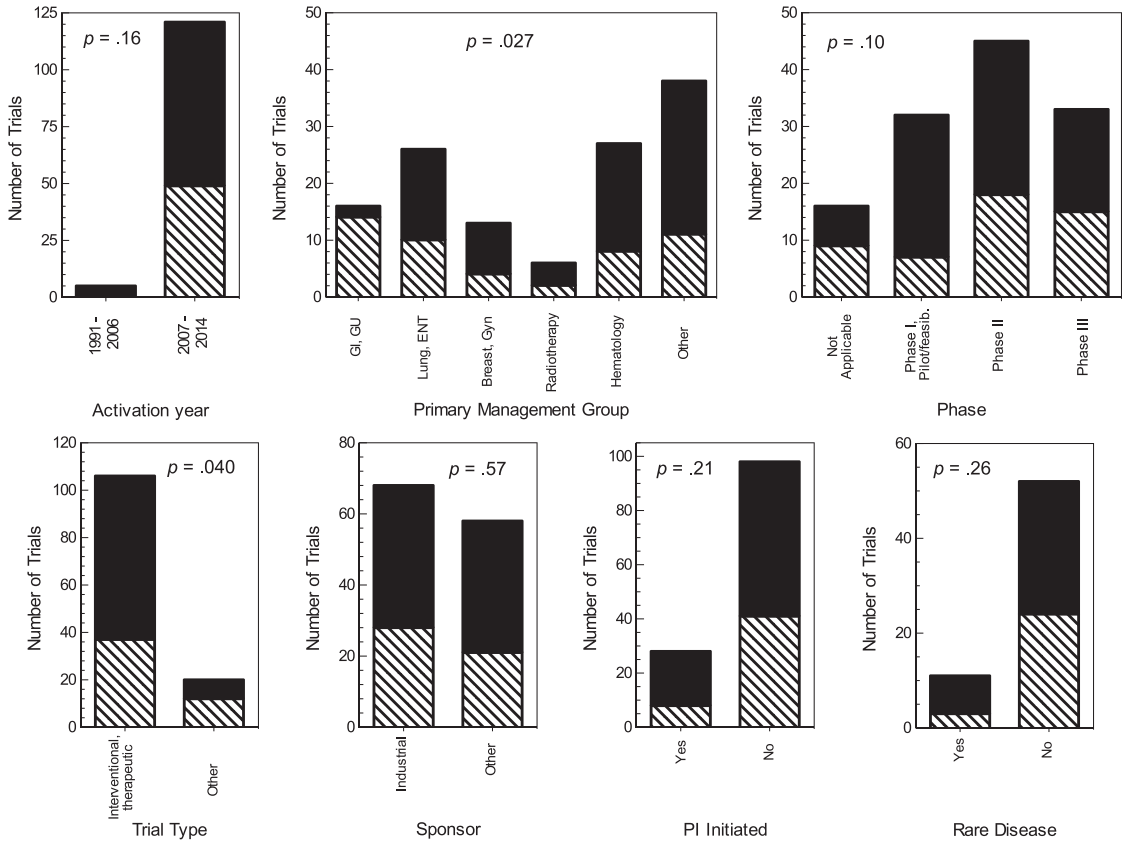

Figure 2. Reasons for safety-net nonactivation according to trial characteristics. Black bars indicate site-related; hatched bars, sponsor-related.

Abbreviations: feasib., feasibility; GI, gastrointestinal; GU, genitourinary; Gyn, gynecology; PI, primary investigator.

and cutting-edge therapies that also threatens to hinder study accrual, completion rates, and generalizability.

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Author Contributions

Conception/Design: David Gerber, Ashley Lakoduk, Laurin Priddy
Collection and/or assembly of data: David Gerber, Ashley Lakoduk, Laurin Priddy
Data analysis and interpretation: David Gerber, Jingsheng Yan, Xian-Jin Xie
Manuscript writing: David Gerber, Ashley Lakoduk
Final approval of manuscript: David Gerber, Ashley Lakoduk, Laurin Priddy, Jingsheng Yan, Xian-Jin Xie

Disclosures

The authors indicated no financial relationships.

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EDITOR'S NOTE: See the related commentary,"Clinical Trials, Disparities, and Financial Burden: It's Time to Intervene," on page 571 of this issue.