

Invisible Barriers to Clinical Trials: The Impact of Structural, Infrastructural, and Procedural Barriers to Opening Oncology Clinical Trials

David M. Dilts and Alan B. Sandler

A B S T R A C T

Purpose

To investigate the administrative barriers that impact the opening of clinical trials at the Vanderbilt-Ingram Cancer Center (VICC) and at VICC Affiliate Network (VICCAN) sites.

Methods

VICC, a National Cancer Institute–designated comprehensive cancer center, and three VICCAN community practice sites were studied. Methodology used was identification and mapping of existing processes and analysis of historical timing data.

Results

At course granularity, the process steps required at VICC and VICCAN main office plus local sites are 20 v 17 to 30 steps, respectively; this gap widens with finer granularity, with more than 110 v less than 60 steps, respectively. Approximately 50% of the steps are nonvalue added. For example, in the institutional review board (IRB) process, less than one third of the steps add value to the final protocol. The numbers of groups involved in the approval processes are 27 (VICC) and 6 to 14 (VICCAN home office and local sites). The median times to open a trial are 171 days (95% CI, 158 to 182 days) for VICC and 191 days (95% CI, 119 to 269 days) for the VICCAN sites. Contrary to expectations, the time for IRB review and approval (median, 47 days) is the fastest process compared with the scientific review committee review and approval (median, 70 days) and contracts and grants review (median, 78.5 days). Opening a cooperative group clinical trial is significantly ($P = .05$) more rapid because they require fewer review steps.

Conclusion

There are numerous opportunities to remove nonvalue-added steps and save time in opening clinical trials. With increasing numbers of new agents, fewer domestic principal investigators, and more companies off-shoring clinical trials, overcoming such barriers is of critical importance for maintenance of core oncology research capabilities in the United States.

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From the Center for Management Research in Healthcare; Management of Technology Program; and the Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN.

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Address reprint requests to David M. Dilts, PhD, MBA, Owen Graduate School of Management, 401 21st Ave S, Nashville, TN 37203; e-mail: david.dilts@vanderbilt.edu.

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INTRODUCTION

Patient and physician barriers to accrual to cancer clinical trials are well known, but there is a dearth of literature on the administrative barriers that take place outside the realm of direct patient-provider interaction. Administrative barriers can be broken up into the following three types: procedural, structural, and infrastructural. Procedural barriers arise from the processes or series of steps required to open a clinical trial. For example, a common procedural barrier in academic medical centers is the number of sequential departmental or functional approvals (a group that performs a specific task but is not a department; eg, intuitional review board [IRB]) required to open a study. It is typical that, initially, an academic medical department or unit must approve

the study for consideration, and then the protocol must be submitted to an IRB, a scientific review committee (SRC), a contracts and grants office, and others for consideration and approval before opening a study.

The second type of administrative barrier, structural (barriers created by the design of the organization; eg, performing x-rays in a different department, such as the radiology department, other than the oncology department), can be created when different groups in the process have different ordering of steps to follow, which can lead to miscommunication and misunderstandings. A common example of such a barrier occurs when one major group in the study approval process, for example the sponsoring agency, requires some information that can only be provided by another group,

say the contracts and grants office, who will only supply the necessary information after the sponsoring agency agrees to some condition. This can lead to a circular mismatch error; the sponsor cannot collect the required information until they approve a condition, but they will not approve the condition without the information. Such a mismatch of structures leads to unnecessary delays and, normally, circumvention of the approval procedures.

Infrastructural barriers, the third administrative barrier type, relates to how the underlying core system foundation is designed and how these elements interconnect. For example, some organizations have insufficient resources to hold IRB meetings in a timely manner, thus delaying the evaluation of potential trials. Other common infrastructural barriers include limited staffing support for developing protocols, intricate and oftentimes conflicting issues in multisite studies, and poor communication systems to support the wide diversity of committees and individuals involved in the evaluation of trials.

Such procedural, structural, and infrastructural obstacles can be as daunting to the creation of new knowledge as patient and physician barriers. Interestingly, there is little research that either documents the various processes involved in the opening of an oncology clinical trial

or that validates any improvements from suggested interventions to overcome such barriers. Although opinions about interventions abound, such as use of a centralized IRB,^{1,2} there is little documentation of the efficacy of these interventions.²

Although procedural, structural, and infrastructural barriers are often criticized by researchers, they remain invisible barriers because they have not been formally documented or evaluated. Our study completes the first evaluation of setup processes in clinical oncology that documents and evaluates such obstacles in a major academic medical center and at three of its affiliated community practices.

METHODS

Study Settings

There are two study settings. The first is the Vanderbilt-Ingram Cancer Center (VICC), a National Cancer Institute–designated comprehensive cancer center. VICC, which is part of the Vanderbilt University Medical Center, has enrolled more than 7,500 patients onto clinical trials since 1998, and it offers more than 150 clinical trials at any one time for adult and pediatric patients.³

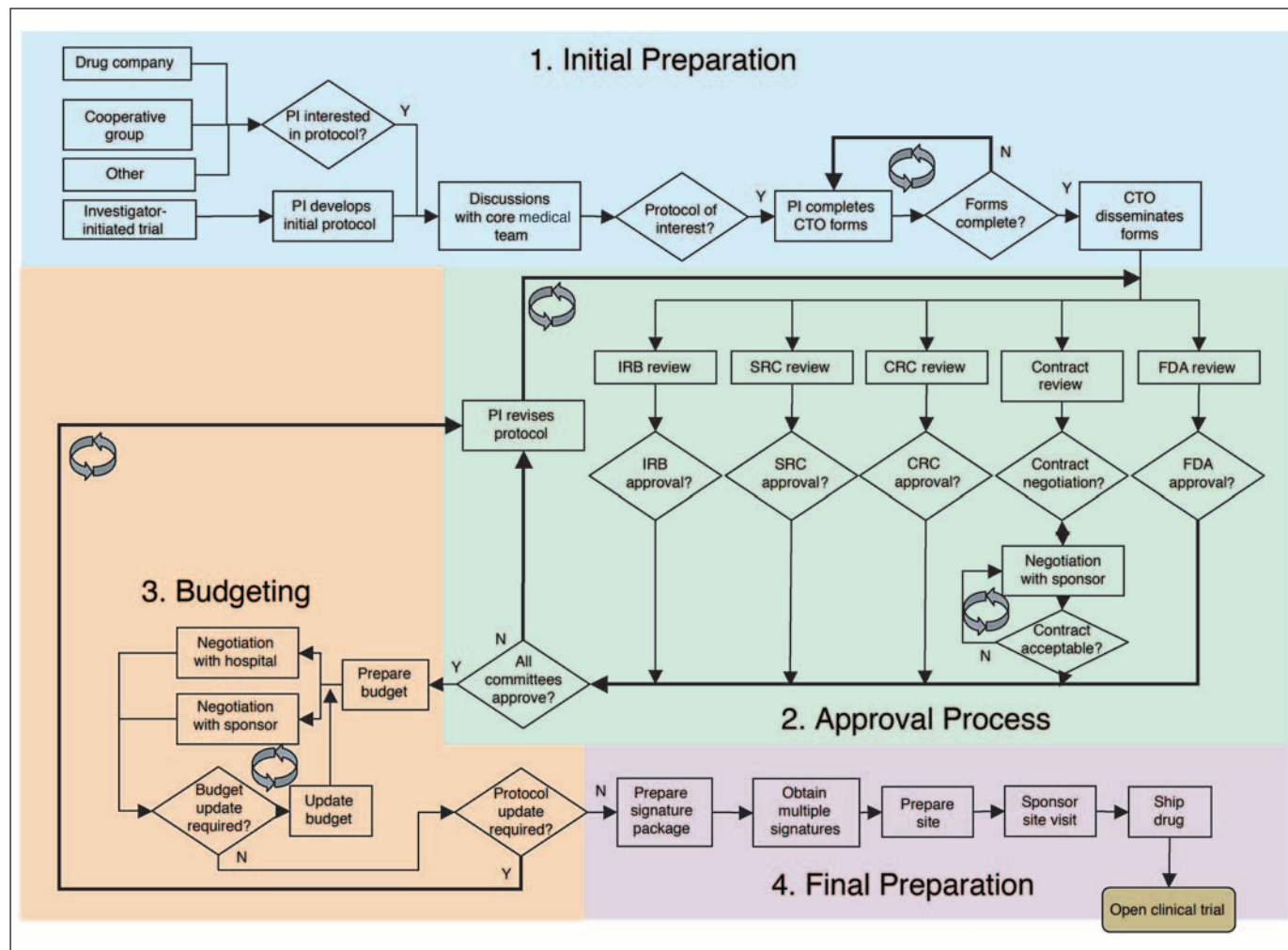


Fig 1. Level 0 process flow map for opening an oncology clinical trial. (As a result of printing restrictions, Figure 1 is a highly aggregated view of the process flow of opening a clinical trial. For a more comprehensive view, go to <http://www.cmhc.org/ClinicalTrialsProcess/ProcessMap.pdf>.) PI, principal investigator; CTO, clinical trials office; IRB, institutional review board; SRC, scientific review committee; CRC, clinical research center; FDA, Food and Drug Administration; Y, yes; N, no.

Table 1. Number of Participants, Steps, Decision Points, and Outcomes in the Opening of an Oncology Clinical Trial

Level	Participants (No.)		Steps			Outcomes (No.)		
	Primary	Other	Value Added (No.)	Nonvalue Added (No.)	% Value Added	Decision Points (No.)	Decline	Accept or NA
Level 0, macroprocess level								
VICC	11	16	15	5	75	13	2	1
VICCAN main office	3	—	7	3	70	3	2	1
VICCAN member sites, range of three sites	3	1-8	6-15	1-5	75	4-13	4-6	1
Subprocess level								
IRB	7	3	12	26	32	23	9	3
IRB amendments	6	—	14	13	52	13	6	3
Scientific review committee	4	—	13	11	54	10	3	1
Regulatory and clinical research center	6	—	13	15	46	7	1	1

Abbreviations: NA, not applicable or appropriate; VICC, Vanderbilt-Ingram Cancer Center; VICCAN, Vanderbilt-Ingram Cancer Center Affiliate Network; IRB, institutional review board.

Community oncology practices face different issues when opening a clinical trial, and hence, they are the second study setting. Specifically, we investigated community-based oncology practices that are part of the VICC Affiliates Network (VICCAN), which is a network of community-based oncology providers in the southeast United States who have united to provide state of the art treatment to patients in their local communities.⁴ One end point of interest is whether there are major differences in process flows and timing to open clinical trials between these two diverse settings.

Phase I: Process Mapping

The methodology had two phases. The first was to identify and map existing process steps required to open an oncology clinical trial at VICC and VICCAN. A process map is a graphical representation of the flow of inputs, resources, steps, and processes required to create an output (in this case, a clinical trial).

For phase I, a team of experts from the VICC, from VICCAN, and from the Vanderbilt Schools of Engineering and the Owen Graduate School of Management was created. This team was composed of an oncologist, research nurse, clinical trials administrator, and oncology fellow from VICC and VICCAN. From the Engineering and Owen schools, three experts in management methodologies for analyzing and evaluating processes were included as team members. The team developed initial process flows for all major activities required to open a clinical trial, including initial submission, IRB, SRC, clinical research center, and contracts and grants. The flows were verified by presenting them to members of the respective committees.

With these initial process maps completed, members of the research team visited the VICCAN sites. Processes used by three community practices (located in Chattanooga, TN; Macon, GA; and Nashville, TN) were investigated using a slightly different process mapping methodology. At each site, key individuals in the process were interviewed by team members. Subsequently, the team created a clinical trial setup process map for each site. These maps were verified at each site.

Phase II: Timing Analysis

The second phase of the study used archival timing data of the time required for each of the major phases of opening a clinical trial. In the VICC, such data are maintained, collected, and logged by the clinical trials office (CTO). Specifically, the CTO logs times of initial receipt from a principal investigator (PI), initial submission to each major functional group, date of final approval by each group, date trial formally opened, and date of first patient placed onto study.

Unfortunately, there were insufficient archival timing data available at the community sites. However, there were data on setup times for clinical trials at VICC, which were used to identify timing for each of the major phases of opening a clinical trial. Data concerning a total of 302 studies managed by the CTO or by the VICCAN Trial Office from January 2001 to June 2005 were collected. Because these data are rarely used, a major activity in phase II was to

scrub and verify the accuracy of the timing data. The final sample analyzed in phase II was 218 trials. Trials were excluded because of missing values or inconsistent timing data; no trial was eliminated as a result of lack of accruals because we are studying the opening of a trial and not the success of the resulting study.

RESULTS

Phase I: Process Mapping

The following are two possible strategies when creating process maps: list all process steps on one large diagram⁵ or create a hierarchy of diagrams, each of which provides additional detail from a master, or

Table 2. Sample Listing of Participants Involved in the Opening of an Oncology Clinical Trial

Participant	Type
Primary	Principal investigators
	Sponsor
	Clinical trials office
	Regulatory staff
	Institutional review board
	Scientific review committee
	Contracts and grants office
	Division chair
	Department head
	Core medical team
	Secondary
Compliance office	
Director, medical affairs/oncology administration	
US Food and Drug Administration	
Finance department	
General hospital review board	
Human subjects radiation committee	
Institutional biosafety committee	
Legal department	
Medical ethics board	
Office of sponsored research	
Pharmacy	
Radioactive drug research committee	
Site coordinator	

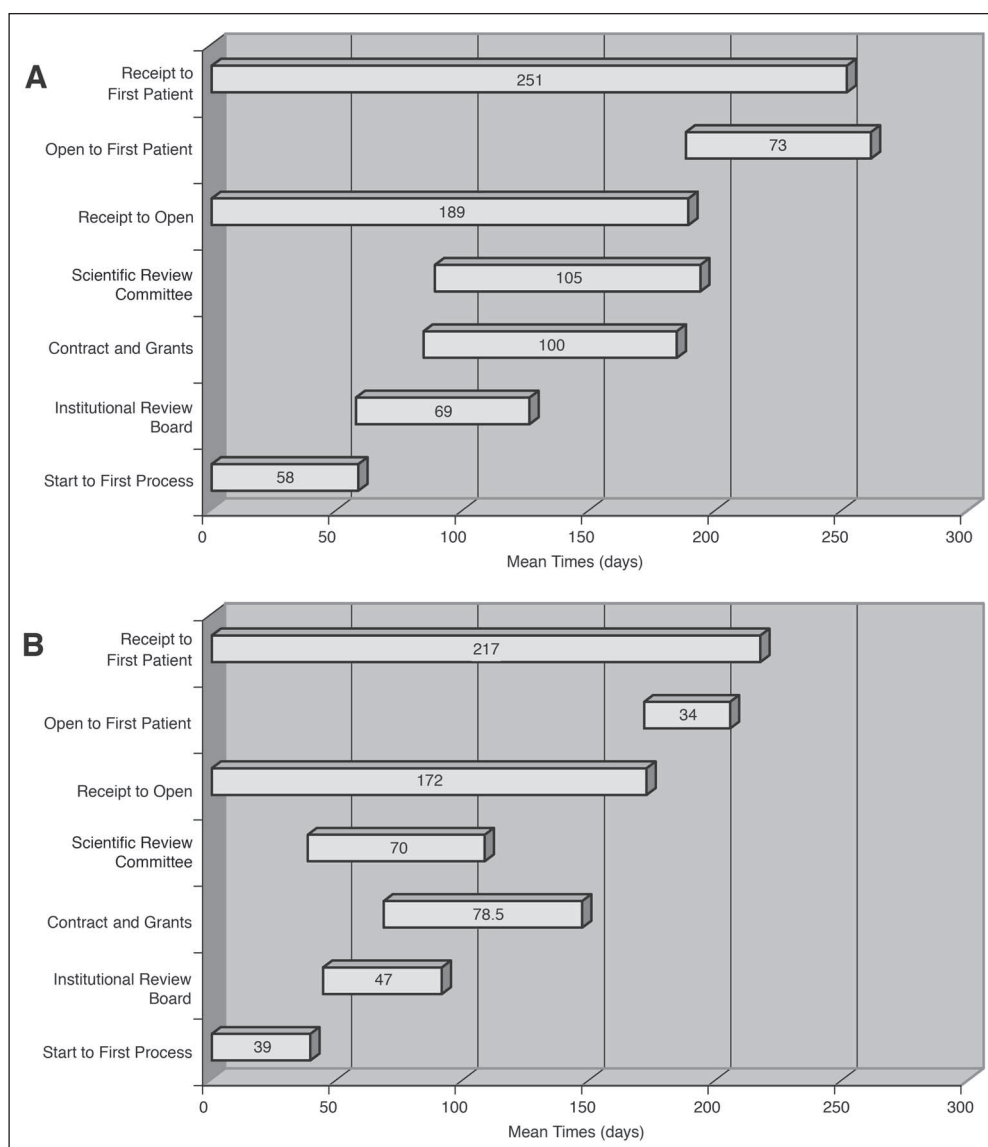


Fig 2. Timeline for opening of an oncology clinical trial. (A) Mean number of days per process ($n = 211$). (B) Median number of days per process ($n = 211$).

level 0, diagram.⁶ The primary advantage of a single diagram is that it is a comprehensive view of the entire process and it tends to create willingness for rapid and dramatic process changes when presented to those involved in the process. Unfortunately, because of its size, it is impossible to reproduce the entire process map in a journal article.

An overview of the process is depicted in Figure 1. Essentially, the process is composed of four parts. The first part is the initial preparation, which includes creation of the protocol for an investigator-initiated trial or the acquiring of a proposed study protocol from a cooperative group study or industry-sponsored study. When this is completed, the proposed protocol is discussed with the core medical team to verify appropriateness and patient availability. If the protocol is accepted, the PI completes the initial forms for review by the CTO. The second part is the approval process, which is a parallel process with review and approvals by the IRB, SRC, clinical research center where appropriate, contracts and grants, and US Food and Drug Administration (if necessary) taking place concurrently. There is a hidden loop in this process of which a PI may only have passing

awareness; the contract department enters into discussions with the sponsor that may take months. If there are any changes required by any of the committees, the PI revises the protocol, and it is resubmitted to all committees. With the necessary approvals gained, the third part is budgeting. This is a distinct step that is independent of contracting, and it is semitransparent to a PI because these negotiations take place primarily outside the vision of the PI. One major delay loop may occur if the agreed on budget requires revision to the protocol, where the PI must revise the protocol and resubmit it to the approval process. Part four, final preparation, includes the steps that are required to gain formal signatures on all documents, site preparation, sponsor site visit, and shipment of study drug.

Table 1 lists the number of participants, steps, decision points, and outcomes to open a trial. At course granularity, there are approximately the same number of process steps and decision points at VICC (20 steps and 13 decision points) compared with a VICCAN site (main VICCAN office plus range of local sites: 17 to 30 steps and four to 16 decision points). However, at finer granularity, VICC, compared with

Table 3. Timing for Studies Received From January 2001 to End of June 2005

Trial by Status or Sponsor	No. of Studies			No. of Patients Accrued			Mean No. of Patients per Study		
	VICC	VICCAN	Total	VICC	VICCAN	Total	VICC	VICCAN	Total
Status									
Accruing	61	9	70	567	145	712	9.3	16.1	10.2
Closed	46	4	50	254	49	303	5.5	12.3	6.1
Follow-up	81	5	86	812	30	842	10.0	6.0	9.8
Suspended	12	—	12	41	0	41	3.4	—	3.4
Sponsor									
Company	118	17	135	1,046	197	1,243	8.9	11.6	9.2
Cooperative group	59	0	59	339	—	339	6.0	—	6.0
Internal	7	—	7	42	—	42	5.7	—	5.7
Other	16	1	17	247	27	274	15.4	27	7.6
Total	200	18	218	1,674	224	1,898	8.4	12.4	8.7

Abbreviations: VICC, Vanderbilt-Ingram Cancer Center; VICCAN, Vanderbilt-Ingram Cancer Center Affiliate Network.

VICCAN, requires more participants (27 v four to 11 participants, respectively) and steps (> 110 v < 60 steps, respectively). For example, community sites do not require an SRC, and the number of individuals involved with contracts is significantly fewer. Table 2 lists primary participants (ie, participants who are normally part of the approval process; eg, IRB) and secondary participants (ie, participants who only may be involved; eg, radiation safety). The number of separate approval signatures required at VICC ranges from 11 to 27 depending on the type of study, whereas the maximum is 11 at a VICCAN main office plus VICCAN sites.

Mapping the process is only the beginning step in evaluating the process. The next step is to determine which steps add value (ie, which steps contribute to the research integrity, participant safety, or usefulness of the trial) and which steps are nonvalue-added activities, such as paperwork delays, batching, or paper movement steps^{7,8} (Table 1). Supplementary Figure A1 is the process map for the IRB, and Supplementary Figure A2 identifies which steps in the process add or do not add value. What is surprising is that there are 29 approval checks required in the IRB process alone by eight primary and three secondary participants; there are nine stopping points (ie, points at which the approval process may be aborted) and only one approval point.

Phase II: Timing Analysis

Data were retrospectively collected on a total of 302 clinical trials initiated from January 2001 to the end of June 2005. The first step in this phase was to verify the completeness of the data and to ensure data consistency. By cross-checking electronic records with paper records, data consistency was established. Some studies were eliminated from the data set because they were not approved by one or more of the setup committees (ie, IRB, SRC, and so on), others were eliminated because they were still in the approval process, and still others were eliminated as a result of missing values. Overall, a final sample of 211 trials (70%) was available for the timing portion of the analysis, and a sample of 218 trials (72%) was available for analysis of accrual rates. It is important to recognize that trials that are slow to open are likely to still be in the approval process, and thus, our estimates represent a lower bound on times.

The median time to open an oncology clinical trial is 172 days (range, 27 to 657 days; Fig 2). Contrary to what might be expected from comments made by PIs, the time for IRB review and approval

(median, 47 days; range, 1 to 426 days) is one of the fastest processes in the chain of processes required to open a clinical trial. By contrast, both SRC review and approval (median, 70 days; range, 3 to 566 days) and contracts and grants review (median, 78.5 days; range, 7 to 461 days) require far more calendar time.

The following three statistical techniques were used for analysis: Kruskal-Wallis, Median test, and CI differences. The statistical package used was SPSS 14.0 (SPSS Inc, Chicago, IL). The dependent variable was the number of days from initial receipt of the study in either the VICC CTO or at VICCAN to opening of the clinical trial. Independent factors were study site (VICC or VICCAN), sponsorship type (company, internal, cooperative oncology group, or other), and clinical trial phase (I, I/II, III, or pilot). There were no statistically significant median differences by study site or phase (Table 6). With regard to sponsorship, results show that a cooperative group clinical trial is significantly faster to open than any other type of trial (median, 120 days v 179 days for company, 230 days for internal, and 197.5 days for other; *P* = .002).

To evaluate potential interactive effects among the three factors, multiple analysis of variance was completed for all possible interaction combinations. No statistically significant interactions were discovered.

From an organizational perspective, improving all of the previously mentioned steps is inconsequential if the study does not result in sufficient accruals. A total of 218 studies contained complete accrual data; 200 were managed by the VICC, and 18 were managed by the

Table 4. Accruals per Trial for All Phases

No. of Accruals per Trial	No. of Studies	Total Studies (%)	Cumulative %
0	45	20.6	20.6
1-4	72	33.0	53.7
5-10	42	19.3	72.9
11-15	24	11.0	83.9
16-20	8	3.7	87.6
> 20	27	12.4	100.0
Total	218		

Table 5. Accrual Percentages by Trial Phase

No. of Accruals per Trial	Studies by Phase (%)							Total Studies (%)
	I	I/II	II	II/III	III	Pilot	Other	
0	3.4	10.0	22.3	0.0	27.5	50.0	36.4	20.6
1-4	31.0	40.0	35.1	71.4	27.5	16.7	18.2	33.0
5-10	27.6	10.0	20.2	—	19.6	33.3	9.1	19.3
11-15	13.8	15.0	10.6	—	11.8	—	9.1	11.0
16-20	6.9	—	3.2	14.3	3.9	—	—	3.7
> 20	17.2	25.0	8.5	14.3	9.8	—	27.3	12.4
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

VICCAN. A total of 1,898 patients were accrued, representing an average of 8.7 patients per trial. It is interesting to note that more than one in five studies (20.6%) that were opened resulted in no actual accruals and that more than half the studies (53.7%) had fewer than five patients accrued (Table 3). Tables 4 and 5 show a more in-depth analysis of accruals. Further investigation of this important issue is required.

DISCUSSION

Our study assesses the impact of process, structural, and infrastructural barriers in such areas as time to IRB approval, number of committee approvals required, and the number of signatures needed before opening an oncology clinical trial. We completed this analysis at VICC and at three VICCAN community oncology practices.

Although documentation of the processes has infrequently been analyzed, numerous opinions on the weaknesses of the process have been described.⁹ These reports have implicated various process aspects as barriers to clinical trial activation, such as contracting,⁹ or have

commented on more global issues, suggesting that trials would be easier to open at nonacademic medical centers because of fewer layers of bureaucracy. Our results reveal that the process can be overly complicated and inefficient but that the causes and subsequent prescription for improvement may not be what has been historically and generally believed.

Our study reveals that the number of steps in opening a clinical trial is quite similar between the VICC and VICCAN practices that are aligned with VICC. However and perhaps not surprisingly, the number of committees or individuals involved in the approval/activation process (27 committees or individuals at VICC v five committees or individuals at VICCAN) and the resultant number of signatories required (16 to 27 signatures at VICC v five to eight signatures at VICCAN) is far greater at VICC compared with VICCAN. Despite these substantial differences in the complexity of opening a trial at these two types of institutions, the actual time to open a trial was not statistically different between the two settings (185.8 v 218.6 days for VICC and VICCAN, respectively; $P = .192$). However, our results may not be applicable to practices not affiliated to an academic medical center.

Table 6. Days From Receipt to Opening of an Oncology Clinical Trial

Trial Phase, Sponsor Type, and Manager	No. of Trials	No. of Days From Receipt to Opening of an Oncology Clinical Trial				
		Mean	Standard Deviation	Median	95% CI	Range
Phase, $P = .151^*$						
Pilot	5	250.0	60.15	231	189 to 344	189-344
I	28	204.9	125.82	176.5	131 to 249	27-614
I/II	20	178.2	81.16	174.5	123 to 235	27-356
II	91	200.2	104.31	181	166 to 204	41-594
II/III	7	154.9	67.68	174	57 to 238	57-238
III	50	173.2	99.64	157	138 to 175	54-657
Other	10	127.9	45.49	120.5	80 to 160	62-228
Sponsor type, $P < .001^*$						
Company	131	208.8	97.0	179	167 to 195	41-614
Internal	8	239.1	95.44	230	158 to 449	158-449
Oncology cooperative group	58	141.6	96.07	120	97 to 147	27-657
Other	14	221.4	115.18	197.5	155 to 259	62-475
Manager, $P = .192$						
VICC	193	185.8	98.99	171	158 to 182	27-657
VICCAN	18	218.6	127.65	191	119 to 269	62-594
Total	211	188.6	101.8	172	159 to 182	27-657

Abbreviations: VICC, Vanderbilt-Ingram Cancer Center; VICCAN, Vanderbilt-Ingram Cancer Center Affiliate Network.

*Excludes phases with less than 11 trials.

To explain these somewhat paradoxical findings, we next analyzed the steps involved and grouped them into the following general processes: submission clean-up (defined as the time from investigator submission to initiation of formal protocol submission), IRB review and approval, SRC review and approval, contracting and budgeting review, and time to accrual of first patient (time from opening of clinical trial for accrual until the first patient is placed onto study). When one evaluates the process in a timeline fashion (Fig 2), it is immediately apparent that the process taking the longest time and, thus, representing the rate-limiting factor is the contract and grants process and not IRB review and approval. This raises two issues. First, improving the IRB process will do little to reduce the time it takes to open a clinical trial unless there is meaningful impact on all other processes, and second, major efforts should be taken to improve the contracting practice.⁹ It also should be noted that, in our study, the contracting process represents a combination of the budgeting process and contract negotiations.

One additional discovery of our study was the identification of a large percentage of opened trials with no or poor accruals. This fact points to an issue that must be addressed when evaluating clinical trial barriers; given limited resource availability, expending time and effort on studies that do not accrue is clearly nonvalue added.

No differences were found in the time to open a trial based on manager or phase of trial (Table 6). Numerically, it may seem that

opening a cooperative group trial is faster than opening a non-cooperative group trial (mean time, 141.6 v 188.6 days, respectively), but one must remember that there is an additional time that must be added to this; the time it takes to activate a study within the cooperative group may take as long as a year or more.

We are currently applying these techniques to the setup process in cancer clinical trials in multiple settings at VICC, VICCAN, and a major cooperative oncology group. We have plans to analyze the barriers at additional National Cancer Institute Comprehensive Cancer Centers and cooperative oncology groups in the future.

As shown in other industries, enhancing the efficiency of opening clinical trials would make the processes faster and enhance overall patient treatment options without compromising research integrity or patient safety. Putting this into perspective, it takes a median of 172 days to open a clinical trial, irrespective of the phase of the study. Given that investigational agents generally undergo three phases of testing, this means that nearly a year and a half of drug development are mired in administrative paperwork of limited value. The end result of our research is to highlight the magnitude of these barriers to opening clinical trials at a comprehensive cancer center and at local, community practice sites. With an increasing number of new agents to evaluate,¹⁰ overcoming such barriers is of critical importance. Clearly this is an area that requires additional study.

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Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
David M. Dilts	Vanderbilt University (N/R)					Vanderbilt University (B)		Vanderbilt University (B)
Alan B. Sandler	Vanderbilt University (N/R)					Vanderbilt University (B)		Vanderbilt University (B)
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Author Contributions

Conception and design: David M. Dilts, Alan B. Sandler
Financial support: David M. Dilts, Alan B. Sandler
Administrative support: David M. Dilts, Alan B. Sandler
Provision of study materials or patients: David M. Dilts, Alan B. Sandler
Collection and assembly of data: David M. Dilts, Alan B. Sandler
Data analysis and interpretation: David M. Dilts, Alan B. Sandler
Manuscript writing: David M. Dilts, Alan B. Sandler
Final approval of manuscript: David M. Dilts, Alan B. Sandler