Time Required to Initiate a Pandemic-Focused Clinical trial in Canada

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Abstract

Background

Randomized control trials (RCTs) provide essential evidence to inform clinical practice. However, there are many necessary steps resulting in lengthy times to initiate trials. This is problematic for RCTs evaluating treatments for rapidly emerging infections, as experienced during the COVID-19 pandemic.

Methods

Participating hospitals in the Canadian Treatments for COVID-19 RCT were surveyed using a structured data abstraction form. We measured durations from protocol receipt to site activation and first patient enrollment, and durations of administrative processes including research ethics board (REB) approval, contract execution, and lead-time between approvals to site-activation.

Results

All 48 sites responded. Median time from protocol receipt to trial initiation was 111 days (interquartile range [IQR]: 39, 189; range: 15, 412). Median time between protocol receipt and REB submission was 41 days (IQR:10, 56; range: 4, 195); REB submission to approval, 4.5 days (IQR: 1, 12; range: 0, 169); REB approval to site activation, 35 days; (IQR: 22, 103; range: 0, 169); protocol receipt to contract submission, 42 days (IQR: 20, 51; range: 4, 237); contract submission to full contract execution, 24 days (IQR: 15, 58; range: 5, 164); and contract execution to site activation, 10 days (IQR: 6, 27; range: 0, 216). Processes took longer in community hospitals than academic hospitals.

Interpretation

RCT initiation in Canada is lengthy and varies among sites. Adoption of model contract trial templates, greater central coordination of ethics submissions, and long-term funding of platform trials that engage academic and community hospitals are potential solutions to improve trial start-up efficiency.

Word count (excl headers): 250

Introduction

There is an imperative to initiate clinical trials rapidly during a health emergency. Unfortunately, during recent infectious disease outbreaks, such as the severe acute respiratory syndrome (SARS) in 2003, pH1N1 influenza in 2009 and Ebola in 2014-16, investigators were generally unable to initiate randomized clinical trials in time to inform management while the outbreaks were still active. [1] [2] [3] In contrast, during the COVID-19 pandemic, hundreds of clinical trials have been initiated, many with overlapping interventions, both globally and within Canada. Many trials did not complete planned enrollment as their start-up was delayed by logistical difficulties and results were superseded by those from jurisdictions that were able to initiate and recruit more quickly.

In Canada, clinical trial initiation requires several steps including: Health Canada approval in the case of novel or repurposed medications; establishing a supply of study medications; ethics approval at each site (facilitated in some provinces by provincial or regional research ethics boards [REBs]); establishment of legal contracts between the trial sponsor (the institution responsible for trial conduct) and each participating site; training of research, pharmacy and clinical staff involved in the study; and site operational approvals to ensure all start-up activities are completed and regulatory standards have been met. The duration of each step depends on site experience, site-specific requirements, the pragmatism of the study design and the availability of multi-site harmonization of processes.

CATCO (Canadian Treatments for COVID-19; NCT04330690) [4] is a CIHR-funded multicentre randomized clinical trial examining therapeutic interventions for hospitalized patients with COVID-19 in Canada. In this paper, we describe the start-up timelines for CATCO at 48 hospitals across Canada during the early phase of the COVID-19 pandemic in 2020 and highlight opportunities for improvement in trial initiation and logistical conduct in Canada, for both pandemic and non-pandemic research.

Methods

Design and Setting

This is a time-motion study of the start-up of CATCO, a multicentre, adaptive, open-label, randomized controlled trial of therapeutics for the treatment of COVID-19 in hospitalized patients [4]. The methods of this study were adapted from a previous study [5]. This study included data from 48 hospitals in 8 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia, Newfoundland and Labrador), as well as 4 regional ethics submission sites (Ontario, Quebec, British Columbia and Alberta).

Data Collection

Sites participating in CATCO were asked to submit the following information electronically via a data abstraction form: 1) date of initial REB submission, 2) date of REB approval, 3) date of contract submission to site legal services, 4) date of full contract execution (defined by receipt of all required signatures), 5) date of site activation (defined by the sponsor as having completed all necessary start-up procedures), and 6) date of first patient enrollment. The date that the CATCO protocol was distributed electronically to the sites was used as a proxy for protocol receipt. Sites were defined as either "academic", or "community" based on self-designation as fully affiliated (or not) with a university, [6] anticipating that different research infrastructure may exist between academic and community sites.

Analysis

Using the survey data, the following durations were calculated: 1) protocol receipt to site activation (i.e. total time required to initiate the trial) 2) protocol receipt to REB submission 3) protocol receipt to legal

contract submission 4) REB submission to approval 5) legal contract submission to execution 6) contract execution to site activation 7) REB approval to site activation. Durations were represented as medians with interquartile and full ranges. Sites were categorized as academic or community based on university affiliation, as defined above. All analysis was done in Excel version 16.57 (Microsoft, Redmond WA, USA).

Results

All 48 sites (26 academic, 22 community) and 4 regional REBs that were surveyed provided data for the study. Figure 1 shows the stepwise and parallel processes required in trial initiation and their respective durations. These included REB submission, contract submission, REB approval, contract execution, and site activation. The median length of time required for each of these steps in CATCO is shown in Table 1, with sites grouped by academic or community hospital status. Overall, the median time to initiate the trial was 111 days (IQR: 39, 189; range: 15, 412). The median time between: protocol receipt and REB submission was 41 days (IQR:10, 56; range: 4, 195); protocol receipt and contract submission was 42 days (IQR: 20, 51; range: 4, 237); REB submission to approval was 4.5 days (IQR: 1, 12; range: 0, 169); contract submission to full contract execution was 24 days (IQR: 15, 58; range: 5, 164); REB approval to site activation was 35 days (IQR: 22, 103; range: 0, 169); and contract execution to site activation was 10 days (IQR: 6, 27; range: 0, 216).

When subdivided by academic or community status, the median duration from protocol dissemination to site activation was 70 days (IQR: 25, 183; range: 15, 392) in academic sites and 118 days ((IQR: 91, 192; range: 28, 412) in community sites. Aside from a similar time between REB submission and approval, all incremental steps in study activation took longer at community sites relative to academic sites (Figure 2).

The CATCO protocol was finalized on March 13, 2020, the first site was activated on April 2, 2020 and the first patient was recruited on April 3, 2020. The cumulative number of activated study sites throughout the first year of the COVID pandemic is illustrated in Figure 3.

Discussion

In this descriptive study of start-up times for a large, multicentre randomized controlled trial, we found that the median time to initiate study enrolment was 111 days (3.5 months). The first site was activated on April 2nd, only two weeks after the CATCO protocol was finalized. However, the majority of sites initiated recruitment after the 1st wave of the pandemic had already passed (Figure 3). This lengthy interval represents a lost opportunity to generate evidence early in the pandemic.

The most time-consuming steps in site initiation were submission and approval of trial contracts. REB approvals and post-approval site activation occurred comparatively quickly, at an average of 7-10 days. Therefore, improving the timeliness of contract writing and execution is crucial to augment the efficiency of clinical trial start-up in Canada.

Currently in Canada, clinical trial agreements are negotiated between the trial sponsor and each individual site, typically via the site's research institute or university. While most sponsors have a template trial agreement, subsequent negotiations proceed in parallel, with legal review required at each site. Although the core elements of such agreements are commonly accepted, there can be substantial back-and-forth negotiations around individual and shared responsibilities, site payments, intellectual property, trial insurance, and indemnification. Prior work establishing model contract trial agreements for pharmaceutical-based trials has been helpful [7] but they are uncommonly used by

Canadian research institutes. Failure to adopt a model clinical trial agreement likely created the single greatest barrier to timely initiation of CATCO. This shortcoming represents an urgent collective responsibility of trialists, legal and paralegal experts, and hospital/research institute administration to improve and re-focus the purpose of these legal agreements. This problem might also be addressed by CIHR, which funds the vast majority of investigator-initiated trials in Canada, as a priority to improve the impact of Canada's investment in health research.

In contrast, our anecdotal experience during the COVID-19 pandemic, reinforced by the findings in this time-motion study, is that individual research ethics boards and regional/provincial collaborative ethics organizations were comparatively rapid in reviewing, commenting upon and subsequently approving pandemic-related proposals. The development of provincial clinical trials ethics organizations has greatly improved research ethics efficiencies since the influenza A(H1N1) pandemic. These organizations encourage trial protocol submission to one collaborating research institute's REB, which subsequently becomes the lead for a submission to the provincial REB and can efficiently vet on behalf of other REBs in the province. Having such a system active within each province would further improve efficiency. In addition, having a representative of each provincial ethics organization populate a national *operational* research ethics committee (*in distinction, or in addition to, a national research ethics board*) could encourage common provincial REB submission platforms and streamline submission activities at individual sites. An inter-provincial agreement on the necessary common research ethics submission elements might also facilitate a national research ethics board that could respond to a set of nationally defined public health emergency triggers and serve as an *occasional* national board of record for multicentre trials.

Importantly, we found substantial variability in total start-up time across sites, ranging from 15 days to 412 days. Typically, the sponsoring site has greater lead time and strong participation incentive, which ensure rapid start-up. Not surprisingly, we found that community sites often lacked the infrastructure to vet protocols, assess ethics submissions and respond to contracting requests, leading to longer site initiation times. Closing this gap is important because community sites look after the vast majority of Canada's critically ill patients. [6] Templated clinical trial agreements developed in consultation with stakeholders and regional ethics organizations would help to meet these infrastructure challenges, potentially encouraging more community sites to participate in research.

While this study examined the timelines of only one large clinical trial, many other observational studies and clinical trials were undertaken during the first phase of the pandemic. Traditional clinical trials assess a single intervention. For each subsequent intervention, a new clinical trial is designed, and the same set of start-up procedures are repeated. CATCO is an adaptive platform trial, meaning that it compares prioritized interventions using a common, durable clinical trial platform that can remain operational throughout the pandemic, with interventions stopped according to efficacy determination, followed by the addition of new interventions. This strategy avoids the need for repeated start-up procedures as described in this study. Durable, year-on-year funding for coordinated, centrally operational adaptive platform trial infrastructure is a necessary evolution in the conduct of clinical trials and learning health systems and could lead to improved efficiency in evaluating interventions as well as reduced per-patient costs. [8] [9] [10] [11]

The strengths of this study are, first, its focus on a pressing contemporary challenge in clinical research. Second, we were able to collect granular timeline information from the largest multicentre COVID-19 clinical trial in the Canadian context and estimate the relative importance of various steps in the

research pathway. Third, we engaged a relatively large number of community sites in this study, better reflecting the balance of where most Canadians receive healthcare. Fourth, based upon our findings we offer concrete solutions to the challenges highlighted.

This study also has a number of limitations. The study survey relied on site staff to retrospectively recall timepoints in the clinical trial initiation process. Accordingly, we encountered missing data at some sites for some milestones. Second, site-to-site variations existed in the process itself, which may have impacted timelines. For example, one site did not require a legal contract and some, but not all, sites used a multi-jurisdictional ethics review board. These factors may have contributed to over- or underestimation of some of the time intervals. Third, the data describes only one trial that took place during the first waves of a pandemic, and while our findings may be generalizable to other large investigator-initiated clinical trials, a broader examination across many trials and studies during the pandemic, and beyond the pandemic, might discover additional important barriers .

Improved clinical trial infrastructure is essential to the timely and efficient conduct of clinical trials that generate evidence to inform the care of patients. [12] [13] Adoption of harmonized clinical trial agreements, greater inter-provincial coordination in research ethics review, streamlining of Health Canada regulations for low-risk clinical trials [14] and a transition towards funding durable research networks across health systems in Canada would address many of the challenges currently faced by clinical trials. A more harmonized clinical trials infrastructure would emulate elements of the United Kingdom's National Institute for Health Research [12] [13], which integrates clinical research with clinical care in the United Kingdom. An ideal system would be embedded and funded from within the Canadian healthcare system and would allow shifting of resources to meet the evolving research needs of the system while alleviating the administrative workload on individual research institutes.

Conclusion

Randomized controlled trials provide essential evidence to inform treatments; however, they are slow to initiate. Even in a pandemic setting, the time required to initiate CATCO, a large clinical trial, was lengthy and varied considerably from site to site. Adoption of model clinical trial agreements, coordination of research ethics vetting, and funding of durable clinical platform trials that engage both academic and community hospitals are all potential solutions to the barriers identified in this study.

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Figure 1: Schematic of processes leading to clinical trial initiation at site

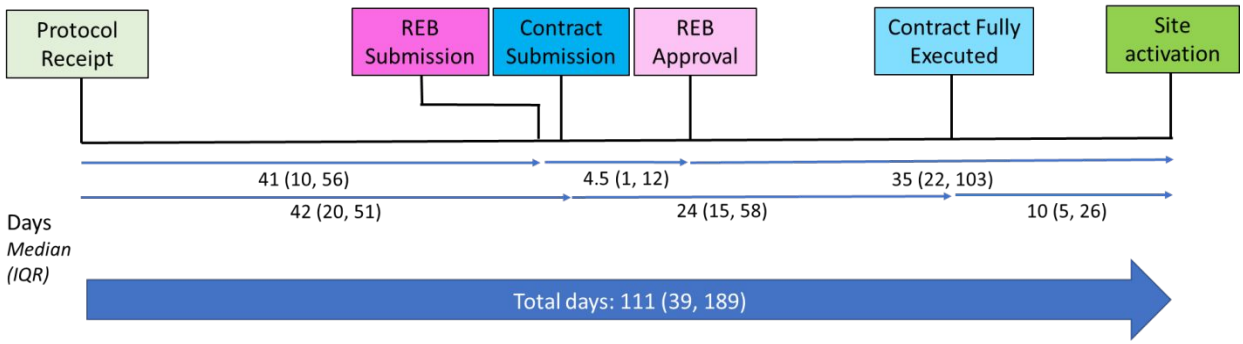

Figure 2. Durations of steps leading to clinical trial initiation at academic and community sites

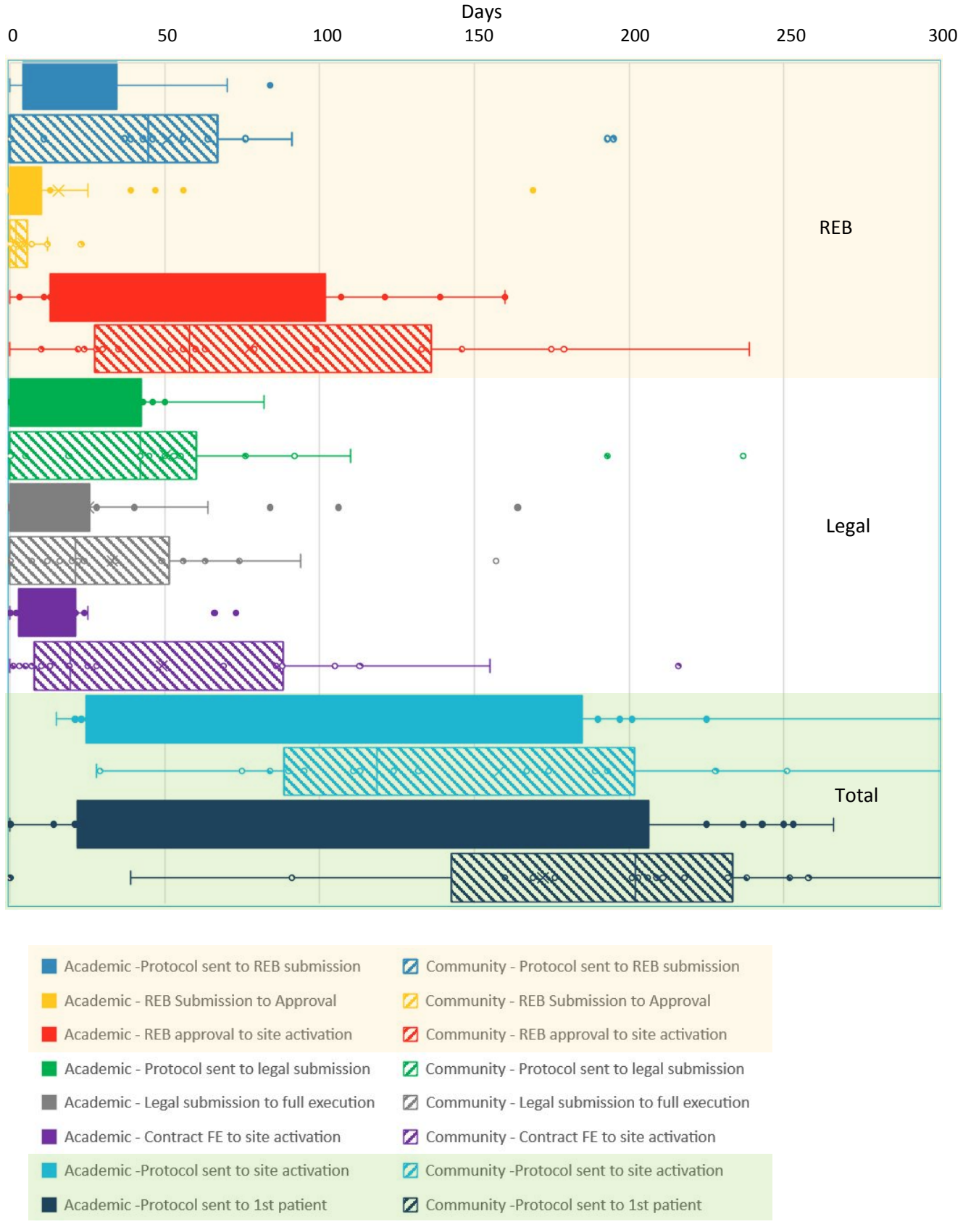

Figure 3: Cumulative number of activated sites for CATCO in the first year of the COVID pandemic

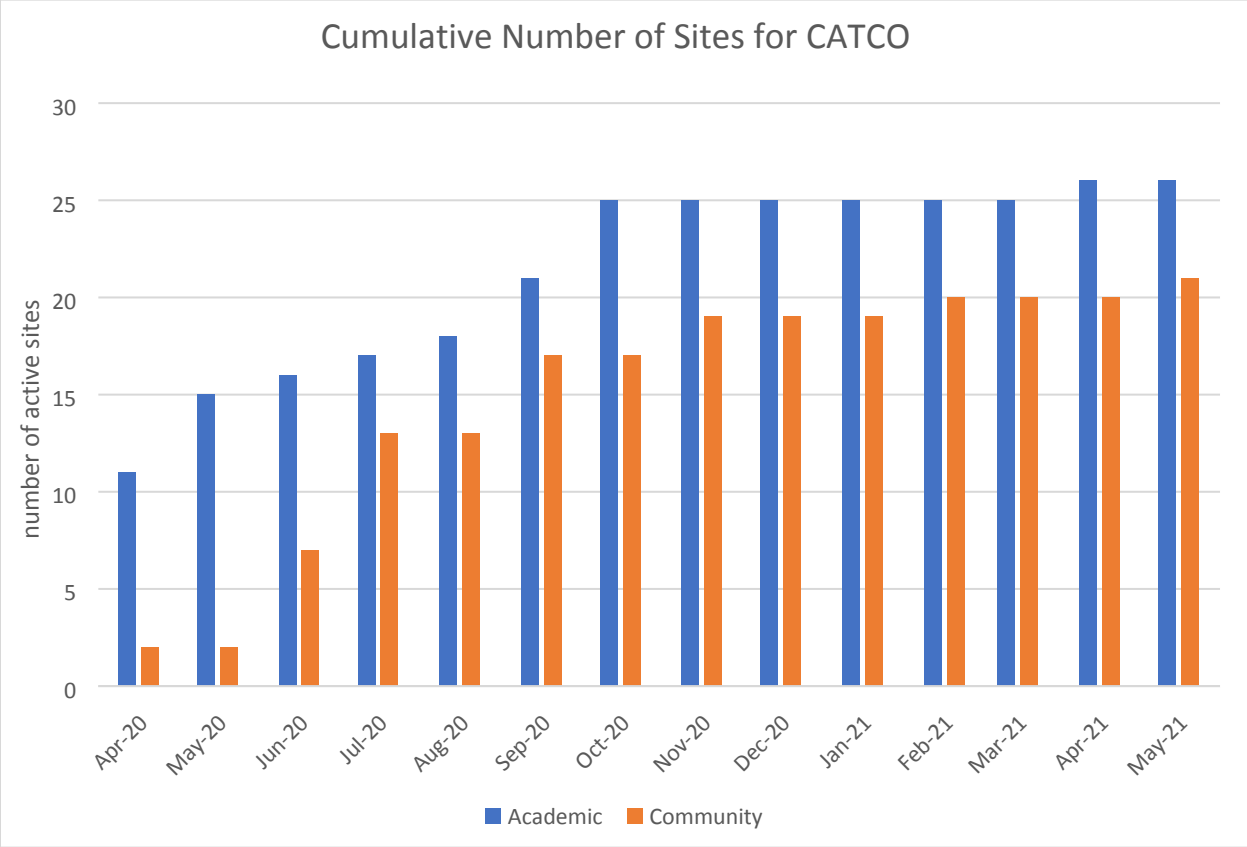

Table 1: Time (days) required for incremental steps in clinical trial initiation across participating sites

	Total (days)			**REB** (days)			**Legal** (days)		
	Protocol sent to site activation	Protocol sent to 1st patient enrolled	Site activation to first patient	Protocol sent to REB submission	REB Submission to Approval	REB approval to site activation	Protocol sent to contract submission	Site activation to first patient	Contract to site activation
All Hospitals									
Mean (SD)	128.0 (99.6)	151.3 (93.3)	48.8 (54.5)	44.8 (44.1)	13.4 (29.4)	65.1 (57.6)	50.7 (49.7)	48.8 (54.5)	31.4 (45.1)
Median (IQR)	111 (38.8-189.3)	169 (53-232)	32 (4-76)	41 (10-56)	4.5 (1-12)	35 (22-103.5)	42 (20.5-50.8)	32 (4-76)	10 (5.5-26.5)
Min-Max	15-412	14-358	1-210	4-195	0-169	0-239	4-237	1-210	0-216
*Academic Hospitals									
Mean (SD)	102.7 (94.4)	109.7 (96.5)	33.9 (47.8)	24.5 (24.2)	19.4 (39.0)	52.4 (50.1)	30.6 (22.4)	33.9 (47.8)	15.9 (21.0)
Median (IQR)	68.5 (25.3-182.3)	71 (27.5-218.8)	5 (2.3-58.5)	16 (5-38)	5 (1-16)	32.5 (13.3-93.5)	41 (4-43)	5 (2.3-58.5)	8 (4-21)
Min-Max	15-392	14-266	1-140	4-84	0-169	0-160	4-82	1-140	0-73
*Community Hospitals									
Mean (SD)	158.3 (101.5)	199.4 (66.3)	65.9 (59.4)	70.1 (51.9)	5.8 (6.2)	80.8 (64.1)	73.5 (63.5)	65.9 (59.4)	49.0 (58.6)
Median (IQR)	118.5 (91.3-192)	206 (169-235)	45 (24-103.5)	51.5 (43-76.3)	4 (1.8-8.3)	60 (30-133)	50 (42-84)	45 (24-103.5)	19.5 (8-87.5)
Min-Max	28-412	39-358	1-210	11-195	0-23	10-239	5-237	1-210	0-216

*Academic Hospitals' response rate = 15/26; Community Hospitals' response rate = 13/22; Regional Research Ethics Centres' response rate = 3/4, results reported in the text.

REB, Research Ethics Board