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Time required to initiate outbreak and pandemic observational research☆,☆☆

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ABSTRACT

Purpose: Observational research focused upon emerging infectious diseases such as Ebola virus, Middle East respiratory syndrome, and Zika virus has been challenging to quickly initiate. We aimed to determine the duration of start-up procedures and barriers encountered for an observational study focused upon such infectious outbreaks.

Materials and methods: At 1 pediatric and 5 adult intensive care units, we measured durations from protocol receipt to a variety of outbreak research milestones, including research ethics board (REB) approval, data sharing agreement (DSA) execution, and patient study screening initiation.

Results: The median (interquartile range) time from site receipt of the protocol to REB submission was 73 (30-126) days; to REB approval, 158 (42-188) days; to DSA completion, 276 (186-312) days; and to study screening initiation, 293 (269-391) days. The median time from REB submission to REB approval was 43 (13-85) days. The median time for all start-up procedures was 335 (188-335) days.

Conclusions: There is a lengthy start-up period required for outbreak-focused research. Completing DSAs was the most time-consuming step. A reactive approach to newly emerging threats such as Ebola virus, Middle East respiratory syndrome, and Zika virus will likely not allow sufficient time to initiate research before most outbreaks are advanced.

1. Introduction

New emerging and reemerging infections such as Ebola virus, Middle East respiratory syndrome (MERS-CoV), and Zika virus are a concern for the public, clinicians, health systems, and public health agencies. Outbreaks and pandemics are perceived to occur at increasing frequency; however, they remain unpredictable in their time and location of onset [1]. Outbreaks increase patient morbidity and mortality, and cause additional burden on health care workers, facilities, and health agencies [2-4]. Surveillance can identify cases at an early stage and lead to prevention of broader spread. Severe acute respiratory syndrome [5]; pandemic influenza A (H1N1) 2009-2010 [6]; and, more recently, Ebola virus [7], MERS-CoV [8], and Zika virus have been characterized by challenges initiating observational research and a near inability to rapidly undertake interventional trials necessary to inform best practice and improve care of patients [9-11]. This has prompted calls from patients, clinicians, funders, and policy makers to improve preparedness, including the capacity to undertake real-time research during such events. However, conducting studies and trials involves time-consuming start-up steps such as development of study protocol, establishing a budget and obtaining funding, research ethics

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board (REB) approval, organizing multisite collaboration, and data sharing agreements. The objective of this study was to determine the delay from protocol completion to study initiation and determine time spent in each of the necessary steps to identify and collect data in real time for new and emerging infection-related critical illness.

2. Methods

2.1. Design and setting

This is a time-in-motion study accompanying a prospective surveillance project to assess the feasibility of screening and real-time data collection for severe acute respiratory infection (SARI)- and outbreak-related critical illness. The parent prospective study aimed to screen all hospitalized critically ill patients on a daily basis for up to 72 hours after admission to detect all cases of SARI, the details of which are published elsewhere [12]. The study included 1 pediatric and 5 adult intensive care units (ICUs) across 6 Canadian provinces. Paper and electronic case report forms and daily and weekly screening log sheets were made available to all the sites to be used for data collection (Appendix). The study was approved by each participating site's REB and was funded by the Public Health Agency of Canada, Canadian Critical Care Trials Group, and Heart and Stroke Foundation (Ontario office).

2.2. Data collection

For the purpose of this study, the following data were collected: time required from protocol receipt by the site to REB submission, time required from REB submission to REB approval, time required from REB approval to data sharing agreement execution, time required from data sharing agreement execution to screening initiation, time required from protocol receipt to data sharing agreement execution, time required from protocol receipt to screening initiation, and overall time required for start-up procedures.

2.3. Statistical analysis

Categorical variables are presented as numbers and proportions. Durations are presented as median, interquartile range (IQR), and ranges. All statistical tests were 2-tailed, and the significance level was set at $P < .05$.

3. Results

Table 1 shows the median time required in each step along the pathway to initiate an observational study of outbreak surveillance in ICUs. Overall start-up procedures required a median (IQR) of 335 (188-335) days (range, 128-335). Median (IQR) duration from protocol receipt to REB submission was 73 (30-126) days (range, 3-127) and protocol receipt to REB approval was 158 (42-188) days (range, 31-218 days). Time from protocol receipt to data sharing agreement receipt was 92 (92-104) days (range, 92-104), protocol receipt to signed data sharing agreement was 276 (186-312) days (range, 177-335), and protocol receipt to screening initiation was 293 (269-391) days (range, 258-412). Time from REB submission to REB approval was 43 (13-85) days (range, 9-178), REB approval to data sharing agreement completion was 118 (58-139) days (range, 8-142), and REB approval to screening initiation was 123 (92-237) days (range, 71-238). Time from data sharing agreement receipt to data sharing agreement completion was 185 (89-215) days (range, 74-244), and data sharing agreement completion to screening initiation was 78 (35-99) days (range, 6-103) (Fig. 1).

Table 1
Median time (in days) spent from receipt of protocol, REB submission, and finalization of data sharing agreements to task completion at study sites

Duration	Median (d)	IQR (d)	Range (d)
Protocol receipt to REB submission	72.5	30.0-126.0	3-127
Protocol receipt to REB approval	158.0	42.0-188.0	31-218
Protocol receipt to DSA receipt	92.0	92.0-104.0	92-104
Protocol receipt to DSA signed	276.0	186.0-311.5	177-335
Protocol receipt to screening initiation	293.0	268.5-391.0	258-412
REB submission to REB approval	42.5	13.0-85.0	9-178
REB approval to DSA completion	118.0	58.0-139.0	8-142
REB approval to screening initiation	123.0	92.0-237.0	71-238
DSA receipt to DSA completion	185.0	89.0-214.5	74-244
DSA completion to screening initiation	78.0	35.0-99.0	6-103
All Start-up procedures	335.0	187.5-335.0	128-335

DSA indicates data sharing agreement.

4. Discussion

In this multicenter study of severe acute respiratory infections, we observed that it took nearly 1 year to complete all necessary start-up procedures before enrolment in the study could begin at all sites. Obtaining an interinstitutional legal data sharing agreement required approximately 9 months from protocol receipt to completion—the most time-consuming process. It took sites approximately 2½ months after protocol receipt to be ready to submit to their REB yet only approximately 1½ months for REB approval. Our findings indicate that despite an existing in-ICU infrastructure and capability for real-time data collection and reporting, observational research during an outbreak or pandemic is at risk of failing because of the time required for start-up procedures. Seasonal influenza outbreaks provide a compelling annual example. If we do not initiate the study start-up process immediately after influenza season, we will not be ready for screening at the next.

The time necessary for appropriate and necessary REB vetting and approvals has been reported previously for various clinical trials [13-18]. However, none of the studies have identified the actual time required in initiating outbreak-related research at multiple sites. Efficient research initiation during an outbreak or pandemic is critical considering the potential for outbreak expansion and greater morbidity and mortality without better understanding of risk factors for illness and transmission, clinical course, outcomes, and responses to treatment. Although we studied timelines to initiate observational research, it is possible and in fact likely that start-up time for a clinical experimental trial would be even longer. This has been the experience during severe acute respiratory syndrome, pandemic influenza, MERS-CoV, Ebola virus, and now Zika virus [9-11].

There are various reasons for delays in initiating outbreak-focused observational research both at the investigator level and at the administrative level. Some of these reasons include (1) developing the study protocol and case report forms in a short span of time [13], (2) preparing REB applications, (3) fixed meeting dates of institutional ethics boards followed by important and necessary back-and-forth communications [16], (4) drafting and finalizing the data sharing agreements, (5) lack of parallel reviewing of REB applications and data sharing agreements across institutions, and (6) finalizing budget and arranging funding. There may be several possible ways to overcome these delays and be prepared ahead of time to conduct an outbreak-related study or trial. First, there is a need to have research-ready protocols-in-waiting for periods when seasonal or outbreak-related infections increase. This can be achieved through research-ready outbreak-related observational studies and trials using national and international networks [19], undertaking preemptive REB review of generic outbreak-related observational study case report forms and protocols, establishing data sharing agreements where necessary ahead of time, and helping other centers similarly prepare.

Although ethical approval is mandatory for research involving human subjects, there are provisions in many jurisdictions for exempt reviews for studies involving public health emergencies, typically consisting of observational studies collecting already available and anonymized data [20,21]. Similarly, collecting data as “quality