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Strategies for successful rapid trials of influenza vaccine

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Background In contrast to the gradual pace of conventional vaccine trials, evaluation of influenza vaccines often must be accelerated for use in a pandemic or for annual re-licensure. Descriptions of how best to design studies for rapid completion are few.

Purpose In August, 2010, we conducted a rapid trial with a seasonal influenza vaccine for 2010–2011 given to persons vaccinated with an adjuvanted H1N1 vaccine in 2009, to determine whether re-exposure to the H1N1₂₀₀₉ component of the seasonal vaccine would cause increased reactions. We describe the strategies that we believe were responsible for success in meeting the desired timeline.

Methods The key means for expediting the study were: use of a few experienced, well-staffed centers; efficient completion of administrative approvals; advance recruitment of volunteers; synchronized start among centers with rapid completion (≤ 1 week) of first visits; rapid data assembly via the Internet; and a well-prepared data analysis plan. We chose to use a randomized, blinded, cross-over design to allow estimation of vaccine-attributable adverse event rates, with sufficient power (320 participants) to detect events occurring at true rates $\geq 1\%$ with $\geq 90\%$ probability.

Results Planned enrollment numbers, center synchronization, and timelines, including review by a safety board prior to the cross-over step (second doses), were achieved. A detailed safety report was delivered to federal health officials just 32 days after study initiation and was used to fine-tune public messaging prior to the mass vaccination programs across Canada.

Limitations This aggressive timeline could not have been met without opportunities for careful planning and the prior existence of a network of experienced, collaborating trial centers.

Conclusions The means used to accelerate this study timeline were successful and could be used in other urgent situations but the mechanics of collaborative trials must be well rehearsed as a precondition. *Clinical Trials* 2011; 0: 1–6. <http://ctj.sagepub.com>

Background

The typical pace of trials to assess vaccine responses is 'slow and steady,' to enable study personnel to give full attention to participants and to observe best practices including progressive documentation of vaccine safety. A rapid pace is warranted when

a new vaccine must be evaluated quickly for regulatory approval, as in an influenza pandemic [1]. During the 2009 H1N1 influenza pandemic, at least five large trials [2–6] completed enrollment within 2 weeks but none of the responsible investigators described the strategies used to accelerate enrollment or study completion.

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Few publications are available to guide the design of rapid vaccine trials [1].

In 2010, Canadian public health officials requested a rapid safety evaluation of the seasonal influenza vaccine for 2010–2011 out of concern that re-exposure to the H1N1₂₀₀₉ component in the new vaccine might cause more frequent or severe adverse reactions in persons with high residual immunity, resulting from prior infection and/or receipt of the adjuvanted pandemic vaccine widely used in Canada. This trial needed to be completed prior to public distribution of the vaccine, with safety details made available to public health authorities across the country. A network of academic trial centers [7,8] successfully met this challenge, completing enrollment in 5 days and issuing a detailed report just 32 days after study commencement [9]. The acceleration strategies believed to be responsible for the success of this study are described in this report.

Methods

Network infrastructure

The rapid trial in 2010 (PCIRN RT06) benefitted from recently created infrastructure. The Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network (PCIRN) was funded in March 2009 by two Canadian federal agencies to demonstrate over 3 years preparedness to conduct essential research, including rapid vaccine trials, in a pandemic [8]. While the plan had been to conduct simulations using seasonal vaccines, the occurrence of the H1N1₂₀₀₉ pandemic shortly after the award was announced required immediate reorientation. Ten centers had volunteered to participate, all having had some experience with vaccine trials. The network funded a coordinator at each center for the remainder of 2009, during which time four concurrent studies were planned and conducted using a pandemic vaccine. None was completed as rapidly as desired, with enrollment spanning 6–12 weeks. Participating investigators volunteered their time.

This infrastructure aided mobilization of centers for the trial in 2010. With year 2 network funding pre-assigned, a new grant application was not required; internal protocol approvals sufficed. Consequently, 6 months were available to operationalize the protocol. Funding agreements were in place with each institution, needing only amendment for the new study. Communication pathways and standard operating procedures had been established network-wide. Center staff

were already trained in good clinical practices and were experienced with use of a commercial web-based data platform (Daciforms™, Montreal) customized for the previous studies. Limited re-programming was needed for this study.

Selection of participating centers

For a single trial of moderate size, it was judged to be most efficient to use 5 of the 10 network centers. This decision reduced the complexity and scale of organizational tasks such as training, monitoring, and supplying centers. We chose centers with the most experience, ample summer staffing, and ready access to potential participants. The project manager and center coordinators (funded for 6 months) were unchanged from the previous year, aiding communication. Each chosen center had two or more participating investigators to ensure continuous study supervision. Each center had capacity for multiple studies so that other work in progress was not hampered by the rapid trial.

Participant numbers and eligibility

The total sample size was set at 320, sufficient to detect severe or unusual adverse events occurring at $\geq 1\%$ incidence rate with $\geq 90\%$ probability, assuming 300 participants ultimately would be evaluable. Each center was asked to enroll 64 participants, a modest number for experienced teams. Loss of a center at the last minute would have added only 16 participants to be recruited by each remaining center and could have been accomplished easily.

For greater ease and speed of recruitment, we chose a wide participant age range (20–59 years) and accepted persons with stable health conditions not associated with immune dysfunction, rather than only healthy persons. This decision also made the study population more representative of the general population. Finding volunteers whose vacation time did not conflict with study participation was part of the challenge as August is a popular vacation month in Canada. Randomization was age-stratified at the central office but centers attempted to enroll equal numbers of younger (20–39 years) and older (40–59 years) participants, all of whom had to have had adjuvanted pandemic vaccine in 2009. The high rate of H1N1₂₀₀₉ vaccination among Canadian adults (approximately 50%) meant that finding eligible persons would not be difficult.

Administrative approvals

Obtaining timely ethics approvals at the five centers was key, as some research ethics boards (REBs) met infrequently in summer or had long waiting lists. Timely distribution of essential documents was necessary. The review process also benefitted from experience with the 2009 trials. Health Canada convened a meeting of REB chairs from network institutions early in 2010 to explore means to expedite the review process for high-priority studies. Outcomes included adoption of an explicit means for investigators to request prompt local review for pandemic-related studies. Moreover, center REBs could opt to conduct a limited local review after the lead center REB completed and shared an in-depth review; however, most REBs opted for full review on their preferred (accelerated) meeting schedule.

Securing a supply of 2010–2011 as yet unlicensed, trivalent, inactivated influenza vaccine required application to the Canadian regulatory agency as well as to the domestic vaccine manufacturer, whose review processes took several weeks. Negotiating a material (vaccine) transfer agreement with the manufacturer added a few more weeks. Using the same lot of vaccine that the manufacturer used for its pre-season study expedited the regulatory review process which was completed in just 17 days from application receipt.

The study was registered promptly with ClinicalTrials.gov (NCT-01140009) with assistance of the lead university's research office.

Volunteer recruitment and enrollment

Centers developed lists of potential volunteers as soon as local REB approval was obtained and before vaccine arrived. Most centers had previously created local databases of persons willing to be contacted about studies (e.g., previous study participants) and set about identifying eligible, available volunteers through e-mail and telephone contacts. With sufficient numbers of volunteers on standby lists, centers could schedule them for a few large clinic sessions to complete formal enrollment and deliver vaccinations very efficiently. In fact, all five centers began first visits on the same day (Monday, August 9, 2010) and completed them by Friday of that week. Two centers completed all first visits in 2 days by deploying many research personnel.

With first visits concentrated to such an extent, the subsequent scheduled contacts and visits followed in close order with minimal overlap. This concentration of contacts allowed efficient

deployment of research staff and accurate prediction of completion dates.

Study design

We preferred a randomized, blinded, placebo-controlled design for best-quality safety data. To avoid increasing participant numbers and costs for a separate control group, we chose a cross-over design in which each participant received vaccine and saline placebo injections 10 days apart, in random undisclosed sequence [10]. We chose a 10-day recovery period in case some adverse effects were unusually severe. Participants readily accepted this design even though it increased demands on their time.

Since common adverse events after influenza vaccination peak at about 24 h and resolve by day 6 [10], we planned a telephone interview at approximately 24 h post-vaccination to record any severe or unusual events and another at day 7 to summarize observations during the week. Participants kept a daily symptom diary as the basis for the day 7 debriefing interview. The same follow-up schedule and procedures were implemented after each 'vaccination.' The cross-over design created an opportunity for a safety review before the second vaccinations commenced.

Personnel training was conducted via a web-based seminar, without an investigator meeting. Monitoring of the study mainly was done remotely by telephone and fax, although on-site monitoring was conducted once at study completion.

Data assembly

An electronic data reporting platform was essential for rapid data assembly and analysis. We used a secure, web-based platform (DaciformsTM, Montreal) for data entry that also managed random assignments. Center staff entered safety data on a same- or next-day basis, enabling the study statistician to monitor adverse events nearly in real time (maintaining blinding). Pre-programmed analysis tables accelerated the interim and final data analyses and report generation.

We shared all day 1 and most day 7 safety data following first doses with the Data Safety Monitoring Board (DSMB) for review prior to commencing second vaccinations [11]. The DSMB did not require any changes to the timeline or safety information provided to participants.

Table 1 Selected trials of H1N1₂₀₀₉ pandemic vaccines with explicit timelines

	Lead author/country	Start date	End date	Enrollment period	N	Age group	Centers	First published
1	Nolan/Australia [12]	August 3, 2009	–	5 weeks	370	Children (2 doses)	5	December 21, 2009 (express)
2	Waddington/UK [13]	September 26, 2009	December 11, 2009	4 weeks	949	Children (2 doses)	5	May 12, 2010 (online)
3	Plennevaux/USA [2]	August 2009	–	2 days	849	Adults	35	December 16, 2009 (online)
4	Wu/China [3]	July 22, 2009	September 7, 2009	8 days	474	Children	1	July 15, 2010 (online)
5	Zhu/China [14]	July 2009	–	4 days	706	Adults	1	July 15, 2010 (online)
6	Greenberg/Australia [4]	July 22, 2009	–	≤8 weeks	2200	Children, adults	1	October 21, 2009 (online)
7	Nicholson/UK [15]	October 19, 2009	March 2010	5 days	240	Adults	1	September 10, 2009 (online)
8	Cheong/Korea [5]	September 21, 2009	November 2009	4 weeks	347	Adults (2 doses)	3	September 10, 2009 (online)
9	Carmona/Spain [16]	September 2009	January 2010	5 days	493	Adults (2 doses)	5	December 17, 2010 (online)
10	Liang/China [6]	July 22, 2009	September 18, 2009	–	157	Children (2 doses)	5	Press release October 23, 2009 Full June 29, 2010 (online)
11	Clark/UK [17]	July 2009	September 2009	~2 weeks	12,691	> 3 years	10	December 16, 2009 (online)
				–	176	Adults	1	September 10, 2009 Full December 17, 2009

Note: N, number of participants.

Results

A detailed safety report was delivered to federal health officials on September 10, just 32 days after study initiation and well before the start of public vaccine distribution in mid-October. The report was widely distributed to national and provincial immunization advisory committees and influenza immunization program administrators and informed their public messaging for the mass campaigns. The opportunity to cite vaccine-attributable rates of adverse events following immunization as a result of the cross-over design was appreciated by report recipients. The actual observations will be the subject of a separate publication [9].

A secondary outcome of the study was measurement of immune responses to vaccination. Blood samples were obtained at baseline and 21–28 days after actual vaccination. To ensure uniform timing of post-vaccination samples, it was necessary to break the randomization code after each participant completed the final safety interview. However, staff involved in query resolutions, data analysis, and laboratory testing remained blinded to the vaccine-placebo sequence. We did not attempt to accelerate sample testing and response analysis as public programs would have been well advanced before results were available. An earlier start by several weeks would have been needed to provide immunogenicity data before the start of public programs.

Discussion

To place our 32-day study completion timeline into perspective, we tabulated the timelines for enrollment and study completion for 11 trials of various H1N1₂₀₀₉ vaccines that provided this information (Table 1). All were undertaken soon after pandemic vaccines became available for field testing. Four studies [2–5] completed enrollment in less than a week, with participant numbers ranging from 240 to 849. Remarkably, a study involving 12,691 participants in China [6] completed enrollment in about 2 weeks. A study by Greenberg et al. [4] reached publication with full serologic data for dose one just 7 weeks after commencing enrollment. None of these 11 studies described the strategies used to accelerate enrollment and study completion, apart from use of multiple centers in some instances.

Sharing our insights into the requirements necessary for successfully conducting a rapid trial may assist others to plan trials in a pandemic or other crisis situation. While we used a cross-over design

for its many advantages, we recognize that other design options exist for speedy trials. In fact, we also used an open design without placebo for a rapid safety trial in children [18] that commenced shortly after we determined that seasonal influenza vaccine reactogenicity was not increased in adults. The second study was stimulated by reports from Australia of increased reactogenicity of another seasonal influenza vaccine in young children [19]. The four PCIRN centers involved in the pediatric trial used similar acceleration strategies to complete it before mass vaccination programs commenced and could again provide reassuring safety data for both primary and repeat vaccinations (i.e., in those newly vaccinated or given adjuvanted H1N1 vaccine in 2009).

The strategies that we used to accelerate both studies are summarized in Table 2, which may serve as a planning tool for others. The most critical features were use of a few experienced, well-staffed centers; efficient completion of administrative approvals; advance recruitment of volunteers; a synchronized start among centers with rapid completion of first visits; rapid data assembly via the Internet; and a well-prepared data analysis plan.

These trials would not have been possible without a pre-existing network of trials centers [8]. These centers worked together during the pandemic in 2009, had experience with the web-based data platform, and had adopted standard operating procedures. Each local team had shepherded urgent requests through their REB and had established

Table 2 Strategies for a successful rapid vaccine trial

1	Selection of experienced, well-staffed trial centers, led by a capable management team
2	A manageable enrollment quota per site, to favor efficiency and success
3	Prior financial agreements with sites, as in a funded network, to speed approval
4	Expedited ethics review and approval, ideally coordinated among sites
5	Timely access to the study vaccine(s), in cooperation with the manufacturer(s)
6	Advance identification or recruitment of volunteers, before vaccine is available for administration
7	Synchronized start among participating centers
8	Rapid completion of enrollment and vaccinations, using large, well-staffed clinics
9	Same or next data entry of data after study contacts, using a web-based data platform
10	Speedy data clean-up and query resolution, also using the data platform
11	Prompt transfer of sera to a laboratory with high throughput capacity for assays
12	Pre-programmed data tables, for speedy analysis and reporting of data

funding arrangements with the network. With the mechanics of collaborative trials well rehearsed, studies with accelerated timelines were feasible. True preparedness for rapid trials in a pandemic requires substantial infrastructure, funding, and rehearsal opportunities, as described.

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