Throughout the development process, strong international multi-stakeholder involvement will involve early phase methodologists and trialists, including clinicians, trial managers and statisticians, journal editors and peer reviewers, ethics committees, funders, regulators and patient and public partners. Involvement will ensure the produced guidance reflects the views of the wider early phase trials community. The Executive Committee will pilot test the near-final guidelines with real-world trial examples to identify any gaps, troubleshoot any problems and incorporate feedback in the final revision.

To maximize awareness and engagement, as well as promote maximum uptake, a detailed dissemination strategy will be implemented. This will include workshops tailored to specific target groups such as journal editors, and the production of lay summary papers as well as publications of the various aspects of the work in academic journals.

Once published, it is expected the Dose-Finding CONSORT Extension will benefit the community in several ways as shown in Table 1. In the medium to long-term, the benefits of this Dose-Finding CONSORT Extension for society include improved efficiency and accuracy of dose-finding trials and the accelerated and safer development of novel therapies.

The Executive Committee would like to invite interested stakeholders to register their interest in taking part in the Delphi Survey process via the Dose-Finding CONSORT Extension project website[10]. ❐

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Author contributions

C.Y., J.d.B., M.D., J.E., S.H., T.J., A.K., S.L., A.M. and C.J.W. were responsible for conception and funding; A.E. and C.Y. drafted the manuscript; all authors critically revised the manuscript for important intellectual content and approved the final version.

Competing interests

The authors declare no competing interests.

The Seattle Flu Study: when regulations hinder pandemic surveillance

To the Editor — Despite the severity of the SARS-CoV-2 Delta and Omicron variants, many people are seeking to move on and re-establish life as they knew it before the COVID-19 pandemic. But public-health policymakers cannot move on unless and until a sustainable surveillance system is in place.

The Seattle Flu Study (SFS) represents a case study in what can go right — and wrong — even when such a surveillance system exists. In 2018, the Brotman Baty Institute, University of Washington School of Medicine, Seattle Children's Hospital and the Fred Hutchinson Cancer Research Center launched a city-wide platform for the surveillance of respiratory pathogens, as well as of pilot interventions, such as home-based testing and delivery of antivirals, to mitigate emerging pandemics[1]. This was one year before the onset of COVID-19, so our experience reflects the collision of a prototype pandemic-surveillance system and a bona fide pandemic.

The SFS platform collected samples through several mechanisms to survey respiratory pathogens in people with various symptoms and levels of severity. We obtained remnant de-identified specimens from area hospitals to monitor respiratory illness in those seeking medical care. To collect samples from people in the community, we created kiosks in high-traffic areas, such as a shopping malls, and developed a swab-and-send procedure for home use. These people signed consent forms approved by our institutional review board. The SFS laboratory was operating in a research capacity, so we could collect and test samples for research but were not authorized to return results to participants.

On 22 January 2020, one day after the nation's first case of SARS-CoV-2 was discovered in nearby Snohomish County, we began discussions with the US Centers for Disease Control and Prevention (CDC) and state and local health agencies about testing our SFS specimens for SARS-CoV-2. After the nationwide emergency was declared on 30 January, the US Food and Drug Administration (FDA) exercised regulatory enforcement over laboratory testing that required emergency use authorization (EUA) for any test that would return results.

This represented a considerable change to existing regulations, which allowed certified laboratories to develop and offer such tests after meeting validation requirements.

Two weeks later, the FDA granted an EUA for the CDC to manufacture and distribute a diagnostic test for public-health laboratories. Subsequently, laboratories discovered that the assays produced inconclusive results due to contamination in one of the controls. During the weeks needed to resolve these problems, testing for SARS-CoV-2 required that samples be sent to the CDC in Atlanta, Georgia, which caused substantial delays. Using one laboratory for the entire nation with a low-throughput test eliminated any effort to contain the emerging outbreaks in the United States[2].

We started testing banked samples for research on 24 February using a robust assay developed internally. Three days later, we discovered our first positive result for SARS-CoV-2: a Seattle-area teenager without any epidemiological risk factors. We had an ethical obligation to inform this person and public-health authorities, but recognized that this would violate our research protocol. We and the institutional review office concluded that in a public-health emergency, the potential societal implications were greater than the risk of breaching individual privacy. The following morning, we informed the hospital clinic at which the teenager had been seen; they, in turn, notified the teenager's family.

Over the next several days, our discussions with the FDA, the CDC and local and state public-health authorities explored an accelerated pathway for approval of an EUA for our test. On 29 February, the FDA issued a policy allowing laboratories to start using validated SARS-CoV-2 diagnostic tests before full review of EUA requests. Separately, the University of Washington institutional review office determined we had an ethical obligation to test all samples. The SFS had already obtained consent from participants to test for other communicable respiratory diseases and return those results to study participants.

By 19 March, our laboratory became clinically certified through the State of Washington Department of Health, and we received an EUA from the state for our SARS-CoV-2 test. Using the foundation of the SFS and its online swab-and-send program, we launched the nation's first community surveillance program for COVID-19. However, additional regulatory and policy hurdles continued to emerge over March and April with conflicting directives from federal and state regulators.

In May, the FDA clarified that an FDA EUA was required for home-collected swabs (not just for home tests), which put the SFS on hold yet again, despite the SFS's meeting all analytical, safety and regulatory requirements from the state[3]

Our efforts to test for SARS-CoV-2 in the community were constrained by the labyrinth of conflicting and uncoordinated actions among state and federal regulators. Regulatory requirements kept changing, necessitating frequent pivots by our team. An effective pandemic response requires flexibility and innovation. We contend that at-home sample collection, coupled with a clinically validated respiratory virus–detection test, exemplifies such flexibility and innovation. One could imagine a future with swab kits in every US home that people would use for self-testing or send to a laboratory when feeling ill. It is imperative that our nation's regulatory systems become nimbler to enable certified laboratories to provide critical information to our communities and healthcare providers in real time.

Toward such a goal, we believe that clinical laboratories, such as our academic laboratory, should continue to be regulated by the Clinical Laboratory Improvement Amendments, whose regulators have the flexibility to implement amended regulations during public-health emergencies. Modernizing the current regulatory structure, without additional regulation by the FDA, would enable healthcare professionals to respond rapidly to emerging outbreaks, including returning individual results. It would also allow the FDA to focus its attention on the agency's core regulatory responsibilities, including vaccines. During a pandemic, the regulatory framework should include five key principles: community surveillance and engagement, as well as ongoing relationships with public-health agencies; data collection and accurate analysis; modeling of transmission dynamics and genomic epidemiology; regulatory oversight of clinical laboratory testing under the Clinical Laboratory Improvement Amendments; and laboratory flexibility in response to new and emerging pathogens and supply-chain disruptions that may emerge[4].

Such a regulatory framework is vital to ensure that research studies and clinical testing are conducted in an ethical manner that does no harm, provides benefits to society and limits risks to people. ❐

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Author contributions

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