Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 39 (2021) 6183–6185

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Community-based hospitals: New partners for government-sponsored clinical research during public health emergencies

Laura A. McNay [a,*], Gretchen Arnoczy [b], Mary Martell [c], Polly Mock [d], Mary E. Wright [a], Shelly Simpson [e], Mary Smolskis [a], Elizabeth S. Higgs [a]

[a] National Institute for Allergy and Infectious Diseases, Bethesda, MD, United States
[b] FirstHealth of the Carolinas, Pinehurst, NC, United States
[c] Cotton O'Neil Clinical Research Center, Topeka, KS, United States
[d] CHRISTUS Spohn Hospital, Corpus Christi, TX, United States
[e] Clinical Monitoring Research Program Directorate, Frederick National Laboratory, MD, United States

ARTICLE INFO

Article history:
Received 23 July 2021
Received in revised form 24 August 2021
Accepted 3 September 2021
Available online 14 September 2021

Keywords:
Clinical research
Public health emergencies
Pandemic planning

ABSTRACT

In the United States, clinical trials of COVID-19 vaccines and therapeutics quickly exhausted available clinical research capacity at large medical centers. The NIAID Division of Clinical Research tapped community hospitals to help fill the gap.

In the United States, early efforts to advance development of Covid-19 therapeutics lacked coordination. A harmonized, agenda-driven effort to advance high priority therapeutics should have begun within two weeks of the public health emergency declaration. In the absence of a prioritized agenda, clinical researchers scrambled to decrease the early COVID-19 death toll by testing any treatment with potential benefit. Far too many poorly designed, underpowered trials were conducted with little coordination [1], many were duplicative, and existing research infrastructure was quickly exhausted. We describe how the U.S. National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Division of Clinical Research (DCR) swiftly expanded its base of research partners to include smaller community hospitals to perform well-designed studies and maintain critical research momentum during the peak of the pandemic. We suggest that this overlooked resource should be part of future pandemic preparedness efforts.

Ideally, clinical research on novel therapeutics during a pandemic relies on randomized placebo-controlled trials that can be rapidly implemented and produce clinically meaningful, quickly actionable results. The early proliferation of small, underpowered trials in the US was driven largely by academic research centers implementing investigator-initiated studies and pharmaceutical company research protocols before any consensus could be reached about which candidate therapeutics were most promising. In April 2020, the U.S. government (USG) centralized efforts to accelerate the development of candidate therapeutics and vaccines through a U.S.-wide public–private partnership coordinated by the Foundation for the NIH. The effort, called Accelerating COVID-19 Treatment Interventions and Vaccines (ACTIV)[2], leveraged USG scientific capacities as well as those of major pharmaceutical companies, with the goal of mitigating morbidity and mortality and accelerating the end of the pandemic. Eventually there would be nine ACTIV master protocols [3], several priority ACTIV-affiliated trials, and a parallel process for prioritizing candidate therapeutics [4]. Unfortunately, by the time these were underway, many of the 70-plus major, university-based research hospitals in the U.S were already conducting other trials. There were so many studies that some research hospitals developed formal adjudication committees to determine which patients would be allocated to which trials. One of the authors heard a biomedical researcher liken the process to *The Hunger Games*.

Enter the community hospital model as force multiplier starting with a priority ACTIV-affiliated trial of SARS CoV-2 hyperimmune IVIg in hospitalized patients known as ITAC, in full the

* Corresponding author at: Division of Clinical Research, National Institutes of Allergy & Infectious Diseases, NIH. 5601 Fishers Lane, #5C11 Rockville, MD 20852, United States.
E-mail address: lmcnay@niaid.nih.gov (L.A. McNay).

https://doi.org/10.1016/j.vaccine.2021.09.008
0264-410X/Published by Elsevier Ltd.

"International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19." ITAC was a collaboration between NIAID and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) and was conducted between October 2020 and February 2021. The ITAC study leadership quickly realized that the customary clinical/ hospital sites were close to capacity. DCR had not previously partnered with community-based hospitals and clinics, even though many of these institutions had substantial potential or were already conducting clinical research [5]. In the specific case of the DCR community-based hospital sites, many sites already had experience with clinical research.

Identifying these new sites began with internet searches for community-based hospitals in COVID-19 hotspots and evolved to incorporate USG-supported analytics in the form of a Predictive Analytics Working Group, working with the HHS Protect data integration hub, an FDA clinical trials registry, and additional, customized data points specific to the pandemic. This gave the site identification effort access to detailed, usable information, including location, projected COVID-19 caseload, clinical research experience, confirmation of a Federal Wide Assurance for the Protection of Human Subjects (FWA), and whether clinical trials were already underway at a given site. A total of 268 sites were contacted of which 74% were considered community-based locations. Once a point of contact was identified, DCR clinical research and operational experts reached out to the site for potential interest in participating. The DCR team reviewed the USG research response architecture, ITAC trial protocol (primary and secondary objectives, study design and endpoints), and key operational issues (pharmacy, lab, follow-up visits, site reimbursement). Potential sites provided information on their patient population, clinical research experience, and human and physical resources available for the trial. In the end, seventeen of the twenty research sites registered by the DCR were community-based hospitals or clinics.

Most community hospital sites contacted were eager to participate in clinical research despite the study occurring during the third and largest wave of the pandemic; indeed, most were already involved to some degree in clinical studies. One of the major barriers to participation in the trial was that many hospitals were already overextended. In some cases, additional resources were offered to help with enrollment and follow-up; these included human resources and laboratory equipment that could be donated to the hospital on completion. Challenges in providing supplementary clinical staff included obtaining required credentials, training and transporting additional staff to the site while observing COVID-19 travel restrictions—all at a time when new clinical staff were scarce.

Managing the new sites required a departure from typical site management procedures. A new organizational structure was developed to make medical and operational support available. A Clinical Trials Associate was assigned to each site to assist with study registration, start-up, implementation, and close-out. Other study personnel assigned to each site included a pharmacist, safety officer, medical officer, and a contracts specialist for site payment. Biweekly site meetings were initiated to discuss study particulars, registration issues, review operational procedures, and tackle problems; they also served as get-to-know-you time for morale and team building, an important facet in a stressful time.

The community hospital sites under the DCR ultimately contributed 153 participants in the ITAC protocol. This number constitutes 94% of DCR enrollment and 29% of the total enrollment for ITAC (533 participants). That success underscores how reducing the barriers that discourage smaller hospitals from participating in clinical research can expand clinical research capacity in an emergency. It also marks a step toward creating a government-responsive clinical research surge capacity for future public health emergencies, which could organize the plethora of underpowered single-site trials into larger multi-center trials with sufficient power.

Bringing community hospitals into the emergency clinical research response can also help build trust in the research enterprise. In a pandemic, when everyone is affected and tension is high, trust in the research enterprise and dialogue between researchers and *all* stakeholders is more critical than ever [6]. Community engagement is necessary to build both public support for the research and confidence in any approved products that may result. Community hospitals give research teams new opportunities for community engagement and access to diverse populations representative of the population as a whole; engaging them could even help smaller hospitals in rural communities keep their doors open to populations that desperately need them. The prospect of doing clinical research may also help community hospitals recruit and retain talented physicians who seek diverse career experience. Expanding the breadth of clinical research sites, in other words, can benefit all of us, and not only during emergencies.

[Sidebar]

Three community Health systems in the COVID-19 response

The U.S. government's research response to COVID-19 relied on community hospitals to help meet new capacity demands. The following three systems exemplify how these health systems contributed to the overall response.

FirstHealth of the Carolinas is a community health care system with four hospitals in rural North Carolina. Previous clinical research in the system included oncology, cardiology, and pulmonary industry trials but few inpatient studies. Despite clinical trial hesitancy among the mostly rural population, the site successfully engaged the community and met recruitment targets. One success was an easily understood illustrated flipbook created to supplement the informed consent process that led to positive word-of-mouth advertising; for example, multiple subjects from a cluster outbreak wound up enrolling based on the recommendation of the first patient from the cluster. FirstHealth was contacted about the study on 9-14-2020, accepted as a site on 9-15-2020 and enrolled the first ITAC participant on 10-7-2020. Total enrollment for this site was 21 subjects.

The **Cotton O'Neil Clinical Research Center** is the research program of Stormont Vail Health, an integrated health care system based in Topeka, Kansas, serving a multicounty region in northeast Kansas. The research center has 26 team members, partners with 35 physician principal investigators, and manages approximately 80 outpatient clinical trials in cardiology, digestive health, endocrinology, hematology, and oncology, among others. Impediments to in-patient trials included lack of infrastructure, reluctance to burden in-patient staff, personal protective equipment shortages, and other logistical challenges. However, personnel requirements were met primarily by the ambulatory research team, available because routine studies had been suspended. Moreover, new systems built by the Center's information technology team allowed informed consent, screening and randomization, and post-infusion follow-up to be done remotely. Cotton O'Neil first learned about the study on November 9, 2020 and enrolled the first subject on December 16, 2020. A total of eighteen subjects were enrolled over nine weeks.

The **CHRISTUS Spohn Hospital** in Corpus Christi, TX has three full-time research staff members, historically focusing on oncology. At first the site declined to participate for lack of staff, but DCR provided a contract research coordinator, and the hospital identified four principal investigators—an Infectious Diseases Specialist, pulmonologist, intensivist, and hospitalist, who were enthusiastic about being involved. Study start-up, including IRB

submission, establishing collaboration with pharmacy, laboratory, nursing etc., was completed in four weeks, and 31 subjects were enrolled in eight weeks. With the hospital at capacity and staff stretched thin, frequent conversations with staff were needed to ensure they understood the protocol and Spohn's commitment to the research. The hospital has no outpatient clinic, so follow-up visits were often conducted with the subjects in their cars in the parking lot.

Funding Statement

This work was supported by the Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health. The content of this publication does not necessarily reflect the views or policies of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, or Department of Health and Human Services. The project was also funded in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. 75N910D00024, Task Order No. 75N91020F00005. The content of this publication does not necessarily reflect the views or policies of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, or Department of Health and Human Services.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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