NEJM Evidence

Published October 22, 2024

DOI: 10.1056/EVIDctcs2300291

CLINICAL TRIAL CASE STUDY

Lessons Learned from National Heart, Lung, and Blood Institute Covid-19 Clinical Trials

Sonia M. Thomas, Dr.P.H.,[1] Robert A. Harrington, M.D.,[2] Clyde W. Yancy, M.D., M.Sc.,[3] Diane Nugent, M.D.,[4] Serpil Erzurum, M.D.,[5] Gordon R. Bernard, M.D.,[6] Mary Cushman, M.D., M.Sc.,[8] Judith S. Hochman, M.D.,[9] Paul M. Ridker, M.D.,[10] Thomas L. Ortel, M.D., Ph.D.,[11] Sean P. Collins, M.D., M.Sc.,[7] Clifton W. Callaway, M.D., Ph.D.,[12] Tracy L. Nolen, Dr.P.H.,[1] Kelsey N. Womack, Ph.D.,[6] Samuel M. Brown, M.D., M.S.,[13] Annetine Gelijns, Ph.D., J.D.,[14] Mark Geraci, M.D.,[11] Adit A. Ginde, M.D., M.P.H.,[15] Nigel S. Key, M.D.,[16] Jerry A. Krishnan, M.D., Ph.D.,[17] Lisa LaVange, Ph.D.,[18] Stephen R. Wisniewski, Ph.D.,[11] Lisa Berdan, P.A., M.H.S.,[19] Antonello Punturieri, M.D., Ph.D.,[19] David C. Goff, M.D., Ph.D.,[19] Amy P. Patterson, M.D.,[19] for the NHLBI Collaborating Network of Networks for Evaluating Covid-19 and Therapeutic Strategies (CONNECTS) Program

Abstract

In response to the Covid-19 pandemic, the National Heart, Lung, and Blood Institute launched five multisite clinical trials testing candidate host tissue–directed medical interventions to hasten recovery, improve function, and reduce morbidity and mortality. Speed, flexibility, and collaboration were essential. This article from the Steering and Executive committees describes the Collaborating Network of Networks for Evaluating Covid-19 and Therapeutic Strategies (CONNECTS) research program that enrolled 6690 participants and evaluated 18 intervention strategies using 10 molecular agents across the care continuum (outpatient, inpatient, and post discharge), and reports lessons learned from this initiative. Successes include rapid trial execution through collaboration and adaptive platform designs. Challenges that impeded efficiency included time required to execute subcontracts, constraints on clinical research workforce, and limited research infrastructure in nonacademic settings.

The goal of the National Heart, Lung, and Blood Institute (NHLBI) Collaborating Network of Networks for Evaluating Covid-19 and Therapeutic Strategies (CONNECTS) program, a component of Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV),[1,2] was to implement rapid, efficient, collaborative clinical trials designed to rigorously evaluate potential host tissue–directed treatments to halt disease progression, speed recovery, improve function, and save lives.

CONNECTS established five multisite randomized trials spanning outpatient, inpatient, and postdischarge care that evaluated 18 medical interventions of 10 molecular agents across care settings (Fig. 1, Table S1 in the Supplementary Appendix, available with the full text of this article at evidence.nejm.org).[3-14] Several trials employed adaptive platform methodologies in which new therapies were added over time.[15,16] Participants (n=6690) were enrolled at more than 300 clinical sites, many contributing as members of established research networks (Table S2). Sites were distributed across the United States (Fig. 2A) plus Spain, Italy, Brazil, Mexico, Germany, and South Africa. In response to disparities in Covid-19 morbidity,[17] an explicit intent to study diverse populations historically underrepresented in research resulted in 48% of U.S. participants (n=6000) being either Hispanic/Latino or non-White, higher than in the U.S. population (Fig. 2B).

Drs. Harrington and Yancy contributed equally to this article.

Harrington and Patterson CONNECTS Executive Committee Co-Chairs; Yancy CONNECTS Steering Committee Chair; and Nugent and Erzurum CONNECTS Steering Committee Vice Chairs.

The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of NHLBI, NIH, or DHHS.

The author affiliations are listed at the end of the article.

Dr. Thomas can be contacted at smthomas@rti.org or at RTI International, 3040 Cornwallis Rd, Durham, NC 27709.

CONNECTS also launched the Collaborative Cohort of Cohorts for Covid-19 Research (C4R), in which 14 established National Institutes of Health (NIH) cohort studies united to collect standardized Covid-19 surveys and serosurveys, combining these results with harmonized health data to form an extensive epidemiology research database of approximately 50,000 U.S. adults.[18,19]

The strategic intent for CONNECTS was to apply an innovative model of collaboration that integrated existing NHLBI clinical research networks under one organizational umbrella to ensure efficiencies, standardization, collaboration, resource and data sharing, and nimble shifting of intervention types based on the changing clinical landscape during the pandemic. A spirit of flexibility, cooperation, and trust among investigators, many of whom came from different medical disciplines and had not collaborated previously, was instrumental in moving the research forward quickly and efficiently. Here, we present lessons learned from this effort (Table 1).

Operationalizing a Rapid Clinical Trial Response

Planning began in March 2020; funding via an NHLBI Other Transaction Authority (OTA) mechanism began in June 2020, and the first three trials began enrolling in August (Clinical Trial of COVID-19 Convalescent Plasma in Outpatients: [C3PO]), September (ACTIV-4A), and October (ACTIV-4B) 2020, with ACTIV-4C initiated in February 2021 (Fig. 1). Planning for ACTIV-4 Host Tissue (ACTIV-4HT),[12] launched in July 2021, started in Fall 2020 based on evolving research on Covid-19 and potential novel treatments. ACTIV-4A was an open-label trial of antithromboinflammation and other medications versus standard of care. Other trials were double blind, placebo controlled, and conducted under Food and Drug Administration (FDA) Investigational New Drug (IND) applications. Time from concept to first patient enrolled (range 4 to 10 months) was

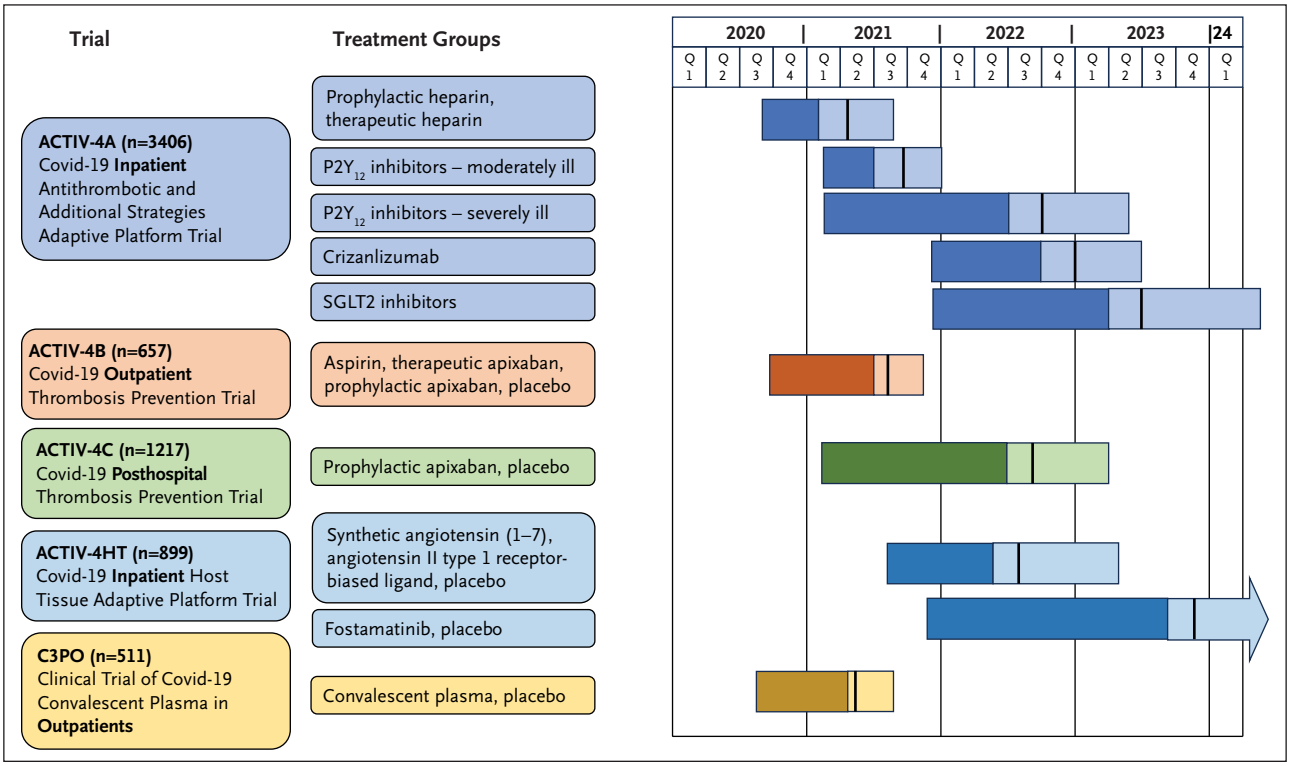

Figure 1. CONNECTS Trials Enrollment and Publications Timelines by Treatment Groups.

Timeline for each trial group shows the start and end of enrollment for each group (dark shading), and online publication of the primary results manuscript (light shading). Time from end of enrollment to publication includes final patient follow-up (denoted by a line within the light shading: 90 days for ACTIV-4A, ACTIV-4C, and ACTIV-4HT, 45 days for ACTIV-4B, 30 days for C3PO), database lock, statistical analysis, manuscript development, revision/acceptance, and article publication. ACTIV denotes Accelerating Covid-19 Therapeutic Interventions and Vaccines; ACTIV-4HT, ACTIV-4 Host Tissue; C3PO, Covid-19 Convalescent Plasma in Outpatients; CONNECTS, Collaborating Network of Networks for Evaluating Covid-19 and Therapeutic Strategies; Q, quarter; and SGLT2, sodium–glucose cotransporter 2.

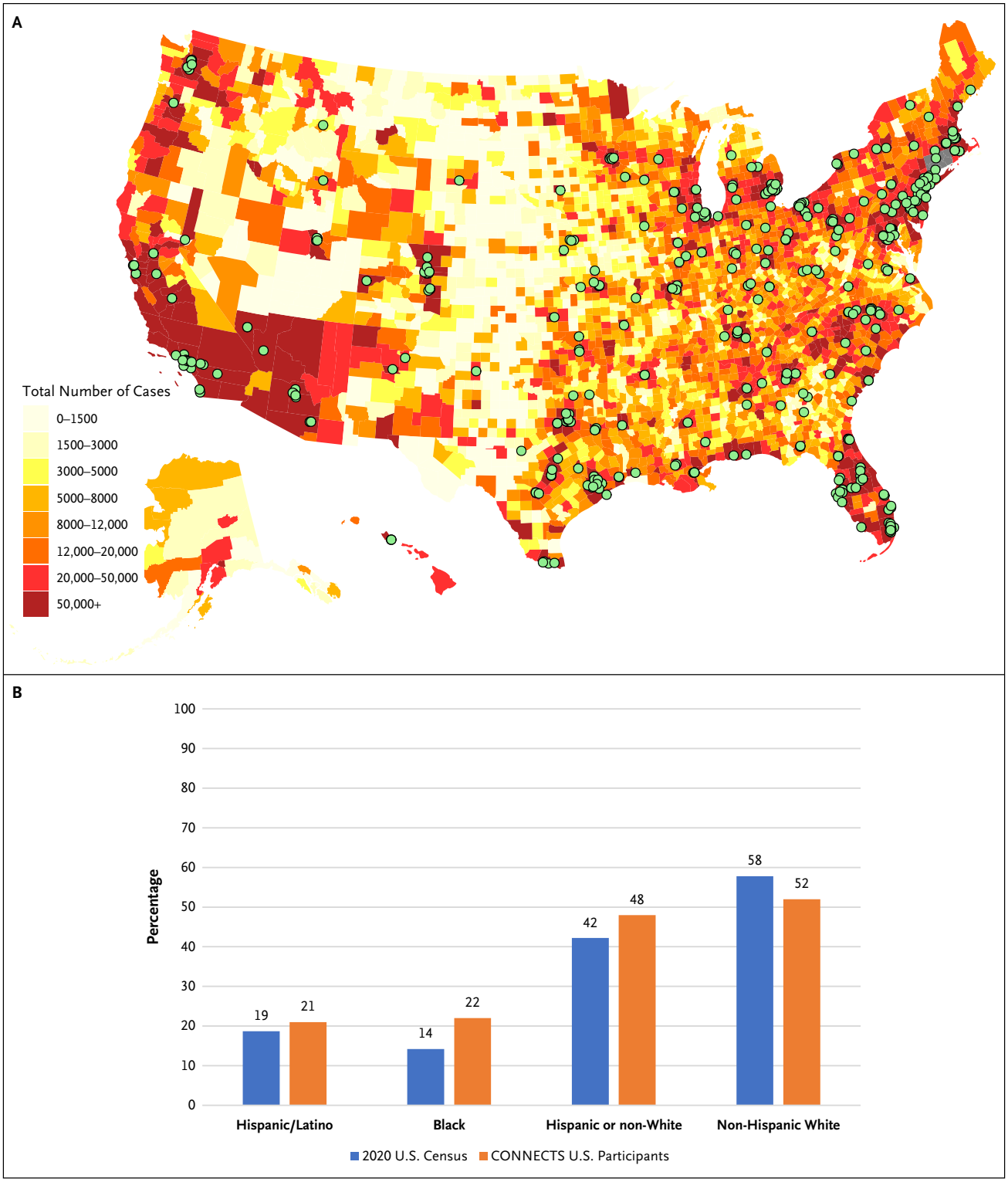

Figure 2. CONNECTS Sites and Participants.

Panel A shows CONNECTS trial sites in the United States and total Covid-19 case counts per U.S. county as of March 2023.[33] Panel B compares CONNECTS trial participants within the United States (n=6000) with the 2020 U.S. Census[34] by self-report of Hispanic/Latino ethnicity or Black race (alone or in any combination). Underrepresented in biomedical research is defined as Hispanic/Latino or non-White, and non-Hispanic White. Including non-US participants (n=6690), distribution is 25% Hispanic, 20% Black, and 49% Hispanic or non-White. CONNECTS denotes Collaborating Network of Networks for Evaluating Covid-19 and Therapeutic Strategies.

Table 1. Key Successes and Challenges.*

Successes
• Collaboration among government agencies and medical researchers contributed to methodological rigor and rapid clinical trial design and start-up
• Institutions shared administration and trial leadership duties to minimize burdens
• Existing clinical research networks shifted from other ongoing NIH-funded projects for immediate capacity
• Administrative Coordinating Center and Science Unit provided flexible, impartial, scalable, and timely program-wide support
• Geographic and care-setting diversity of study sites facilitated enrollment of the populations most impacted by Covid-19
• International sites increased enrollment, effectively engaging preexisting collaborative relationships
• A multidisciplinary agent prioritization committee reviewed potential interventions rapidly, efficiently, and thoroughly
• Platform trials facilitated the addition of new agents as we adapted to emerging findings during Covid-19
• Use of common data elements enhanced the scientific value of the trials, although they were not available at study start-up
• Collection of biospecimens for mechanistic studies increased the scientific value of the trials. A tiered approach allowed sites with differing capabilities to contribute to the biorepository and enhanced trial feasibility
• International research teams, studying similar interventions in separate protocols, collaborated to combine for a single primary analysis to obtain conclusive results sooner
• Adaptive analysis designs provided needed efficiency and flexibility, including interim analyses and futility assessments
Challenges to address
• Site contracts were not executed fast enough. Nationwide adoption of streamlined site contract templates and processes is needed to reduce contracting burden and timelines for all clinical research
• Many sites were insufficiently staffed to conduct clinical research, especially community hospitals, which often lacked research infrastructure. Workforce development and expansion of health research in the community care setting are needed to provide adequate resources nationally
• The process for clinical site IRB reliance agreements and HIPAA authorization as well as central IRB approval caused study start-up delays, including new treatment groups in platform trials. Nationwide adoption of more streamlined and standardized processes is needed to facilitate and expedite informed consent development and centralized review without local level duplication
• Efforts to leverage retail pharmacies as sites for clinical research were not efficient or productive. Additional strategies are needed to tap this potentially valuable resource to expand geographic reach of clinical research
• Contract Research Organizations added capacity and collaboration. Up-front communications and planning are critical for ensuring efficient integration of workflow processes across study management partners
• Proactive conversations should continue among clinical trial clinicians and statisticians, including FDA (and EMA), to develop alignment on statistical designs and primary outcome selection for trials of urgent public health emergencies
• Standardized EMR extraction for clinical trials that is easily implemented within any EMR system would ease data entry burden of limited site staff

*EMA denotes the European Medicines Agency; EMR, electronic medical record; FDA, the Food and Drug Administration; HIPAA, the Health Insurance Portability and Accountability Act; IRB, institutional review board; and NIH, National Institutes of Health.

substantially accelerated compared with the typical 2-year minimum for NIH trials.[20-23] Enrollment during the first two trials (C3PO, ACTIV-4A heparin treatment group) was swift, and results of both trials were published less than 12 months after the first patient was enrolled.[4,5,11] Time from first enrollment to publication across the program's trial treatment groups (median 19.5 months, range 11 to 36 [expected]) was accelerated, even compared with trials reported in top-tier journals based on a shorter milestone of midpoint of data collection (median 34 months [interquartile range 23 to 46 months]).[24]

PROGRAM ORGANIZATION

Each trial was led by a Clinical Coordinating Center and a Data Coordinating Center selected by NHLBI. A CONNECTS-wide Steering Committee composed of multidisciplinary scientific experts, government agency representatives, and trial principal investigators (PIs) provided recommendations for trial designs, trial treatment groups, and ancillary studies to NHLBI via an Executive Committee. Chairs of both committees (R.A.H., C.W.Y., D.N., S.E.) were independent experienced clinical researchers. NHLBI received further input from an independent Protocol Review Committee and Data and Safety Monitoring Board (DSMB). NHLBI maintained central, informed decision-making, with the goal of ensuring the NIH response to the pandemic remained scientifically and financially focused.

Success of each trial was dependent on the experience, capacity, leadership, flexibility, and innovation of trial PIs, and the clinical and data coordinating centers. NHLBI and study investigators collectively contributed to the

immediate needs of Covid-19 trials by shifting research priorities and staff from ongoing NIH-funded projects, sharing trial leadership roles across institutions, or subcontracting components to contract research organizations (CROs) when necessary.

An Administrative Coordinating Center (1) assisted NHLBI in selection and quality oversight of subawardees, (2) managed contracts and invoices, (3) shared information via a public and private web portal with integrated program-level graphical enrollment reports,[3] and (4) provided support for FDA IND filing, biospecimen data reconciliation, submission of public-use trial data to BioData Catalyst,[25] and program committee administration. The Science Unit (1) developed and led therapeutic agent prioritization and protocol development committees, (2) maintained a continually updated landscape analysis of potential Covid-19 treatments, (3) supported protocol and analytic strategy development, and (4) developed and monitored implementation of common data elements for standardization of data across trials.[26] By independently supporting all trials, the Administrative Coordinating Center and Science Unit provided flexible, scalable, and timely support, allowing NHLBI to focus on decision-making and the trial teams to focus on trial conduct.

COLLABORATION ACROSS FEDERAL AGENCIES

The collaboration of federal agencies and entities including NIH, Biomedical Advanced Research and Development Authority (BARDA), FDA, and Operation Warp Speed was vital for organizing national research efforts toward rigorous trials of the most promising interventions and laid the cornerstone for success of CONNECTS trials. Cross-agency collaboration contributed to effective knowledge sharing of trial design, investigated agents, and regulatory and operational status across the ACTIV clinical trial program.[1] To facilitate communication and foster multidisciplinary expertise within CONNECTS, leaders from NHLBI, National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Neurological Disorders and Stroke (NINDS), BARDA, and FDA participated as members of the Steering and Executive committees. NIAID and NHLBI also collaborated for completion of the ACTIV-3 trials of antivirals for hospitalized patients.[27-32] These trials were overseen by NIAID yet achieved over 60% of enrollment through two NHLBI-funded networks (Prevention and Early Treatment of Acute Lung Injury [PETAL] and Cardiothoracic Surgical Trials Network [CTSN], Table S2). Pharmaceutical manufacturers contributed drug and matching placebo for double-blind CONNECTS trials via contracts and service agreements with trial coordinating centers but were uninvolved in trial oversight.

CONTRACTING

A critical goal of CONNECTS was to rapidly fund coordinating centers and sites. NIH employed the OTA mechanism, which allowed for flexible modification and rapid innovation in response to the changing research landscape. CONNECTS funds flowed from NHLBI to the Administrative Coordinating Center in a single OTA award, then through subawards to clinical or data coordinating centers that contracted with clinical sites, often via network lead sites or CROs, to spread the burden of site contracts across organizations (Fig. S1). Flexibility and innovation exceeded that of typical NIH funding mechanisms. The OTA award was modified, generally within a week, to incorporate changes such as new treatments or trials. Subawards to trial coordinating centers were prompt. Initial subawards started with a kick-off meeting of contracts and science representatives from all parties, and all groups collaborated with a sense of urgency. Median time from kick-off to signed subaward was 4 weeks (interquartile range 3 to 10 weeks), and subsequent modifications were faster. NHLBI also exercised normative preaward authority by allowing center invoicing for within-scope design and planning work to begin before the negotiated subaward was finalized.

However, contract subawards from coordinating centers to enrolling sites were not fast enough. Site contracting was dependent on each site's contract policies, status of existing agreements between institutions, and bandwidth of the contracts staff to process start-up of multiple trials early in the pandemic. For greatest speed, network lead sites often subcontracted to sites with whom they had previous contractual relationships, and contracts staff at sites often prioritized Covid-19 trial agreements. Despite these attempts, site contracting was no faster than usual, and was a major source of enrollment delays. Median time to site contract was 9 weeks (interquartile range 3 to 16 weeks; n=463 of 591 contracts with available data), similar to the median previously reported from all types of trials (8 weeks) and academic-specific trials (10 weeks), although notably faster than reported for in-hospital trials (15 weeks).[18,21] Fortunately, time from contract to first enrolled patient (median 9 weeks, interquartile range 5 to 15 weeks; n=342 of 394 enrolling sites) was swifter than previously reported from all types of trials (12 weeks), because many sites did not wait for a contract before beginning site activation steps. A National Center for Advancing Translational Sciences/ Clinical and Translational Science Awards streamlined

master agreement is approved by many major U.S. academic institutions but does not cover trials with a third party (e.g., a pharmaceutical company providing a medication),[33] which was the case for most CONNECTS trials, and may not be in place for nonacademic hospitals or care settings less involved in clinical research. Nationwide adoption of streamlined site contract templates and processes is needed to reduce contracting burden and timelines for all clinical research.

SITE IDENTIFICATION, ENGAGEMENT, AND STAFFING

CONNECTS was effective in convening experienced multidisciplinary researchers to implement trials. Members of existing research networks, including some focused in nonrelated disease areas, shifted priorities from previously funded work, to contribute as a group toward enrolling CONNECTS participants (Table S2). Several trials, especially ACTIV-4A, effectively used a Network Lead Site management model wherein voluntary lead sites provided oversight for their network sites, following trial-wide oversight from the trial PI and Coordinating Centers. While managed like a hub-and-spoke model, all sites were viewed as equal trial contributors.

During the pandemic, geographic and care-setting diversity of study sites was imperative to enroll the populations most adversely impacted by Covid-19. Geographic diversity (Fig. 2A) maximized enrollment as Covid-19 peaks spread across regions.[34,35] Academic health systems with ongoing network studies and a skilled research workforce could shift to Covid-19 trials. However, many community hospitals that were often caring for larger numbers of potential participants, often from more diverse backgrounds, lacked research infrastructure and required additional resources to mobilize the needed research workforce. We attempted to provide remote coordinators to hospitals that lacked research staffing via an NIH contract with a remote coordinator provider; however, this approach failed, with few exceptions. Contract research coordinators were scarce during the pandemic, and the time required for local site onboarding was substantial. Workforce development and expansion of research in the nonacademic care setting are urgently needed so all communities can be optimally represented in future trials.

In the ACTIV-4B outpatient trial, enrollment via retail pharmacies, a previously untested point of entry in NHLBI clinical trials, was operationalized to engage populations not usually approached for clinical trial participation. Despite the potential benefits, the effort was not efficient and was only modestly successful at participant recruitment.[10] However, retail pharmacies, blood collection laboratories, and home health service providers with large geographic coverage still hold potential as clinical trial sites. This concept is worth continued development to extend research within communities.

For some CONNECTS trials, experienced CROs were contracted to identify and manage additional sites. We found that CROs effectively added capacity and collaborated within the research ecosystem. However, CROs were

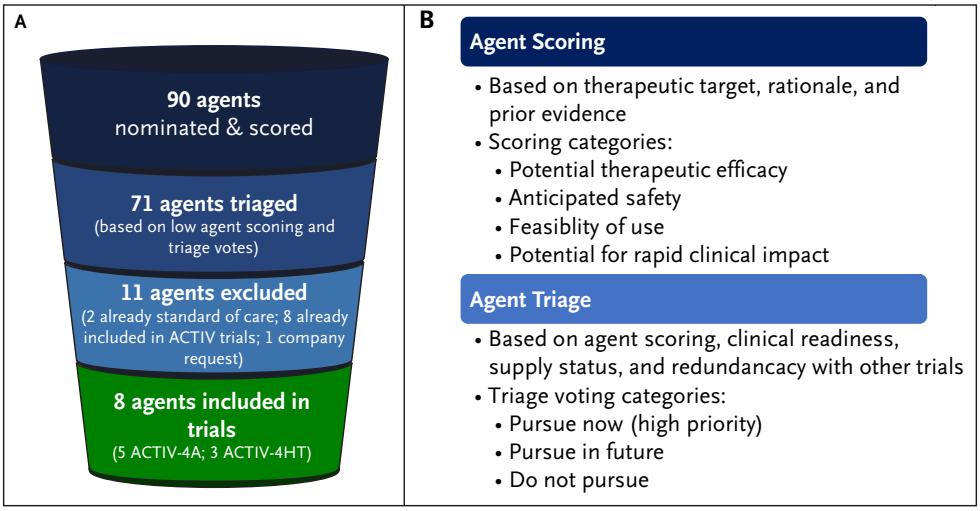

Figure 3. CONNECTS Agent Prioritization Process.

Panel A reports the agents triaged for inclusion in ACTIV-4 trials; Panel B describes review criteria assessed by the Agent Prioritization Committee members. ACTIV denotes Accelerating Covid-19 Therapeutic Interventions and Vaccines; ACTIV-4HT, ACTIV-4 Host Tissue; and CONNECTS, Collaborating Network of Networks for Evaluating Covid-19 and Therapeutic Strategies.

onboarded after trial start, and sometimes unanticipated differences in standard procedures, such as regulatory document management and site monitoring systems, were encountered. We learned that up-front communications and planning for integration of workflow processes across study management partners is critical.

Enrollment for ACTIV-4A and ACTIV-4HT inpatient trials was accelerated through international sites which could include patients during Covid-19 peaks in their regions. Country-specific Academic Research Organizations (AROs) or CROs managed these sites. In ACTIV-4A, the engagement of international AROs was built upon preexisting relationships from prior trials and contributed to rapid study enrollment. This experience underscores the importance of forging and maintaining collaborations with international researchers that can be leveraged during global public health emergencies.

INSTITUTIONAL REVIEW BOARDS

CONNECTS trials relied on central institutional review boards (IRBs). However, the rapid influx of pandemic research applications stressed IRB capacity, and only a limited number of central IRBs could promptly review trials with many sites. Initiation of IRB reliance agreements and HIPPA authorization at each site also delayed trial start-up. Nationwide adoption of streamlined processes, such as usage of model agreements and elimination of duplicative local review, would greatly facilitate efficient IRB review and expand capacity. Several CONNECTS protocols were adaptive platforms, allowing modification to add investigational treatments. However, each new treatment required central IRB approval of each site's updated consent, which impeded rapid implementation of new trial treatment groups. Streamlining the process of IRB review of informed consent updates such as for addition of treatments is critical for efficient multicenter adaptive platform trials.

Collaborative Science

IDENTIFICATION OF POTENTIAL TREATMENTS

The Administrative Coordinating Center Science Unit convened 20 multidisciplinary medical experts from academia, NHLBI, FDA, and BARDA as a Therapeutic Agent Prioritization Committee responsible for evaluation of potential interventions. The Science Unit developed a summary of each agent's potential Covid-19 efficacy and feasibility, including biologic/pharmacologic rationale, published evidence, and potential impact on thromboinflammation/vascular integrity or other host-tissue response based on emerging knowledge from multiple sources. Members independently scored each agent for prioritization into CONNECTS trials. The committee discussed combined scores and provided top recommendations to NHLBI. Committee members signed confidentiality agreements so that information about agents under IND were sharable. The committee evaluated more than 90 agents (Fig. 3), and prioritized interventions were added to the adaptive inpatient trials. This process succeeded in evaluating potential interventions rapidly, efficiently, and rigorously.

CLINICAL TRIAL PROTOCOL DESIGN

Protocols needed to change to add or modify treatment groups or data collection as more was learned about Covid-19. Use of adaptive platform trials conducted under a master protocol and designed by multidisciplinary expert committees with chapters for new agents added over time increased trial efficiency. At the design stage, clinical and statistical contributors engaged in discussions to define trial outcomes to align the pathophysiology targeted by the planned trial agents with the Covid-19 patient outcomes of most concern. Longer-term symptoms and quality-of-life outcomes were added to protocols as postacute sequelae of Covid-19 became apparent.

Efficient statistical analysis of these novel outcomes was important. All trials included flexible plans for interim analysis of efficacy or futility to reach conclusions as quickly as possible. Adaptive inpatient trials ACTIV-4A and ACTIV-4HT each shared applicable control patients across analyses.[8,12] Four of the trials were conducted under an FDA IND. FDA provided prompt reviews and responses to maintain fast timelines while providing rigorous and thoughtful regulatory review. This example of conversations among clinical trial clinicians and statisticians, including FDA, to develop alignment on the most efficient statistical designs and most relevant trial outcomes can inform future clinical trials addressing public health emergencies.

Standardized common data elements and data collection case report forms were a goal; however, because of the very quick start-up by separate teams, development of common data elements[26] was concurrent with data collection, and harmonization across trials happened later in the process. Harmonized data from all trials were promptly submitted to BioData Catalyst for public data sharing.[25]

Site research staff shortages were a major problem during Covid-19, particularly for inpatient trials. Trial design

elements to minimize research staff efforts included using electronic informed consent and streamlining data collection and entry to the extent possible. Programmatic data extraction from the electronic medical record (EMR) would have saved staff time[36] but was not possible. Standardized EMR data extraction for clinical research that can be easily implemented within any EMR system would improve efficiency of clinical trial data collection.

BIOSPECIMEN COLLECTION

Collecting biospecimens to create a central biorepository[37] enabled "correlative science" mechanistic studies to evaluate the pathophysiology of disease within the clinical trials, thus generating insights that might lead to more optimal treatment. To date, nearly 20 funded mechanistic studies have researched biomarkers of illness severity and treatment response, or mechanisms underlying antibody and cellular responses to Covid-19. CONNECTS publications are linked on the program website.[38]

Collection of blood samples was complicated given patient isolation protocols, shortages of personal protective equipment early in the pandemic, and the extra staff burden to accomplish this task. We implemented a tiered approach for collection of biospecimens that reimbursed sites for sample collection but did not penalize sites unable to participate in biospecimen collection, allowing inclusion of sites with differing capabilities.

PARTICIPANT ENGAGEMENT

A Research Communication Center implemented strategies to promote and sustain participant trust in research during the ACTIV-4B outpatient and ACTIV-4C postdischarge trials, including animated videos, participant-focused websites, printed materials mailed with study medications, and a call center to support and motivate participants to complete these low-touch trials.[9]

COLLABORATION ACROSS INTERNATIONAL TRIALS

Investigators outside the United States conducted trials of the same or similar interventions as CONNECTS.[39,40] ACTIV-4A joined with two other ongoing open-label trials studying heparin in hospitalized patients (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia [REMAP-CAP], Antithrombotic Therapy to Ameliorate Complications of Covid-19 [ATTACC]) to form a multiplatform trial spanning nine countries.[1,2] The trials collaboratively modified protocols to specify a single primary analysis from the combined patients, were simultaneously halted by DSMBs for meeting stopping boundaries with 3300 patients (1064 from ACTIV-4A), and published the results indicating benefit of therapeutic heparin for noncritically ill patients in August 2021.[5] Early harmonization of primary end point and data analysis was essential. Furthermore, use of the same independent statistical group and collaboration among DSMBs enabled data sharing for joint interim analyses through documented communication plans. Additional cross-trial collaborations included a preplanned meta-analysis for sodium–glucose cotransporter-2 inhibitors in ACTIV-4A, Randomized Evaluation of Covid-19 Therapy (RECOVERY) and Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19)[41] collaboration between ACTIV-4HT and REMAP-CAP investigators on separate yet complementary trials of interventions modulating the renin–angiotensin system, and a meta-analysis of C3PO with other trials on the use of convalescent plasma in outpatients.[42]

Conclusion

The United States faces urgent public health challenges, not just from Covid-19, but from multiple widespread causes of declining health with increasing death rates since 2013.[43,44] Systems to fund and conduct community-engaged clinical research in important causes of declining health must modernize by adopting approaches that highlight efficiency and innovation, including multinetwork and international multiplatform collaboration. The U.S. research infrastructure should build on successes realized during the Covid-19 pandemic and develop plans and technologies to address and overcome the identified challenges. We can use lessons learned from Covid-19, such as those provided here, to make changes now to develop more nimble, robust, and collaborative clinical trial infrastructure and practices for responding to not just future pandemics, but also major ongoing public health crises.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

Acknowledgments

The authors wish to acknowledge the many patients who served as research participants, without whose contributions none of this work would have been possible. We also thank the federal government CONNECTS Steering and Executive Committee members, other federal government contributors, Study Investigators/co-Investigators, members of the RTI International Administrative Coordinating Center and

the Vanderbilt University Medical Center Administrative Coordinating Center Science Unit.

Author Affiliations

[1] RTI International, Durham, NC

[2] Weill Cornell Medicine, New York

[3] Northwestern University Feinberg School of Medicine, Chicago

[4] CHOC Children's Hospital, Orange, CA

[5] Cleveland Clinic, Cleveland

[6] Vanderbilt University Medical Center, Nashville

[7] Vanderbilt University Medical Center and Veterans Affairs Tennessee Valley Healthcare System, Geriatric Research, Education and Clinical Center (GRECC), Nashville

[8] University of Vermont, Burlington

[9] New York University Grossman School of Medicine, NYU Langone Health, New York

[10] Brigham and Women's Hospital, Boston

[11] Duke University, Durham, NC

[12] University of Pittsburgh, Pittsburgh

[13] Intermountain Health/University of Utah, Salt Lake City

[14] Icahn School of Medicine at Mount Sinai, New York

[15] University of Colorado School of Medicine, Aurora

[16] University of North Carolina School of Medicine, Chapel Hill

[17] University of Illinois Chicago, Chicago

[18] University of North Carolina Gillings School of Global Public Health, Chapel Hill

[19] National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD

References

1. Collins F, Adam S, Colvis C, et al. The NIH-led research response to COVID-19. Science 2023;379:441-444.

2. Shulkin D. What health care can learn from operation warp speed. NEJM Catal Innov Care Deliv 2021;2(1). DOI: 10.1056/CAT.21.0001.

3. CONNECTS. Programs conducting studies to test if medications are safe and can help individuals recover from COVID-19, 2020. July 25, 2023 (https://nhlbi-connects.org).

4. Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic anticoagulation with heparin in critically Ill patients with Covid-19. N Engl J Med 2021;385:777-789. DOI: 10.1056/NEJMoa2103417.

5. Lawler PR, Goligher EC, Berger JS, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021;385:790-802. DOI: 10.1056/NEJMoa2105911.

6. Berger JS, Kornblith LZ, Gong MN, et al. Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: a randomized clinical trial. JAMA 2022;327:227-236. DOI: 10.1001/jama.2021.23605.

7. Berger JS, Neal MD, Kornblith LZ, et al. Effect of P2Y12 inhibitors on organ support-free survival in critically ill patients hospitalized for COVID-19: a randomized clinical trial. JAMA Netw Open 2023;6:e2314428. DOI: 10.1001/jamanetworkopen.2023.14428.

8. Solomon SD, Lowenstein CJ, Bhatt AS, et al. Effect of the P-selectin inhibitor crizanlizumab on survival free of organ support in patients hospitalized for COVID-19: a randomized controlled trial. Circulation 2023;148:381-390. DOI: 10.1161/CIRCULATIONAHA.123.065190.

9. Kosiborod MN, Windsor SL, Vardeny O, et al. Effect of sodium-glucose co-transporter-2 inhibitors on survival free of organ support in patients hospitalised for COVID-19 (ACTIV-4a): a pragmatic, multicentre, open-label, randomised, controlled, platform trial. Lancet Diabetes Endocrinol 2024;12:725-734. DOI: 10.1016/S2213-8587(24)00218-3.

10. Connors JM, Brooks MM, Sciurba FC, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. JAMA 2021;326:1703-1712. DOI: 10.1001/jama.2021.17272.

11. Connors JM, Brooks MM, Sciurba FC, et al. Outpatient randomized controlled trials in the Covid-19 era and beyond. NEJM Evid 2022;1(12). DOI: 10.1056/EVIDctcs2200149.

12. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early convalescent plasma for high-risk outpatients with COVID-19. N Engl J Med 2021;385:1951-1960. DOI: 10.1056/NEJMoa2103784.

13. Self WH, Shotwell MS, Gibbs KW, et al. Renin-angiotensin system modulation with synthetic angiotensin (1–7) and angiotensin II type 1 receptor-biased ligand in adults with COVID-19: two randomized clinical trials. JAMA 2023;329:1170-1182. DOI: 10.1001/jama.2023.3546.

14. Wang TY, Wahed AS, Morris A, et al. Effect of thromboprophylaxis on clinical outcomes after COVID-19 hospitalization. Ann Intern Med 2023;176:515-523. DOI: 10.7326/M22-3350.

15. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 2017;377:62-70. DOI: 10.1056/NEJMra1510062.

16. Lawler PR, Hochman JS, Zarychanski R. What are adaptive platform clinical trials and what role may they have in cardiovascular medicine? Circulation 2022;145:629-632. DOI: 10.1161/CIRCULATIONAHA.121.058113.

17. Romano SD, Blackstock AJ, Taylor EV, et al. Trends in racial and ethnic disparities in COVID-19 hospitalizations, by region—United States, March–December 2020. Morb Mortal Wkly Rep 2021;70:560. DOI: 10.15585/mmwr.mm7015e2.

18. Oelsner EC, Krishnaswamy A, Balte PP, et al. Collaborative cohort of cohorts for COVID-19 research (C4R) study: study design. Am J Epidemiol 2022;191:1153-1173. DOI: 10.1093/aje/kwac032.

19. CONNECTS. C4R collaborative cohort of cohorts for COVID-19 research. July 25, 2023 (https://www.c4r-nih.org/).

20. Lamberti MJ, Wilkinson M, Harper B, Morgan C, Getz K. Assessing study start-up practices, performance, and perceptions among sponsors and contract research organizations. Ther Innov Regul Sci 2018;52:572-578. DOI: 10.1177/2168479017751403.

21. Abbott D, Califf R, Morrison BW, Pierre C, Bolte J, Chakraborty S. Cycle time metrics for multisite clinical trials in the United States. Ther Innov Regul Sci 2013;47:152-160. DOI: 10.1177/2168479012464371.

22. Clinical Trials Transformation Initiative. Study start-up timelines: identifying challenges & opportunities for change. July 25, 2023 (https://ctti-clinicaltrials.org/wp-content/uploads/2021/07/CTTI_Study_StartUp_Report.pdf).

23. National Institute of Allergy and Infectious Diseases. Illustrated application and grant timelines, 2019. October 13, 2023 (https://www.niaid.nih.gov/grants-contracts/timelines-illustrated#:~:text=Your%20overall%20).

24. Welsh J, Lu Y, Dhruva SS, et al. Age of data at the time of publication of contemporary clinical trials. JAMA Netw Open 2018;1:e181065. DOI: 10.1001/jamanetworkopen.2018.1065.

25. National Institutes of Health, BioData Catalyst. About BDC COVID-19 data, 2020. July 25, 2023 (https://biodatacatalyst.nhlbi.nih.gov/covid-19/).

26. Weissman A, Cheng A, Mainor A, et al. Development and implementation of the national heart, lung, and blood institute COVID-19 common data elements. J Clin Transl Sci 2022;6:e142. DOI: 10.1017/cts.2022.466.

27. Murray DD, Babiker AG, Baker JV, et al. Design and implementation of an international, multi-arm, multi-stage platform master protocol for trials of novel SARS-CoV-2 antiviral agents: therapeutics for Inpatients with COVID-19 (TICO/ACTIV-3). Clin Trials 2022;19:52-61. DOI: 10.1177/17407745211049829.

28. Lundgren JD, Grund B, Barkauskas CE, et al. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. N Engl J Med 2021;384:905-914. DOI: 10.1056/NEJMoa2033130.

29. ACTIV-3/Therapeutics for Inpatients with COVID-19 Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis 2022;22:622-935. DOI: 10.1016/S1473-3099(21)00751-9.

30. Barkauskas C, Mylonakis E, Poulakou G, et al. Efficacy and safety of ensovibep for adults hospitalized with COVID-19: a randomized controlled trial. Ann Intern Med 2022;175:1266-1274. DOI: 10.7326/M22-1503.

31. Brown SM, Barkauskas CE, Grund B, et al. Intravenous aviptadil and remdesivir for treatment of COVID-19-associated hypoxaemic respiratory failure in the USA (TESICO): a randomised, placebo-controlled trial. Lancet Respir Med 2023;11:791-803. DOI: 10.1016/S2213-2600(23)00147-9.

32. ACTIV-3-Therapeutics for Inpatients with COVID-19 Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. Lancet Respir Med 2022;10:972-984. DOI: 10.1016/S2213-2600(22)00215-6.

33. ARA4US. Accelerated clinical trial agreement. July 25, 2023 (https://ara4us.org/acta/about/).

34. Johns Hopkins. Coronavirus resource center, 2020. July 25, 2023 (https://coronavirus.jhu.edu/data).

35. United States Census Bureau. Supplementary tables on race and Hispanic origin: 2020 census redistricting data (P.L. 94-171), 2020. July 25, 2023 (https://www2.census.gov/programs-surveys/decennial/2020/data/redistricting-supplementary-tables/redistricting-supplementary-table-package.pdf).

36. Cheng AC, Banasiewicz MK, Johnson JD, et al. Evaluating automated electronic case report form data entry from electronic health records. J Clin Transl Sci 2023;7:e29. DOI: 10.1017/cts.2022.514.

37. ACTIV. ACTIV virtual biorepository. July 25, 2023 (https://activ-biorep.org/).

38. CONNECTS Publications. July 25, 2023 (https://nhlbi-connects.org/publications).

39. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study. Rationale and design. Ann Am Thorac Soc 2020;17:879-891. DOI: 10.1513/AnnalsATS.202003-192SD.

40. Normand S-LT. The RECOVERY platform. N Engl J Med 2021;384:757-758. DOI: 10.1056/NEJMe2025674.

41. Vale C, Godolphin PJ, Fisher D, et al. Sodium-glucose co-transporter-2 inhibitors for hospitalised patients with COVID-19: a prospective meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2024;12:735-747. DOI: 10.1016/S2213-8587(24)00219-5.

42. Levine AC, Fukuta Y, Huaman MA, et al. Coronavirus disease 2019 convalescent plasma outpatient therapy to prevent outpatient hospitalization: a meta-analysis of individual participant data from 5 randomized trials. Clin Infect Dis 2023;76:2077-2086. DOI: 10.1093/cid/ciad088.

43. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2023 update: a report from the American heart association. Circulation 2023;147:e93-e621.

44. Macrotrends. U.S. death rate 1950-2023, 2019. July 25, 2023 (https://www.macrotrends.net/countries/USA/united-states/death-rate).