Research protocol and recruitment redesign of a study of pregnant women and their infants during the COVID-19 pandemic: Childhood Allergy and the NeOnatal Environment (CANOE)

Tonia S. Afshan, MD, MPH,[a] Aishwarya Kulkarni, MPH,[b] Jennifer M. Smith, BS,[a] Elizabeth Tesson, BSN,[c] Talissa Blackshere, RN, BSN,[d] Christine Joseph, PhD,[b] Edward M. Zoratti, MD,[e] Katherine Rivera-Spoljaric, MD,[c] Tina Hartert, MD,[d] James E. Gern, MD,[a] and Anne Marie Singh, MD,[a] for the ECHO Children's Respiratory and Environmental Workgroup *Madison, Wis; Detroit, Mich; St Louis, Mo; and Nashville, Tenn*

Background: Recruitment for research studies is a challenging endeavor that was further complicated by the coronavirus disease 2019 pandemic. We launched a new multicenter birth cohort, Childhood Allergy and the NeOnatal Environment (CANOE), supported by the National Institutes of Health in January 2020 across 4 sites. Although the pandemic temporarily halted clinical research, we restructured the study and instituted novel recruitment methods that we hypothesized would enable brisk enrollment when research activities resumed.

Objective: We sought to develop protocol modifications and recruitment methods that promote successful recruitment of diverse populations in clinical research despite a global pandemic.

Methods: Even though study activities were suspended, we modified recruitment strategies to limit in-person contact, shifting toward alternative HIPAA-compliant methods such as clinician referrals, institutional social media, and telemedicine screening and consent procedures. Protocol changes included reducing the frequency of in-person visits, leveraging clinical care visits to collect biospecimens, expanded self-collection of samples at home, and making study materials available online.

Results: Remote methods, including targeted social media posts, mailed letters, and email, combined with in-clinic recruitment with modifications for social distancing led to successful recruitment at all sites. Rates of consent have been similar across recruitment sites, with the highest rates of enrollment of mother-infant dyads realized by sites that implemented multiple recruitment strategies.

Conclusions: Study procedures that prioritize health and safety measures such as social distancing, study participant convenience, and use diverse recruitment strategies enable successful enrollment of pregnant women and their newborns into clinical research while adhering to public health restrictions during a global pandemic. (J Allergy Clin Immunol Global 2024;3:100270.)

Key words: *Study recruitment, protocol redesign, COVID-19 pandemic, public health, women and infants, pregnancy, childhood allergy*

The arrival of the coronavirus disease 2019 (COVID-19) global pandemic in early 2020 affected all aspects of the academic and health care mission. Patient care and delivery, health care worker training and education, and medical research were affected in significant and unanticipated ways.[1-3] Efforts to limit virus spread led to a halt for most clinical research activity as essential health care was prioritized.[4-8] Before the start of this pandemic, in January 2020, we had launched a new observational birth cohort study called the Childhood Asthma and the NeOnatal Environment (CANOE) at 4 large medical centers and their universities across the United States. CANOE focuses on identifying early-life causes of allergic diseases, and the study is fully integrated into the Environmental Influences on Child Health Outcomes (ECHO) program of the National Institutes of Health (NIH). ECHO is a large multicenter birth cohort consortium that includes 69 additional cohorts focused on identifying early-life environmental determinants for diseases in 5 main outcome areas: airway biology, obesity, perinatal outcomes, neurocognitive development, and positive health.

About 1 month after study launch, all CANOE clinical research activities were suspended for 9 months at the 4 participating sites. During that time, CANOE research staff redesigned the study protocol to facilitate patient participation and recruitment when research activity resumed while also adhering to public health recommendations during the ongoing pandemic. These efforts enabled enrollment into CANOE despite ongoing pandemic restrictions and have provided strategies that may be used to enhance recruitment of any clinical study even during non-pandemic times. Even before the pandemic, there have been trials of remote ways to engage research participants and address

From [a]the Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, University of Wisconsin-Madison School of Medicine and Public Health, Madison; [b]the Department of Public Health Sciences, Henry Ford Health, Detroit; [c]the Division of Allergy, Immunology, and Pulmonary Medicine, Washington University, St Louis; [d]the Division of Allergy, Pulmonary, and Critical Care Medicine, Center for Asthma Research, Vanderbilt University Medical Center, Nashville; and [e]the Department of Medicine, Henry Ford Health System, Detroit.

Received for publication May 15, 2023; revised January 16, 2024; accepted for publication February 3, 2024.

Available online May 1, 2024.

Corresponding author: Anne Marie Singh, MD, Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, University of Wisconsin-Madison School of Medicine and Public Health, K4/916, 9988 Clinical Science Center, 600 Highland Ave, Madison, WI 53792. E-mail: amsingh@wisc.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

2772-8293

https://doi.org/10.1016/j.jacig.2024.100270

Abbreviations used
CANOE: Childhood Allergy and the NeOnatal Environment
COVID-19: Coronavirus disease 2019
ECHO: Environmental Influences on Child Health Outcomes
NIH: National Institutes of Health

barriers to research participation, such as distance and transportation, personal illness or decreased mobility, and work and childcare responsibilities.[9] The COVID-19 pandemic gave researchers, including us, the opportunity to focus efforts on some of these virtual research methods and to reduce the risk of virus transmission while facilitating patient participation. This article describes the steps taken and the results of relaunching clinical research safely while following public health guidance and promoting patient participation during a challenging time.

METHODS

Study overview

The goal of the CANOE birth cohort is to identify and understand early-life risk factors for developing childhood allergic diseases and asthma. To accomplish this goal, we aimed to enroll pregnant women before delivery, enroll the infant at birth, and then follow the family prospectively through the infant's first 3 years of life.

This study was designed to identify early-life environmental exposures that modify nasal mucosal immune development and the risk of allergic diseases. The primary study hypothesis is that airway cell gene expression profiles measured between birth and age 4 months are associated with subsequent development of early aeroallergen sensitization and recurrent wheeze. In addition, we hypothesize that environmental exposures (eg, microbes and allergens) during the prenatal and early postnatal period will modify patterns of nasal epithelial cell gene expression and the risk for developing recurrent wheeze and early aeroallergen sensitization (Fig 1). The primary and secondary outcomes are provided in Table E1 (in the Online Repository available at www.jaci-global.org).

The CANOE birth cohort and its procedures have been approved by the institutional review boards and research ethics committees at each participating site. All study procedures have been performed in accordance with the Declaration of Helsinki. Informed consent to participate in the study was obtained from all participants.

Recruitment

Patient recruitment was launched and has been ongoing at 4 large academic medical centers: Henry Ford Health (Detroit, Mich), Washington University (St Louis, Mo), University of Wisconsin (Madison, Wis), and Vanderbilt University (Nashville, Tenn). Locations were chosen to be inclusive of varying demographic characteristics including race and ethnicity and population density. Inclusion criteria are expectant mothers 18 years or older planning to deliver at a study site or affiliated hospital, and the expected child with at least 1 biological parent or sibling with asthma, allergic rhinitis, or atopic dermatitis. Exclusion criteria are maternal HIV infection at time of delivery, non–English-speaking, maternal receipt of progesterone during pregnancy to prevent preterm birth, infant birth at less than 34 weeks of gestation, and known or planned family relocation away from study site during the study period. Before the COVID-19 pandemic, we planned that the primary recruitment method would be in person, with potential study participants to be identified and approached through obstetrics and gynecology clinics associated with the study site hospitals.

Study visits and procedures

The original study protocol consisted of 15 total points of contact: 8 in person and 7 via telephone. Once consented into the study, expectant mothers begin with a prenatal visit; following this and after the infant's birth, the additional points of contact are scheduled and include questionnaires, infant examination, and biospecimen collection occurring intermittently throughout the 3-year study period. Examples of collected biospecimens include nasal swab, nasal filter paper, skin swab, stool sample, peripheral blood, and urine (Table I). Questionnaires collect information about demographic characteristics, environmental exposures, medications, prenatal history, pets, and diet. Additional information collected includes Patient-Oriented Eczema Measure[10] and SCORing Atopic Dermatitis[11-14] scores along with infant anthropomorphic measurements and physical examination findings. Table E2 (in the Online Repository available at www.jaci-global.org) lists the study visit and sample collection schedule of the original CANOE study protocol.

RESULTS

The study protocol redesign process

When all research activities were halted because of the COVID-19 global pandemic 1 month after the launch of CANOE, study investigators realized that there would be new challenges to recruitment and study participation for an unknown duration of time. With the intent of redesigning the CANOE study protocol to accommodate pandemic-related restrictions to clinical research activities, we conducted an online survey and focus groups with potential participants. We solicited this feedback to understand patient attitudes, opinions, preferences, and barriers regarding participation in a research study during the COVID-19 pandemic.

Stakeholder engagement

A group of 50 pregnant women participated in an online survey and/or virtually conducted focus group. Although most women (74%) stated that they would still participate in a research study during the pandemic, many participants had additional conditions or preferences to be able to do so. For example, procedures such as masking, cleaning and sanitizing equipment, telemedicine, and physical distancing were reported as ways to make study participation acceptable and feasible. In addition, almost half the women surveyed (47%) stated that they would not be willing to participate in research studies in a hospital setting during the pandemic and that no procedures would make them comfortable doing so. Most women surveyed (75%) indicated greater comfort with completing research-related activities at their primary care provider's or pediatrician's office. Finally, 88% of the surveyed women stated that they would be willing to participate in a research study if the required biologic samples could be

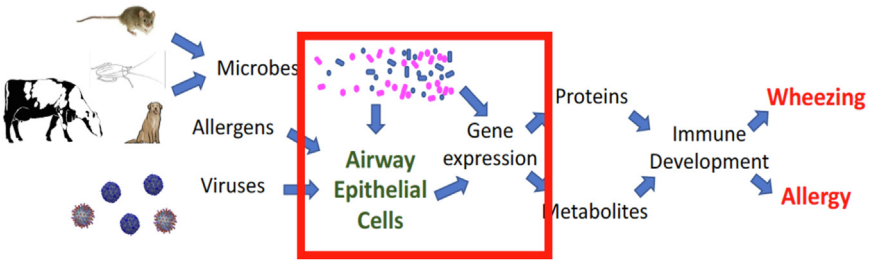

FIG 1. Conceptual model and hypothesis of CANOE birth cohort study.

TABLE I. Biospecimen samples collected in the CANOE birth cohort study

Maternal samples	Infant samples
Placenta	Cord blood
Blood	Blood
DNA	DNA
Toenail clipping	Toenail clipping
Hair	Hair
Urine	Urine
Stool	Stool
Skin swab	Skin swab
Breast milk	Nasal swab, mucus, and filter paper

self-collected at home. Therefore, we sought to redesign the protocol and study methods to address stakeholder concerns. We hypothesized that (1) providing home collection and virtual visits when feasible would allow for successful recruitment despite a global pandemic and (2) flexibility and virtual options would promote enrollment of minoritized populations.

Redesigning the study protocol

In light of public health guidance and the feedback from potential participants, the CANOE study protocol was redesigned. Several key changes were intended to facilitate study recruitment and enrollment when research activities resumed. Specifically, virtual and electronic consent procedures were designed and then implemented, whereas in-person consent practices were restricted because of the pandemic. This strategy allowed participants to talk to study staff via telephone or video conferencing, ask questions about the study, undergo eligibility screening, and sign informed consent forms via an electronic platform, DocuSign (https://go.docusign.com).

In addition, we combined some study visits with existing clinical encounters or converted them to virtual visits to reduce face-to-face interactions and comply with social distancing recommendations as part of COVID-19 pandemic policies and guidelines. For example, we added a birth visit while enrolled mothers and their newborn babies were already in the hospital to assess the perinatal/postnatal period. At this visit, study staff (including collaborating hospital neonatologists and pediatricians) collected various samples from the mother and the baby, including placenta, cord blood, meconium/stool, skin swabs, nasal swabs, and a transepidermal water loss measurement, without requiring a separate or additional face-to-face encounter after hospital and nursery discharge (as was initially designed in the study protocol). With the addition of this birth visit, the 2-month visit, originally intended to be in person, was converted to a telephone/virtual visit. We aimed to enhance enrollment, including in minoritized populations, by addressing stakeholder concerns and easing the burden on participants.

Furthermore, we revised sample collection protocol to remove aerosolized procedures (eg, nasal wash) and encouraged home collection of select samples (eg, stool). Although home collection of biospecimens was an option in the original study, we put greater emphasis on home collection in the revised protocol by developing additional collection instructions and providing home collection kits and equipment to all participants (via mail or provided at one of the in-person visits). Again, this reduced in-person interactions and improved the safety and convenience of biospecimen collection for the study participants.

Finally, across all sites, Amazon Kindle tablets were given as a retention gift and resource for data collection (see Fig E1 in this article's Online Repository at www.jaci-global.org). This allowed participants to access study materials in an electronic format from home. Some sites provided the tablet directly after consent procedures, whereas others opted to give them later as an incentive at a clinic visit. In addition, women who lacked reliable wi-fi were provided hot spots to ensure internet access would not limit participation. Two women received hot spots. To promote equity, we did not want lack of internet access to affect enrollment. Key changes to the protocol are summarized in Table II (see also Table E3 in this article's Online Repository at www.jaci-global.org).

Study relaunch and recruitment during a global pandemic

The revised protocol was approved by site institutional review boards on October 16, 2020, and research activities and recruitment were reinitiated at each site in the following months as each institution permitted clinical research to restart. Targeted recruitment for this birth cohort at its launch was 500 mother-infant dyads. Recruitment concluded on October 1, 2022, with the total recruitment duration equaling 24 months following study relaunch. At recruitment close, 573 mothers had been enrolled, with 482 consented and actively participating in the study. At enrollment close, 416 babies had been born to the consented mothers, with births continuing.

Along with traditional recruitment methods, such as flyers and in-clinic eligibility screening, we have used many additional recruitment strategies. These strategies complement the protocol changes to adhere to public health and safety recommendations during the pandemic. Examples of multimodal recruitment methods that have increased research study participation include

TABLE II. Summary of key protocol changes after COVID-19 redesign process

Initial protocol	Key changes
Many visits (8) required return to hospital setting in person	Two visits converted to virtual/telephone or combined with preexisting medical encounters (birth of child)
Sample collection in person with optional home collection	Emphasis on home sample collection by participants, including nail clippings, hair, urine, stool, nasal filter paper, and home dust Collection equipment/instructions provided
Aerosolized procedures/nasal washing sample collection	Aerosolized procedures removed Nasal washing sample collection removed
Study materials and requirements reviewed/completed in person	Virtual consent procedures and electronic signature Online access to study materials, with participants given an Amazon Kindle device to be able to access study materials Study surveys and procedures fulfilled virtually whenever possible and preferred by patient/family

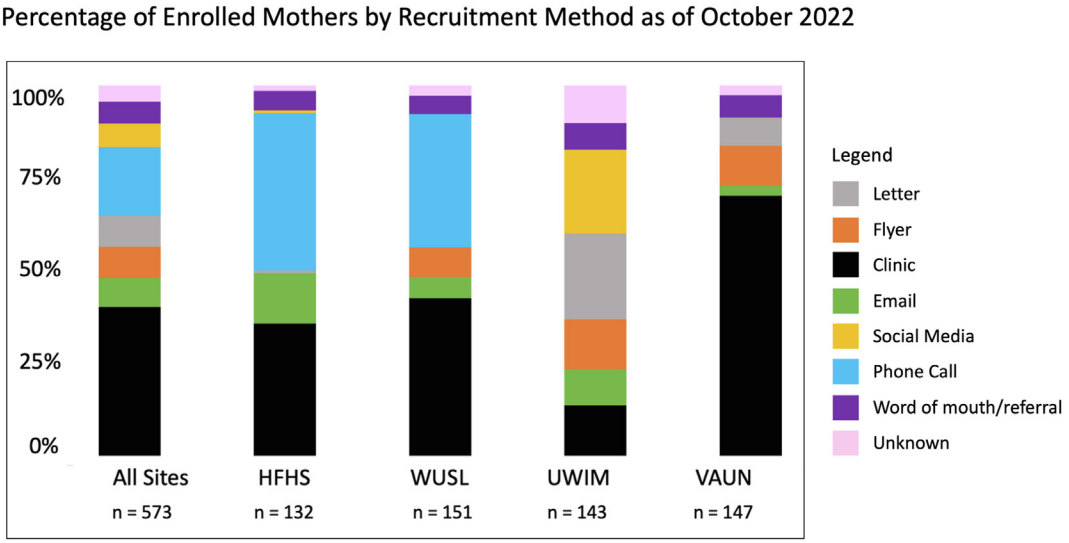

FIG 2. Percentage of enrolled mothers by recruitment method across all sites and by each site until enrollment was closed. *HFHS*, Henry Ford Health; *UWIM*, University of Wisconsin-Madison; *VAUN*, Vanderbilt University; *WUSL*, Washington University, St Louis.

mailing "congratulations" letters to pregnant women in the health system (see Fig E2 in this article's Online Repository at www.jaci-global.org), telephone calls, emails, and targeted social media and website posts that include Twitter, Facebook, Instagram, and maternal health/pregnancy-related blogs (see Fig E3, *A-C*, in this article's Online Repository at www.jaci-global.org). In addition, both print and electronic materials featuring QR codes allow potential and enrolled participants to access the study website and information in a touchless fashion (see Fig E4, *A* and *B*, in this article's Online Repository at www.jaci-global.org).

The various recruitment methods differ slightly across individual sites, ultimately tailored to each site on the basis of the specific institutional policies and local community preferences and resources; thus, each site has their own "portfolio" of recruitment methods. For example, some sites use telephone calls to potential participants as a method of recruitment, whereas others do not because of institutional policies. Similarly, the research staff at some sites, but not others, are able to visit partnered obstetrics and gynecology clinics in person to directly recruit mothers into the study. The ability to use institutional social media to advertise the study also varies by site. Ultimately, despite these differences, recruitment at each site has been robust. Fig 2 shows the percentage of enrolled mothers by recruitment method overall across all sites and at each site.

Enrollment

Through the changes described, we were successful in recruiting 573 pregnant women across 4 cities, with diverse race and ethnicity of enrolled families, despite a global pandemic and public health guidance (including physical distancing) (Table III). Of note, we overenrolled to replace families that discontinued the study because of predefined exclusion criteria, such as premature birth or health issues in infants, or to replace mothers who dropped out early in the study. We currently have a very high retention rate of 93.6% of target mothers currently enrolled and 94.6% of the target number of children still enrolled. In addition, our birth cohort study enrollment was diverse, including 16.8% who self-identified as Black, 4.7% who self-identified as Asian, 1.4% American Indian/Alaska Native, and 3.5% Hispanic/Latino participants. Participants were willing to enroll despite the

TABLE III. Characteristics of pregnant women consented into CANOE

Characteristics	n (%)
Age (y)	
18-24	54 (9.4)
25-29	103 (17.9)
30-34	220 (38.3)
35-39	166 (28.9)
40+	31 (5.4)
Unknown/not reported	0 (0)
Race	
American Indian/Alaska Native	9 (1.5)
Asian	29 (4.9)
Black	195 (17.8)
Native Hawaiian/Pacific Islander	0 (0)
White	317 (53.7)
Other	4 (0.7)
Unknown/not reported	126 (21.4)
Ethnicity	
Hispanic/Latino	22 (3.8)
Not Hispanic/Latino	429 (74.7)
Unknown/not reported	123 (21.4)
Parity	
G1	149 (26.0)
G2	98 (17.1)
G3+	134 (23.4)
Unknown	193 (33.5)

Total consents exceed current enrollment because overenrollment occurred to replace mothers who were removed from the study (because of prematurity, other health issues, etc) or who dropped out. Race numbers are higher than age/ethnicity because participants could choose more than 1 race.

complexity of the study and accepted a combination of home and in-person collection of samples and virtual and in-person visits. These strategies may aid recruitment and retention in future studies. In addition, this flexibility may help recruit diverse study populations.

We next asked enrolled mothers to indicate whether various life stressors were present in their lives. Life stressors assessed included health concerns; financial concerns; impact on work and family; access to food, baby supplies, and personal/household supplies; access to medical care; social distancing; and quarantine (see Table E4 in this article's Online Repository at www.jaci-global.org). We were successful in recruiting pregnant women despite a high number of life stressors, with 43.3% of participants reporting 4 or more stressors (Fig 3). Ninety-nine percent of participants reported at least 1 stressor. Thus, we were successful in recruiting a diverse participant population despite an ongoing pandemic and a high number of life stressors.

DISCUSSION

The CANOE birth cohort study protocol is an example of a complex, longitudinal, and observational research study that includes extensive biospecimen collection, many questionnaires, and a 3-year commitment from participants and their families. The redesigned protocol has maintained rich collection of prenatal and postnatal data elements while accommodating study participants' preferences and adhering to public health and safety guidelines during the COVID-19 pandemic. Furthermore, diverse recruitment strategies across the 4 sites have proven successful, with excellent enrollment and retention of study participants despite the ongoing

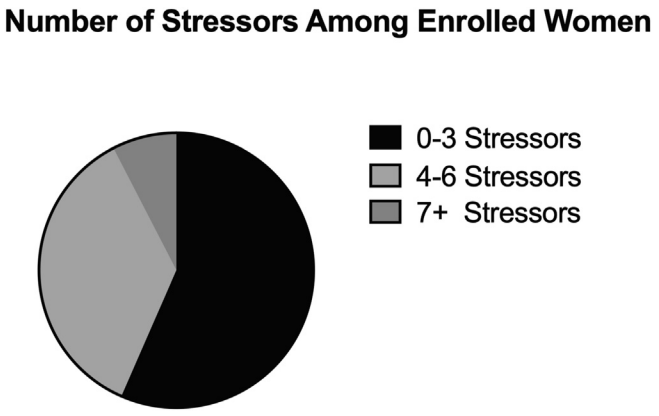

FIG 3. Number of stressors reported among enrolled pregnant women. Stressors assessed included health concerns, impact on work, impact on child/children, impact on community, impact on family, access to food, access to baby supplies, access to personal care products/household supplies, access to medical care including mental health care, social distancing, and quarantine.

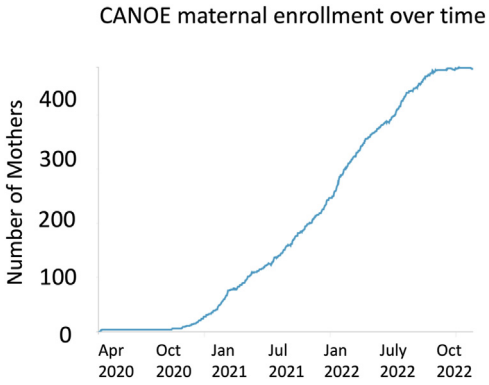

FIG 4. Mother-infant dyad enrollment across all sites over time until enrollment was closed.

pandemic, subsequent infection "waves," and waxing and waning public health recommendations. By altering the protocol to include virtual and touchless options for research study visits, sample collection, and information-seeking as well as launching and leveraging novel and varied recruitment strategies, we were successfully meeting recruitment goals for the CANOE study during a global public health emergency. These experiences demonstrate that restructuring methods of recruitment and study visits can enable successful perinatal research despite unprecedented changes in the academic and health care environment during the global pandemic (Figs 3 and 4).

Finally, now that the CANOE study population has achieved full enrollment, we will further examine additional implications of conducting research during the pandemic. We will examine specific recruitment strategies and their success as potentially related to factors such as patient experiences during the pandemic, vaccination availability and status, and other social and logistical barriers to better understand how to prioritize equity in research participation. In addition, given the many changes that occurred during protocol redesign and relaunch, we will determine how CANOE implementation and participation were viewed from the perspective of research staff and participants. We hope that the processes described in this article and additional

information from future analyses of our completed cohort will help inform the design of future research activities.

DISCLOSURE STATEMENT

This work was supported by the CREW consortium, Office of the Director, National Institutes of Health (NIH; award no. 5UH3 OD023282) and NIH awards UG3 OD035509, UG3 OD035518, UG3 OD035517, UG3 OD035521. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosure of potential conflict of interest: T. Hartert reported grants from the National Institutes of Health (NIH) and the World Health Organization during the conduct of the study; and received personal fees from the American Thoracic Society, Pfizer, and Sanofi-Pasteur, outside the submitted work. J. E. Gern reported grants from the NIH during the conduct of the study; and received personal fees from AstraZeneca, outside the submitted work. A. M. Singh reports grants from the NIH during the conduct of the study, and is on the Data Safety Monitoring Board for a Siolta Therapeutics Inc, study. The rest of the authors declare that they have no relevant conflicts of interest.

We thank CANOE participants and families, Rho Clinical Data Management, Rachel Lisi, Caitlin Suddueth, Gina Crisafi, ECHO-CREW Publications Committee, Carole Ober, Cindy Visness, Jomol Mathew, Leonard Bacharier, Diane Gold, Lisa Martin, and Chris Reyes. Availability of data and materials: The data presented are internal for examination of study recruitment successes and challenges; however, these data are available from the corresponding authors on reasonable request.

Clinical implications: Study procedures that prioritize health and safety and diverse recruitment strategies enable successful enrollment into clinical research despite challenging circumstances, including enrollment of minoritized populations.

REFERENCES

1. Bratan T, Aichinger H, Brkic N, Rueter J, Apfelbacher C, Boyer L, et al. Impact of the COVID-19 pandemic on ongoing health research: an ad hoc survey among investigators in Germany. BMJ Open 2021;11:e049086.
2. Ramos S. COVID-19's impact felt by researchers: scientists, graduate students talk about conducting research during a pandemic. Washington, DC: American Psychological Association; 2021. https://www.apa.org/science/leadership/students/covid-19-impact-researchers. (Last accessed May 27, 2024).
3. Weiner DL, Balasubramaniam V, Shah SI, Javier JR. Pediatric Policy Council. COVID-19 impact on research, lessons learned from COVID-19 research, implications for pediatric research. Pediatr Res 2020;88:148-50.
4. van Dorn A. COVID-19 and readjusting clinical trials. Lancet 2020;396:523-4.
5. Audisio K, Lia H, Robinson NB, Rahouma M, Soletti G Jr, Cancelli G, et al. Impact of the COVID-19 pandemic on non-COVID-19 clinical trials. J Cardiovasc Dev Dis 2022;9:19.
6. Unger JM, Xiao H. The COVID-19 pandemic and new clinical trial activations. Trials 2021;22:260.
7. Anderson KE, McGinty EE, Presskreischer R, Barry CL. Reports of forgone medical care among US adults during the initial phase of the COVID-19 pandemic. JAMA Netw Open 2021;4:e2034882.
8. Czeisler MÉ, Marynak K, Clarke KEN, Salah Z, Shakya I, Thierry JM, et al. Delay or avoidance of medical care because of COVID-19–related concerns—United States, June 2020. MMWR Morb Mortal Wkly Rep 2020;69:1250-7.
9. Masoli JAH, Down K, Nestor G, Hudson S, O'Brien JT, Williamson JD, et al. A report from the NIHR UK working group on remote trial delivery for the COVID-19 pandemic and beyond. Trials 2021;22:911.
10. Simpson EL, de Bruin-Weller M, Bansal A, Chen Z, Nelson L, Whalley D, et al. Definition of clinically meaningful within-patient changes in POEM and CDLQI in children 6 to 11 years of age with severe atopic dermatitis. Dermatol Ther (Heidelb) 2021;11:1415-22.
11. Schram ME, Spuls PI, Leeflang MMG, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy 2012;67:99-106.
12. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997;195:10-9.
13. Stalder J-F, Barbarot S, Wollenberg A, Holm EA, De Raeve L, Seidenari S, et al. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. Allergy 2011;66:1114-21.
14. Barbarot S, Aubert H, Stalder J-F, Roye S, Delarue A. The Patient-Oriented Scoring of Atopic Dermatitis and SCORAD in young children: new data on interpretability and clinical usefulness. J Eur Acad Dermatol Venereol 2024;38:175-81.