Published in final edited form as:

Am J Public Health. 2021 September ; 111(9): 1645–1653. doi:10.2105/AJPH.2021.306372.

Best Practices for Conducting Clinical Trials With Indigenous Children in the United States

Jennifer L. Shaw, PhD,

Southcentral Foundation Research Department, Anchorage, AK.

Erin Semmens, PhD, MPH,

University of Montana, Missoula

May Okihiro, MD,

University of Hawaii at Manoa, Honolulu

Johnnye L. Lewis, PhD,

University of New Mexico Health Sciences Center, Albuquerque.

Matthew Hirschfeld, MD, PhD,

Alaska Native Medical Center, Anchorage

Timothy M. VanWagoner, PhD,

University of Oklahoma Health Sciences Center, Oklahoma City

Lancer Stephens, PhD,

University of Oklahoma Health Sciences Center, Oklahoma City

David Easa, MD,

University of Hawaii at Manoa, Honolulu

Judith L. Ross, MD,

Alfred I. duPont Hospital for Children, Wilmington, DE

Niki Graham, MPH,

University of Montana, Missoula

Sara E. Watson, MD,

CORRESPONDENCE: Correspondence should be sent to Jennifer L. Shaw, Southcentral Foundation Research Department, 4085 Tudor Centre Drive, Anchorage, AK 99508 (jshaw@southcentralfoundation.com). Reprints can be ordered at <http://www.ajph.org> by clicking the “Reprints” link.

CONTRIBUTORS

J. L. Shaw made substantial contributions to the conceptualization and critical review and revision of important intellectual content, synthesized co-author contributions, and led the writing. R. Singleton, E. Semmens, M. Okihiro, and J. L. Lewis made substantial contributions to the conceptualization, writing, and critical review and revision of important intellectual content and approved the final version for publication. M. Hirschfeld, D. Easa, and N. Graham made substantial contributions to critical review and revision of important intellectual content and approved the final version for publication. T. M. VanWagoner, J. L. Ross, S. E. Watson, E. G. Szyld, D. A. Dillard, L. A. Pyles, P. M. Darden, J. C. Carlson, P. G. Smith, R. J. McCulloh, J. N. Snowden, and S. H. Adeky made substantial contributions to critical review of important intellectual content and approved the final version for publication. L. Stephens made substantial contributions to conceptualization and critical review and revision of important intellectual content and approved the final version for publication.

CONFLICTS OF INTEREST

The authors have no potential or actual conflicts of interest from funding or affiliation-related activities.

HUMAN PARTICIPANT PROTECTION

This study describes published research and did not involve human participants.

University of Louisville, Louisville, KY.

Edgardo G. Szyld, MD,

University of Oklahoma Health Sciences Center, Oklahoma City

Denise A. Dillard, PhD,

Southcentral Foundation Research Department, Anchorage, AK.

Lee A. Pyles, MD,

West Virginia University, Morgantown.

Paul M. Darden, MD,

University of Oklahoma Health Sciences Center, Oklahoma City

John C. Carlson, MD, PhD,

Tulane University, New Orleans, LA

Paul G. Smith, DO,

University of Montana, Missoula

Russell J. McCulloh, MD,

University of Nebraska Medical Center, Omaha

Jessica N. Snowden, MD,

University of Arkansas for Medical Sciences, Little Rock.

Sarah H. Adeky, BA,

Ramah Navajo Community, Pinehill, NM

Rosalyn Singleton, MD, MPH

Alaska Native Tribal Health Consortium, Anchorage.'

Abstract

We provide guidance for conducting clinical trials with Indigenous children in the United States. We drew on extant literature and our experience to describe 3 best practices for the ethical and effective conduct of clinical trials with Indigenous children. Case examples of pediatric research conducted with American Indian, Alaska Native, and Native Hawaiian communities are provided to illustrate these practices.

Ethical and effective clinical trials with Indigenous children require early and sustained community engagement, building capacity for Indigenous research, and supporting community oversight and ownership of research. Effective engagement requires equity, trust, shared interests, and mutual benefit among partners over time. Capacity building should prioritize developing Indigenous researchers. Supporting community oversight and ownership of research means that investigators should plan for data-sharing agreements, return or destruction of data, and multiple regulatory approvals.

Indigenous children must be included in clinical trials to reduce health disparities and improve health outcomes in these pediatric populations. Establishment of the Environmental Influences on Child Health Outcomes Institutional Development Award States Pediatric Clinical Trials

Network (ECHO ISPCTN) in 2016 creates a unique and timely opportunity to increase Indigenous children's participation in state-of-the-art clinical trials.

The US population includes nearly 7 million Indigenous people, including 5 million American Indian and Alaska Native (AI/AN) people and 1.5 million Native Hawaiian and other Pacific Island people.¹ Overall, Indigenous people in the United States experience lower life expectancies, higher disease burden, and higher rates of all-cause mortality than other demographic groups, especially non-Hispanic White populations.² These health disparities include disproportionately high rates of infectious diseases, diabetes, behavioral health conditions, and many chronic conditions.³ Indigenous children share this burden, with disproportionately high rates of asthma,⁴ obesity,⁵ and respiratory infections⁶ compared with the general pediatric population.

Increasing evidence suggests that social and environmental determinants of health contribute significantly to these health disparities.⁷ Among the more than 2 million Indigenous children in the United States in 2017, approximately 33% of AI/AN children and 21% of Native Hawaiian/Pacific Islander children lived in poverty, compared with 20% of the overall pediatric population.¹ AI/AN children are more likely than their peers in all other racial groups to live in rural areas, with limited access to health care.⁸ Furthermore, Indigenous communities experience disproportionate rates of household crowding, lack of indoor plumbing and running water, indoor air pollutants, and environmental contamination.⁹ These inequities are deeply rooted in historical policies of forced relocation, assimilation, and extermination of Indigenous societies that continue to threaten the health of Indigenous people today.^{10,11} There is growing attention to Indigenous cultural values and practices as key mechanisms for achieving positive health outcomes¹²; substantial work remains, however, to address health disparities in Indigenous communities, including children. One aspect of this work is ensuring that Indigenous children and their communities have access to state-of-the-art health care and clinical research.

NEED FOR PEDIATRIC TRIALS WITH INDIGENOUS CHILDREN

With limited exceptions such as cardiology and oncology, few clinical trials have been conducted with children, relative to adults.¹³ Among 266 119 interventional studies registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (as of May 7, 2020), only 47 049 (18%) planned to enroll people aged 0 to 17 years. In the National Library of Medicine PubMed database, an unfiltered search combining terms for “clinical trial” and “pediatric,” across all article types and all years, yielded about 56 000 citations. Adding “American Indian,” “Native Hawaiian,” or “Alaska Native” returned fewer than 100 articles total (Table 1). Thus, among articles in the database that contain the term “clinical trial,” only 5% include the term “pediatric,” and 0.007% mention Indigenous children in the United States.

The lack of pediatric clinical trials has resulted in fewer evidence-based therapies for children in all racial and ethnic groups, requiring clinicians to often rely on pharmacological treatments that have been researched in adults only.¹³ This is problematic given age-based differences in pathophysiology and drug metabolism.¹⁴ Congress passed the Pediatric Exclusivity Provision in 1997 to incentivize pediatric drug trials, followed by the Pediatric

Research Equity Act of 2003, requiring pediatric tests of new drugs that are likely to be used in children.¹⁵ However, no such requirements exist for pediatric trials to include Indigenous children, who may not benefit from interventions developed with general population samples.

Substantial challenges exist in enrolling Indigenous children in clinical trials, particularly those living in rural areas. Trials typically occur at large academic medical centers in urban areas; travel and financial burdens associated with participation limit access for children in rural areas, where many Indigenous children live.¹⁶ Experiences with research misconduct in Indigenous communities have also resulted in distrust of researchers and clinical research, especially that involving children. Furthermore, Western scientific standards or practices may directly conflict with community priorities and values. For example, “gold standards” of clinical study design, such as randomization, may be fundamentally unacceptable in Indigenous communities that prioritize cultural values of equity and community benefit over equipoise. Understanding and overcoming these challenges is necessary for increasing Indigenous children’s participation in clinical trials and improving child health outcomes.

BEST PRACTICES FOR CLINICAL TRIALS WITH INDIGENOUS CHILDREN

The Environmental Influences on Child Health Outcomes Institutional Development Award States Pediatric Clinical Trials Network (ECHO ISPCN) was established in 2016 to increase pediatric trials in rural and medically underserved areas.¹⁷ The network’s focus on environmental influences on child health aligns with the health needs and priorities of many Indigenous communities. However, little explicit guidance exists on how to develop and implement pediatric trials with Indigenous communities. Although a growing literature has emerged on the ethics of conducting clinical research with Indigenous communities, few of these articles mention children.¹⁸ Through consideration of this literature and our experience conducting clinical research with Indigenous communities, we suggest 3 best practices for conducting pediatric clinical trials with Indigenous communities in the United States (Box 1). These practices are not novel, nor do we claim that they are original approaches for conducting clinical research with Indigenous communities. Rather, we advocate here for their application to increase the clinical trial participation of Indigenous children, a population with substantial health disparities that is underrepresented in pediatric research. To illustrate each practice, we provide examples of clinical research with Indigenous children in Alaska, Hawaii, Montana, New Mexico, and Oklahoma. These studies preceded establishment of the ECHO ISPCN and offer lessons for increasing pediatric clinical trials with Indigenous communities.

Early and Sustained Community Engagement

Early and sustained community engagement is essential to conducting clinical trials with Indigenous communities, particularly on sensitive topics such as child health. Community engagement is arguably the most important practice of doing research with Indigenous populations. Various models of community-engaged research exist, including community-based participatory research, participatory action research, and community engaged research. Woolf et al.¹⁹ use “authentic engagement” to describe research in which

Indigenous communities are “full partners in setting research priorities, forming research questions, and shaping the design, funding, conduct, and dissemination of studies.”^{19(p2)} The different models of community engagement all conceptualize research as an equitable, collaborative process between researchers and communities. Equitable research requires that all partners understand the importance of having a shared interest and emphasizes the development of meaningful, sustained relationships built on mutual trust and respect among all partners, by their own standards. Such partnerships center the unique and critical expertise of community partners, who are involved in some capacity in all aspects of the research. The processes by which researchers can identify appropriate community partners is an important consideration and will vary greatly by setting.

The Family Spirit intervention provides an example of effective university-based research using a community-based participatory research approach to engage Indigenous communities in clinical trial design and implementation.²⁰ Family Spirit is an evidence-based, culturally tailored home-visiting intervention program designed specifically for rural Native American families, and the first to provide evidence for the value of Indigenous home visitors for improving behavioral health disparities. The intervention is a 43-session curriculum administered by Indigenous paraprofessionals to adolescent mothers from 28 weeks’ gestation until the child’s third birthday. Expectant American Indian adolescents (n 5 322; mean age 5 18.1 years) from 4 southwestern reservation communities were randomly assigned in stratified blocks to Family Spirit plus optimized standard care or optimized standard care alone. Maternal and child outcomes were evaluated at 28 and 36 weeks’ gestation, and 2, 6, 12, 18, 24, 30, and 36 months postpartum. The intervention improved parenting and maternal and child outcomes, and the trial had a retention rate of 83% at 36 months. Study partners attributed the trial’s success to the community-based participatory research approach that involved Indigenous research staff who understood the culture, language, and local resources, and who were trusted by study participants. The study also helped build a sustainable, scalable Indigenous workforce in participating communities.

Another example of effective community engagement in pediatric research is the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, a multicenter clinical trial aimed at improving treatment of diverse youths with type 2 diabetes.^{21,22} Researchers at the University of Oklahoma site of the study engaged Native American community leaders for several years before the study and built relationships within the community as clinical care providers. The researchers proposed a preliminary research design and then worked with the community to identify potential obstacles to participation, such as travel distances for families. This resulted in a modified design in which researchers provided the study intervention at a local tribal clinic, rather than a distant medical center. This trust-building process between university researchers and community partners on all aspects of the study included development of legal agreements and day-to-day operations that facilitated achieving study objectives. The TODAY study illustrates that community engagement is not a single event, but an ongoing, continual process of building and sustaining relationships that are experienced by all partners as mutually beneficial.

Thus, clinical research with Indigenous populations requires longitudinal community engagement from before study conceptualization to beyond completion. Community

members participate actively in the research, not only as sources of data but also as consultants, decision-makers, recruiters, data collectors, analysts, authors, and regulatory authorities.

Build Indigenous Research Capacity

The term “capacity building” in health science research typically means the development of independent (principal) investigators, research networks, and scientific infrastructure. The National Institute of General Medical Sciences’ Division for Research Capacity Building, for example, partners with other National Institutes of Health (NIH) agencies and the Indian Health Service to fund Native American Research Centers for Health (NARCH). NARCH grants are awarded to tribes and tribal organizations to build scientific expertise and infrastructure to conduct research and career enhancement activities that meet the health needs prioritized by the community. Building Indigenous research capacity requires developing necessary knowledge, skills, and resources to promote scientific studies selected by the AI/AN community and conducted by partnerships of health researchers from within and outside these communities. Walters and Simoni describe this as “decolonizing research capacity” and contend that research partners must work to “dismantle [colonial research paradigms] by embracing indigenous [sic] worldviews, engaging in collaborative research partnerships, building research capacity within universities and tribal communities, changing reward systems, and developing mentoring programs.”²³(pS71)

A slogan of the disability rights movement of the 1990s, the Latin idiom *nihil de nobis, sine nobis* (nothing about us without us), describes many Indigenous communities’ resolve to not only benefit from clinical research but also to lead these efforts. To this end, some communities have established research infrastructures to develop and employ Indigenous health researchers and promote Indigenous-led research. For example, the Alaska Native Tribal Health Consortium and Southcentral Foundation, both Alaska Native–owned and –operated health organizations, established research departments within the organizations, with principal investigators, researchers, and grant administration personnel, many of whom are AI/AN. Both organizations have policies and procedures that govern how studies are selected, approved, implemented, and disseminated to community and scientific audiences.²⁴ Building capacity for state-of-the-art pediatric clinical trials in Indigenous communities requires the infrastructure, training, and opportunities for Indigenous people to lead these efforts.

One example of building Indigenous community capacity is the Wood Stove Interventions and Child Respiratory Infections in Rural Communities (KidsAIR) study, a randomized controlled trial aimed at reducing risk of lower respiratory tract infections through improvements in indoor air quality in young children residing in homes heated by wood stoves.²⁵ KidsAIR grew out of multiple community- and household-level intervention studies that highlighted the importance of community capacity building. Before KidsAIR, several rural communities implemented community-wide wood stove changeout programs to replace old heating units with improved technology stoves to reduce ambient exposures.²⁶ In 1 such program on the Nez Perce Indian Reservation in Idaho targeting indoor exposures, investigators recorded improvements in ambient exposures in 10 of 16 participating homes

and noted the need for a community-engaged approach to maximize both recruitment and the effectiveness of the intervention.²⁷ In addition, local research staff were critical to the conduct of the Asthma Randomized Trial of Indoor Air Quality and Smoke (ARTIS) study, a randomized trial designed to improve symptoms and related health measures in children with asthma residing in homes that used an older model wood stove as a primary heating source.²⁸

KidsAIR includes children from rural and Indigenous communities in Montana and Alaska, as well as the South-west. Extensive community engagement and community capacity building laid the foundation for the KidsAIR study. In addition to the ARTIS study, which demonstrated the importance of targeting indoor air quality in western Montana homes with wood stoves, results from more than 300 surveys administered in rural parts of Alaska identified specific air quality concerns as potential contributors to disparities in respiratory health in children.²⁹ Of note, community coordinators residing in each of the study areas were essential members of the research team and assisted with survey design and administration. The inclusion of Southwest communities in KidsAIR was based on findings, relationships, and needs identified during previous research with a pediatric cohort in the region, exemplifying the key role of sustained, long-term, and collaborative relationships in clinical research with Indigenous communities. Community staff outreach and feedback indicated community concerns about asthma and the need to do research, as well as provide solutions, setting the stage for expanding the study. Community coordinators lead data collection efforts at each KidsAIR study site, an approach that both builds research capacity in the community and facilitates the successful conduct of study-related activities.

The development of the 13-valent pneumococcal conjugate vaccine (PCV13) provides another illustration of building Indigenous research capacity. In the late 1990s, the rate of invasive pneumococcal disease among Indigenous children in Alaska's Yukon Kuskokwim (YK) Delta was 10 times that of their non-Native peers.³⁰ After introduction of the 7-valent pneumococcal conjugate vaccine, invasive pneumococcal disease rates among YK Delta children declined initially, only to increase dramatically again by 2007 because of the emergence of nonvaccine serotype disease.³¹ During a tribal gathering, Indigenous Elders voiced support for the tribally owned YK Health Corporation's (YKHC's) participation in the late phase 3 clinical trial of the prelicensure PCV13 vaccine. The YKHC implemented the study in 24 rural villages, using a local research coordinator, and training tribal nurses and Indigenous community health aides to administer study vaccine. The PCV13 study enabled YKHC to develop and fund its own research program, which currently employs 3 permanent staff and 4 research nurses in 3 clinical studies. Furthermore, within 6 months of licensure, 91% of children in the region aged younger than 5 years received PCV13 vaccine, and invasive *Streptococcus pneumoniae* cases decreased 73%.³²

Support Ownership and Oversight of Research

An increasing number of Indigenous communities have formed institutional review boards under 45 CFR 46, as well as Tribal Research Review Committees that do not fall under this statute.³³ These entities function to ensure that, in addition to meeting federal requirements, all research activities are ethical by community standards, that individuals and organizations

in the community are appropriately engaged, and that the research aligns with community priorities. The levels and types of community approval vary. Oetzel et al.³⁴ investigated the relationship between the type of final approval for community-engaged projects and governance processes, productivity, and perceived outcomes among 294 federally funded studies in 2009. Tribal government or “government-type” agency approval was associated with communities having greater control of research, greater share of research resources, and more formal agreements about data ownership and research dissemination. These authors conclude that it is an “ethical imperative for communities (especially Native communities and other vulnerable populations) to adopt a model of governance focusing on [research] stewardship,” similar to those established by many tribal health organizations in Alaska such as the Alaska Native Tribal Health Consortium and Southcentral Foundation.^{24(p1161)} Researchers should be prepared to invest the necessary, often extensive, effort to identify and engage the individuals and entities with authority to approve research activities, as well as to establish a clear understanding of approval processes and expectations, which takes time and may involve navigating new or developing community structures, as well as modifying research plans or designs as deemed appropriate by community research oversight authorities.

For example, in response to several negative experiences with research, the Waianae Coast Comprehensive Community Health Center in Hawaii developed its own Health Center Research Committee, Community Advisory Group, and institutional review board. A research group proposed a maternal health study that involved obtaining and analyzing salivary cortisol samples. However, some Native Hawaiian community members on the Health Center Research Committee voiced concerns that the saliva samples were biological specimens that contained cells and DNA and, therefore, needed special consideration. The community members stated that Native Hawaiians have traditionally believed, as with many other Indigenous cultures, that one’s body, including hair and fluids, can be considered sacred or spiritual and should not be given away. Researchers relied heavily on the Health Center Research Committee and Community Advisory Group members for ways to better explain the research, including the purpose of the sampling, how procedures would be conducted in a way that respected the community, and the potential value of these test results to the community. Researchers’ formative understanding of community concerns, demonstration of respectful testing, and working with the research laboratory on procedures to ensure the proper, culturally acceptable disposal of the human samples, showed respect for the Indigenous population and their worldview. This process took considerable time, but the study was eventually approved and successfully completed because, in part, of the researchers’ willingness to adapt the study based on feedback from community authorities.

Pediatric trialists should be prepared to establish the appropriate type of agreement (e.g., memorandum of understanding, contract, tribal resolution) with legitimate approval bodies to formalize shared understanding and expectations about data ownership, management, storage, disposal, or return, as well as dissemination. These processes can take substantial time and should be factored into study timelines in funding applications. Researchers should expect that ownership of data (e.g., biospecimens, medical records, surveys, and interviews) will be retained by the community with additional consent required for secondary use

and dissemination. Communities may assert their sovereign right to decline for data to be included in data repositories or used for future studies.

CONCLUSION

Indigenous children in the United States experience significant health disparities yet remain substantially underrepresented in clinical trials. Improving health outcomes in this pediatric population of more than 2 million children requires increasing their enrollment in clinical trials to ensure the development of effective, population-based interventions that can be successfully implemented. The dearth of clinical trials in Indigenous communities in the United States has resulted in little explicit guidance for researchers on the ethical conduct of pediatric trials with these populations. We have drawn on extant literature and our own experiences to identify 3 best practices for conducting pediatric trials with Indigenous communities: (1) early and sustained community engagement, (2) building Indigenous research capacity, and (3) supporting community ownership and oversight of research.

These practices are not specific to clinical trials or pediatric populations. Nor are they specific to research with Indigenous people in rural settings, although urban contexts may require other considerations—for example, how to identify of appropriate community partners. Applying these practices does not guarantee a successful trial; it is the minimum requirement for one. Researchers should have no illusion that that these practices necessarily prevent conflicts, missteps, or even occasional crises in relationship between partners. For example, randomization, particularly to placebo or parallel group designs, may be unacceptable in some communities. While alternative trial designs (e.g., stepped wedge, delayed entry) may be acceptable, these conflicts may be irreconcilable and require a scientifically less rigorous approach in favor of a culturally more appropriate one. In our experience, however, these challenges can usually be overcome with relationships built on trust, equity, commitment, shared interests, and mutual benefit.

The case examples herein provide only an introduction, not a comprehensive guide, for conducting pediatric trials with Indigenous communities. As previously mentioned, decolonizing Indigenous research requires more than simply hiring local staff onto studies; it requires sustained commitment on the part of noncommunity researchers and funders (e.g., NARCH) to building Indigenous research capacity that goes beyond a single study and actively supports development of research structures that respect Indigenous peoples and sovereignty, including the right to data ownership and oversight. For example, the Alaska site of the ECHO ISPCTN reached a data-sharing agreement with the NIH that makes tribal approval a requirement for any researcher seeking to access or disseminate results from data collected from Alaska Native families participating in a network study. We have noted that identifying appropriate community partners and understanding research approval processes and expectations requires navigating complex Indigenous community structures, necessitating researchers' time and effort to build relationships, trust, knowledge, and understanding. This is a critical process that will vary greatly by setting, and the importance of which cannot be overemphasized.

Pediatric trials have contributed to advances in the prevention, diagnosis, and treatment of many childhood illnesses. However, children remain underrepresented in clinical trials, and many treatments provided to children are based on research conducted with adults only. Indigenous children are not only underrepresented in pediatric clinical trials but also experience health disparities and environmental conditions that may differentially impact their health as well as the effectiveness of interventions compared with their peers. The need for increased inclusion of Indigenous children in clinical trials is particularly highlighted by the emergence of complex diseases, such as COVID-19, that manifest differently in children and disproportionately affect Indigenous communities.

The NIH Institutional Development Award (IDeA) program builds research capacity in states that historically have low levels of NIH funding (Figure A, available as a supplement to the online version of this article at <http://www.ajph.org>).³⁵ In fiscal year 2020, the 23 IDeA-designated states and Puerto Rico received only 7% of the \$33 billion awarded for extramural research (Table 2). ECHO ISPCNTN aims to increase pediatric clinical trials in these states, particularly in rural and medically underserved areas. Several of these states have the highest proportions of Indigenous children, presenting pediatric researchers with a unique and timely opportunity to partner with Indigenous communities on state-of-the-art clinical trials. Doing so requires understanding the challenges and necessary considerations in doing this type of research. We suggest 3 best practices for conducting pediatric trials with Indigenous communities. We hope that future research elaborates on these practices as more pediatric researchers successfully engage with Indigenous communities to conduct clinical trials to reduce health disparities and improve child health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health, Office of the Director, Environmental Influences on Child Health Outcomes program through awards made to the Institutional Development Award States Pediatric Clinical Trials Network, U24OD024957 (Data Coordinating and Operating Center), UG1OD024944 (Alaska site), UG1OD024948 (Hawaii site), UG1OD024952 (Montana site), UG1OD024950 (Oklahoma site), UG1OD024958 (Delaware site), and UG1HD090904 (Kentucky site), as well as to the Navajo Birth Cohort Study, UG3/UH3OD023344. Other support for this work came from the National Institute for Environmental Health Sciences (NIEHS) Metals Exposure and Toxicity Assessment on Tribal Lands in the Southwest Superfund Research and Training Center, P42ES025589; the Center for Native Environmental Health Equity Research P50ES026102, co-supported by NIEHS, National Institute of Minority Health and Health Disparities, and US Environmental Protection Agency (STAR RD8361570); and the NIEHS-funded study, Wood Stove Interventions and Child Respiratory Infections in Rural Communities (KidsAIR), R01ES022649.

We thank the tribal leaders and community members who reviewed this article and provided critical feedback.

REFERENCES

1. US Census Bureau. American Community Survey. Available at: <https://www.factfinder.census.gov>. Accessed November 3, 2019.
2. Jacobs-Wingo JL, Espey DK, Groom AV, Phillips LE, Haverkamp DS, Stanley SL. Causes and disparities in death rates among urban American Indian and Alaska Native populations, 1999–2009. *Am J Public Health*. 2016;106(5):906–914. 10.2105/AJPH.2015.303033 [PubMed: 26890168]

3. Bauer UE, Plescia M. Addressing disparities in the health of American Indian and Alaska Native people: the importance of improved public health data. *Am J Public Health*. 2014;104(suppl 3):S255–S257. 10.2105/AJPH.2013.301602 [PubMed: 24754654]
4. Oraka E, Iqbal S, Flanders WD, Brinker K, Garbe P. Racial and ethnic disparities in current asthma and emergency department visits: findings from the National Health Interview Survey, 2001–2010. *J Asthma*. 2013;50(5):488–496. [PubMed: 23544662]
5. Berge JM, Trofholz A, Tate AD, et al. Examining unanswered questions about the home environment and childhood obesity disparities using an incremental, mixed-methods, longitudinal study design: the Family Matters study. *Contemp Clin Trials*. 2017;62:61–76. 10.1016/j.cct.2017.08.002 [PubMed: 28800894]
6. Foote EM, Singleton RJ, Holman RC, et al. Lower respiratory tract infection hospitalizations among American Indian/Alaska Native children and the general United States child population. *Int J Circumpolar Health*. 2015;74(1):29256. 10.3402/ijch.v74.29256 [PubMed: 26547082]
7. Walters KL, Mohammed SA, Evans-Campbell T, Beltran RE, Chae DH, Duran B. Bodies don't just tell stories, they tell histories: embodiment of historical trauma among American Indians and Alaska Natives. *Du Bois Rev*. 2011;8(1):179–189. 10.1017/S1742058X1100018X [PubMed: 29805469]
8. Office of Minority Health. Profile: American Indian/Alaska Native. 2018. Available at: <https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=3&lvlid=62>. Accessed May 11, 2020.
9. Bulkow LR, Singleton RJ, DeByle C, et al. Risk factors for hospitalization with lower respiratory tract infections in children in rural Alaska. *Pediatrics*. 2012;129(5):e1220–e1227. 10.1542/peds.2011-1943 [PubMed: 22508919]
10. Walls ML, Whitbeck LB. The intergenerational effects of relocation policies on Indigenous families. *J Fam Issues*. 2012;33(9):1272–1293. 10.1177/0192513X12447178 [PubMed: 23024447]
11. Brave Heart MY, Chase J, Elkins J, Altschul DB. Historical trauma among Indigenous Peoples of the Americas: concepts, research, and clinical considerations. *J Psychoactive Drugs*. 2011;43(4):282–290. 10.1080/02791072.2011.628913 [PubMed: 22400458]
12. Walters KL, Johnson-Jennings M, Stroud S, et al. Growing from our roots: strategies for developing culturally grounded health promotion interventions in American Indian, Alaska Native, and Native Hawaiian communities. *Prev Sci*. 2020;21(suppl 1): 54–64. 10.1007/s11121-018-0952-z [PubMed: 30397737]
13. Bourgeois FT, Murthy S, Pinto C, Olson KL, Ioannidis JP, Mandl KD. Pediatric versus adult drug trials for conditions with high pediatric disease burden. *Pediatrics*. 2012;130(2):285–292. 10.1542/peds.2012-0139 [PubMed: 22826574]
14. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics*. 2011;3(1):53–72. 10.3390/pharmaceutics3010053 [PubMed: 24310425]
15. Institute of Medicine Forum on Drug Discovery and Translation. Addressing the barriers to pediatric drug development: workshop summary. Washington, DC: National Academies Press; 2008.
16. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. *Contemp Clin Trials Commun*. 2018;11:156–164. 10.1016/j.conctc.2018.08.001 [PubMed: 30112460]
17. Snowden J, Darden P, Palumbo P, Saul P, Lee J. The Institutional Development Award States Pediatric Clinical Trials Network: building research capacity among the rural and medically underserved. *Curr Opin Pediatr*. 2018;30(2):297–302. 10.1097/MOP.0000000000000597 [PubMed: 29517535]
18. Vaughn LM, Wagner E, Jacquez F. A review of community-based participatory research in child health. *MCN Am J Matern Child Nurs*. 2013;38(1):48–53. 10.1097/NMC.0b013e31826591a3 [PubMed: 23232779]
19. Woolf SH, Zimmerman E, Haley A, Krist AH. Authentic engagement of patients and communities can transform research, practice, and policy. *Health Aff (Millwood)*. 2016;35(4):590–594. 10.1377/hlthaff.2015.1512 [PubMed: 27044956]
20. Walkup JT, Barlow A, Mullany BC, et al. Randomized controlled trial of a paraprofessional-delivered in-home intervention for young reservation-based American Indian mothers. *J Am*

- Acad Child Adolesc Psychiatry. 2009;48(6):591–601. 10.1097/CHI.0b013e3181a0ab86 [PubMed: 19454915]
21. Chadwick JQ, Copeland K, Daniel M, et al. Partnering in research: a national research trial exemplifying effective collaboration with American Indian Nations and the Indian Health Service. *Am J Epidemiol*. 2014;180(12):1202–1207. 10.1093/aje/kwu246 [PubMed: 25389367]
 22. Walders-Abramson N, Anderson B, Larkin ME, et al. Benefits and barriers to participating in longitudinal research of youth-onset type 2 diabetes: results from the TODAY retention survey. *Clin Trials*. 2016;13(2):240–243. 10.1177/1740774515613949 [PubMed: 26531295]
 23. Walters KL, Simoni JM. Decolonizing strategies for mentoring American Indians and Alaska Natives in HIV and mental health research. *Am J Public Health*. 2009;99(suppl 1):S71–S76. 10.2105/AJPH.2008.136127 [PubMed: 19246668]
 24. Hiratsuka VY, Beans JA, Robinson RF, Shaw JL, Sylvester I, Dillard DA. Self-determination in health research: an Alaska Native example of tribal ownership and research regulation. *Int J Environ Res Public Health*. 2017;14(11):1324. 10.3390/ijerph14111324
 25. Noonan CW, Semmens EO, Ware D, et al. Wood stove interventions and child respiratory infections in rural communities: KidsAir rationale and methods. *Contemp Clin Trials*. 2020;89:105909. 10.1016/j.cct.2019.105909 [PubMed: 31838259]
 26. Ward T, Palmer C, Bergauff M, Hooper K, Noonan C. Results of a residential indoor PM_{2.5} sampling program before and after a woodstove changeout [erratum in *Indoor Air*. 2008;18(6):529]. *Indoor Air*. 2008;18(5):408–415. 10.1111/j.1600-0668.2008.00541.x [PubMed: 18665872]
 27. Ward T, Boulafentis J, Simpson J, et al. Lessons learned from a woodstove changeout on the Nez Perce Reservation. *Sci Total Environ*. 2011;409(4): 664–670. 10.1016/j.scitotenv.2010.11.006 [PubMed: 21144555]
 28. Noonan CW, Ward TJ. Asthma Randomized Trial of Indoor Wood Smoke (ARTIS): rationale and methods. *Contemp Clin Trials*. 2012;33(5):1080–1087. 10.1016/j.cct.2012.06.006 [PubMed: 22735495]
 29. Ware DN, Lewis J, Hopkins S, et al. Household reporting of childhood respiratory health and air pollution in rural Alaska Native communities. *Int J Circumpolar Health*. 2014;73(1):1–10. 10.3402/ijch.v73.24324
 30. Rudolph KM, Parkinson AJ, Reasonover AL, Bulkow LR, Parks DJ, Butler JC. Serotype distribution and antimicrobial resistance patterns of invasive isolates of *Streptococcus pneumoniae*: Alaska, 1991–1998. *J Infect Dis*. 2000;182(2):490–496. 10.1086/315716 [PubMed: 10915080]
 31. Singleton RJ, Hennessy TW, Bulkow LR, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska Native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *JAMA*. 2007;297(16):1784–1792. 10.1001/jama.297.16.1784 [PubMed: 17456820]
 32. Singleton R, Wenger J, Klejka JA, et al. The 13-valent pneumococcal conjugate vaccine for invasive pneumococcal disease in Alaska Native children: results of a clinical trial. *Pediatr Infect Dis J*. 2013;32 (3):257–263. 10.1097/INF.0b013e3182748ada [PubMed: 23001026]
 33. Kelley A, Belcourt-Dittloff A, Belcourt C, Belcourt G. Research ethics and indigenous communities. *Am J Public Health*. 2013;103(12):2146–2152. 10.2105/AJPH.2013.301522 [PubMed: 24134372]
 34. Oetzel JG, Villegas M, Zenone H, White Hat ER, Wallerstein N, Duran B. Enhancing stewardship of community-engaged research through governance. *Am J Public Health*. 2015;105(6):1161–1167. 10.2105/AJPH.2014.302457 [PubMed: 25880952]
 35. National Institute of General Medical Sciences. Institutional Development Award. Available at: <https://www.nigms.nih.gov/Research/DRCB/IDeA/Pages/default.aspx>. Accessed December 15, 2020.
 36. US Department of Health and Human Services, NIH Research Portfolio Online Reporting Tools (RePORT). NIH awards by location & organization. Available at: <https://report.nih.gov/award/index.cfm>. Accessed December 15, 2020.

BOX 1—**Best Practices for Conducting Pediatric Clinical Trials With US Indigenous Communities**

Practice	Description
Early and sustained community engagement	Community leaders or delegates are involved in formulating research questions and approaches to ensure that research addresses only problems of interest to the community, involves participation of community members in research activities (not only as participants) in a manner that creates equitable and trusted partnership with shared interests and goals, and involves researcher commitment to the community and continuing relationship beyond any specific study.
Build Indigenous research capacity	Research and other activities that build research capacity in Indigenous communities, particularly among community members, in academic and nonacademic settings (e.g., tribal health organizations), through various roles (e.g., researcher, community advisor, institutional review board member) with the explicit intention of increasing knowledge, skills, resources, and leadership in self-determined research by Indigenous peoples for Indigenous peoples.
Support community ownership and oversight of research	Formal recognition (e.g., memorandum of understanding, contract, tribal resolution) that Indigenous community owns all data (e.g., recordings, transcripts, biospecimens) and has oversight authority over all research activities, including data storage and management procedures and dissemination activities, and that research is preapproved by community-led institutional review boards and other local regulatory entities as deemed appropriate and required by community leadership.

TABLE 1—
PubMed Advanced Search for Pediatric Clinical Trials With American Indian, Alaska Native, or Native Hawaiian Populations Unfiltered

Search Terms	Items Retrieved, No.
clinical trial	1 181 619
pediatric	912 165
(clinical trial) AND (pediatric)	56 288
((clinical trial) AND (pediatric)) AND (American Indian)	51
(((((clinical trial) AND (pediatric)))) AND (Native Hawaiian)	22
(((((clinical trial) AND (pediatric))) AND (Alaska Native)	8

Note. As of May 7, 2020; 3:57 Alaska Time.

TABLE 2—

Total National Institutes of Health Extramural Funding to Institutional Development Award (IDeA) Program and Non-IDeA Program States, Combined and by Location: United States, Fiscal Year 2020

State	Funding, \$
Non-IDeA states ^a	30.8 billion combined
California	4 873 379 566
Massachusetts	3 254 611 912
New York	3 112 927 263
Pennsylvania	2 012 759 114
North Carolina	1 968 510 312
Washington	1 588 938 213
Texas	1 495 164 387
Maryland	1 246 582 971
Illinois	1 100 476 076
Ohio	918 576 423
Michigan	890 081 214
Georgia	735 589 203
Florida	727 819 822
Connecticut	679 750 577
Tennessee	676 130 402
Missouri	670 766 929
Minnesota	669 561 614
Wisconsin	530 039 381
Colorado	475 284 058
Virginia	422 324 832
Oregon	420 261 738
Indiana	374 365 757
Alabama	369 367 577
New Jersey	330 270 251

State	Funding, \$
Arizona	281 551 338
Utah	247 425 348
Foreign	242 351 436
District of Columbia	234 692 091
Iowa	217 827 324
Guam	2 058 324
American Samoa	497 841
Virgin Islands	403 329
IDEA states ^b	2.2 billion combined
Kentucky	239 834 370
Rhode Island	229 105 661
South Carolina	213 196 155
Louisiana	176 480 826
Nebraska	133 512 380
Oklahoma	125 197 845
Kansas	119 625 766
New Hampshire	119 623 590
New Mexico	112 437 059
Maine	103 673 732
Arkansas	75 960 965
Vermont	71 427 751
Delaware	54 867 373
Hawaii	52 881 131
Puerto Rico	49 611 681
West Virginia	45 482 645
Nevada	43 936 449
Mississippi	43 914 422
Montana	43 398 838
South Dakota	26 583 066

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

State	Funding, \$
North Dakota	24 743 701
Idaho	18 296 519
Alaska	15 887 731
Wyoming	12 808 992

Source: US Department of Health and Human Services.³⁶

^a Includes 27 states, Guam, Virgin Islands, American Samoa, and foreign locations outside the United States or territories.

^b Includes 23 states and Puerto Rico.