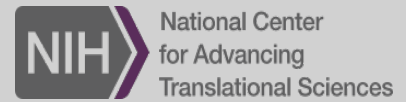


2024 RFI DCT REPORT



Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials

INTRODUCTION

The mission of the National Center for Advancing Translational Sciences (NCATS) is to catalyze the generation of innovative methods and technologies that enhance the development, testing and dissemination of effective medical/behavioral interventions diagnostics and therapeutics across a wide range of human diseases and conditions. The NCATS Clinical and Translational Science Awards (CTSA) Program supports a consortium of CTSA located at medical research institutions across the Nation. During the Fiscal Year 2023 more than 60 hubs across the United States were funded through the CTSA Program (Figure 1). The focus of the consortium is to foster impactful, collaborative translational science, essential to meeting the NCATS mission. This is achieved through innovation in translational science, workforce development, infrastructure support, trans-consortium collaboration, and community engagement (see <https://ncats.nih.gov/ctsa/about>).

Figure 1. CTSA Program Hubs



*As of 09.30.2023

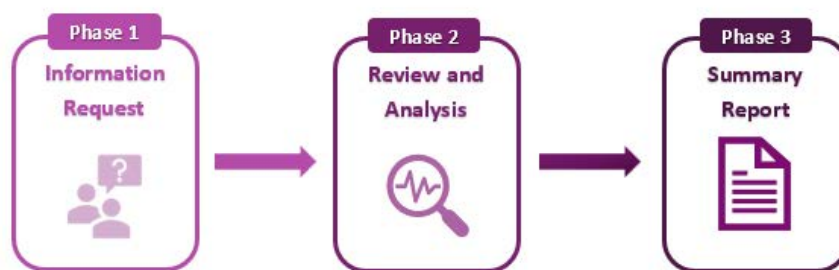
An evolving trend in clinical trial design has been for their decentralization or their ability to be performed in part, or entirely away from traditional medical research institutions. Decentralized clinical trials (DCTs) have the potential to improve the efficiency and speed of implementation for interventions, treatments, and/or diagnostics to be brought to individuals and populations. Decentralized or hybrid clinical trials are the common terms for these types of trial designs. For the purposes of this report, decentralized clinical trials are defined as a clinical trial (or clinical research) that leverages technology and local partners to enable remote research participation and data collection, for some (hybrid) or all (virtual) of the trial or study design. To enable their partially or entirely offsite designs, DCTs can be performed through a combination of software, digital health technologies (including in-home objective measures, wearables, etc.), internet/cellular connectivity, telehealth, community healthcare providers, local pharmacies, mobile research units, point-of-care diagnostics, and more. The goal is to decrease the burden on trial participants (*e.g.*, distance, monetary, logistical, emotional); improve recruitment and retention enabling medical/health interventions to succeed or fail faster without early termination; and deliver more real world, generalizable clinical research findings from broader participation. However, challenges do exist to accelerating this clinical research approach.

Overcoming these challenges is in line with the mission of NCATS and the CTSA Program. To consistently and successfully conduct DCTs, much is needed, including: a deeper understanding of the interplay of the clinical and translational processes inherent to offsite clinical trials, such as clinical workflow integration and patient reporting; robust community engagement and human-centered design; bespoke resources that could be leveraged to rapidly implement and operationalize studies; collaborations and partnerships; and iterative development, validation and implementation of tools that enable DCTs (*e.g.*, informatics systems, digital health technologies, data integration platforms, including machine learning or artificial intelligence technology to integrate disparate data types).

NCATS issued a Request for Information (RFI) [NOT-TR-23-006](#) to help identify challenges, gap areas, existing technologies and opportunities that would help in the advancement of clinical and translational science through the design, implementation and dissemination of research from DCTs. This RFI invited stakeholders throughout the scientific research, advocacy, clinical practice, industry, patient, and lay communities to comment on how DCTs may be designed to be more effective, efficient, and equitable to bring more interventions to all people, faster. Further, comments were sought on ways to engage and enable participants from diverse backgrounds (*e.g.*, which includes, but is not limited to race, ethnicity, socioeconomic status, background, gender, and mental or disability status) and those who are underserved (*e.g.*, used in the context of health disparities related to population-based health).

Herein we provide a summary and analysis of the responses received, key areas of interest and future directions.

Figure 2. RFI process and outcomes



BACKGROUND

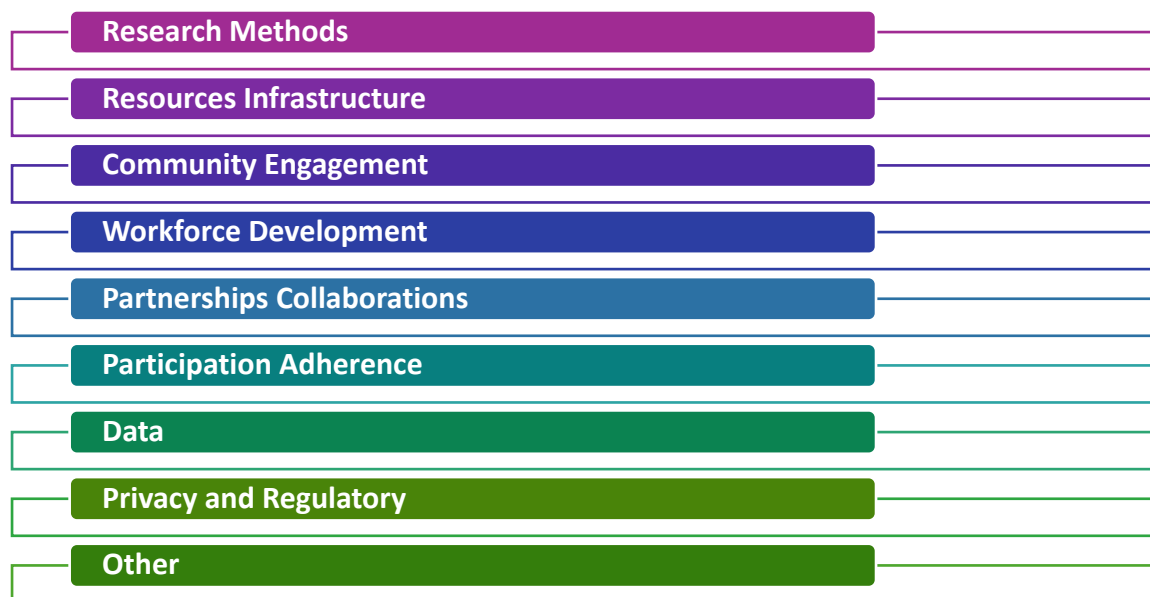
According to the U.S. Food and Drug Administration (FDA), a “decentralized clinical trial” is when some or all the trial related activities occur at locations other than traditional clinical trial sites¹. Decentralization helps facilitate clinical trial activities and interactions between the study team and the participants with the potential to decrease participant burden while maintaining the quality, adherence, safety and potentially improve participant satisfaction and willingness to participate in future trials^{2,3}. Decentralized clinical trial approaches are not necessarily new, as the first classified as a ‘virtual trial’ begun in 2011. This trial was designed to assess the safety and efficacy of tolterodine tartrate, a treatment for overactive bladder⁴; yet these designs have not

been leveraged, as often as contemporary clinical trials, since. The trial was a learning experience for the industry as to what was needed to implement this type of trial design and did offer many benefits to the sponsor. However, challenges remained, for example, could DCT approaches compromise the quality of the data collected during a clinical trial and what was needed to ensure the data was as rigorous as more traditional trials enabled. Furthermore, a proposed benefit of DCTs is for increasing diversity in clinical trials (as well as increasing the robustness of the data generated) by reducing challenges and hurdles to participation⁵ – yet participant access to technologies, lack of infrastructure, research mistrust, ethical considerations and technology literacy are some of the challenges faced^{2,5,6}; this remains a need to be addressed before DCTs can be more widely implemented and, in particular, to reach populations whom may be the largest beneficiaries of these types of approaches.

During the COVID-19 Public Health Emergency, there was an immediate need to continue, or start new clinical trials, that were decentralized to adhere to local and/or regional social distancing mandates and decrease the participant fear of COVID-19 transmission during research visits^{7,8}. During this period of 2020-2023, clinical trials adopted various DCT aspects, from minimal requirement for on-site visits to fully remote studies. Several innovative study elements were incorporated, including remote informed consent, partnering with local pharmacies and nationwide chains for basic medical services and administration of experimental drugs, shipping of investigational drugs or devices to participants' homes, shipment of samples collected remotely to central laboratory, follow-up electronic forms remotely completed by participants, in-home study visits, and coordinator navigation resources to assist participants throughout the study. During this period, much was learned as to best practices and where challenges were still present that needed to be overcome. Further recognized during this period was how many aspects of these designs were still nascent and in need of resources and solid evidence to support their use in particular scenarios or use cases.

As there had been much learned during the pandemic, and sustained emphasis on DCTs post-pandemic, this RFI sought all comments, whether positive and/or negative, about DCTs for translational science endeavors. The RFI was published March 1st, 2023 and was open to public comment until May 12th, 2023. The feedback and comments from the public were lengthy, robust and are discussed next.

Figure 3. RFI response categories by area of interest



Key terms definitions in this RFI Report

- **Artificial Intelligence:** A machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations or decisions influencing real or virtual environments⁹.
- **Big Data:** Big data refers to datasets that are too large to process on a personal computer¹⁰.
- **CTSA Program:** Under the National Center for Advancing Translational Sciences, the Clinical and Translational Science Awards (CTSA) Program supports a national network of medical institutions to speed the translation of research discoveries into improved care¹¹.
- **Decentralized Clinical Trial (DCT):** A clinical trial (or clinical research) that leverages technology and local partners to enable remote research participation and/or data collection, for some (hybrid) or all (fully virtual) of the trial or study design.
- **Digital divide:** Difficulty in accessing digital health and telehealth technologies by complex range of users whose level of adoption changes over time influenced by infrastructure, socioeconomic environment and individual characteristics such as educational background and physical disability⁸.
- **Digital Health Technology:** Devices and/or systems that leverage computing platforms, connectivity, software, and/or sensors for healthcare and related uses. These tools, and approaches, cover a broad cadre of types including mobile health apps, health information technology, wearable devices, and more.
- **Large Language Models:** is a language model notable for its ability to achieve general-purpose language generation and understanding¹².
- **Machine learning:** Machine Learning (ML) refers to the field and practice of using algorithms that are able to “learn” by extracting patterns from a large body of data. This contrasts to traditional rule-based algorithms¹³.
- **Real-world data (RWD):** Includes data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status¹⁴.
- **Real-world evidence (RWE):** Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD¹⁴.
- **Telehealth:** Use of electronic information and telecommunication technologies to support and promote long-distance clinical care, patient and professional health-related education, public health and administration¹⁵.
- **Type of Institution:** Defined according to the mission and funding source. Includes: academic health/medical centers, non-profit foundations/associations, individuals, and industry.

RESULTS

In total, we received 50 responses. Of those, most came from academic institutions (42.6%) and industry (40.7%), with non-profit organizations (11.1%) and individuals (3.7%) next in frequency (Figure 4). There was a small % of responses from unknown sources. Most responses agree with the timing and need to address the key topics outlined in the RFI. The overall analysis of these RFI-specific topic areas is discussed, in more depth, later in sections below. Several respondents added important aspects of DCTs, including validation of DCTs and utilized technologies by standardizing methods to compare DCTs to the Standard (on-site) approach. Top three areas of responses (pre-defined) included Methods, Resources and Infrastructure, and Community Engagement (Appendix 4. Figure 7). Overall, there was agreement in the topic areas responses from most institution types with some emphasis on participants (industry and foundations) and data (industry) (Figure 5). This points to some of the highest priority needs by sector based on their most pressing challenges.

As part of the RFI responses’ analysis, the top 50 most frequent words were extracted from the responses according to each area of interest/them (see Methods section for more details). The combined list was then inspected for synonyms and further combined into word categories. Based on this word frequency analysis, the top 5 terms (out of 20) included Participant Engagement, Digital Health, Study Site, Resources and Infrastructure and Diversity Inclusion Equity and Access (DEIA) (Figure 6).

Most responses were submitted under the following themes/areas of interest questions (Appendix 4. Figure 8):

- Community Engagement: Question a. Identifying the needs of participants.
- Research Methods: Question a. Demonstrating how DCTs advance and accelerate the implementation of clinical trials.
- Resources, Infrastructure, and Enabling Technologies: Question d. Identifying resources, tools, or technologies to collect and analyze large data sets during a DCT as well as post-approval indications utilizing Real World Evidence derived from Real World Data post-approval for Real-World Data and Real-World Evidence.
- Partnerships and/or Collaborations: Question a. Identifying partnerships and/or collaborations essential for DCTs to be successful (inclusive of government agencies, industry, non-profit organizations, academia, etc.).
- Community Engagement: Question b. Identifying partnerships and/or collaborations essential for DCTs to be successful (inclusive of government agencies, industry, non-profit organizations, academia, etc.).

Figure 4. Respondents by organization type

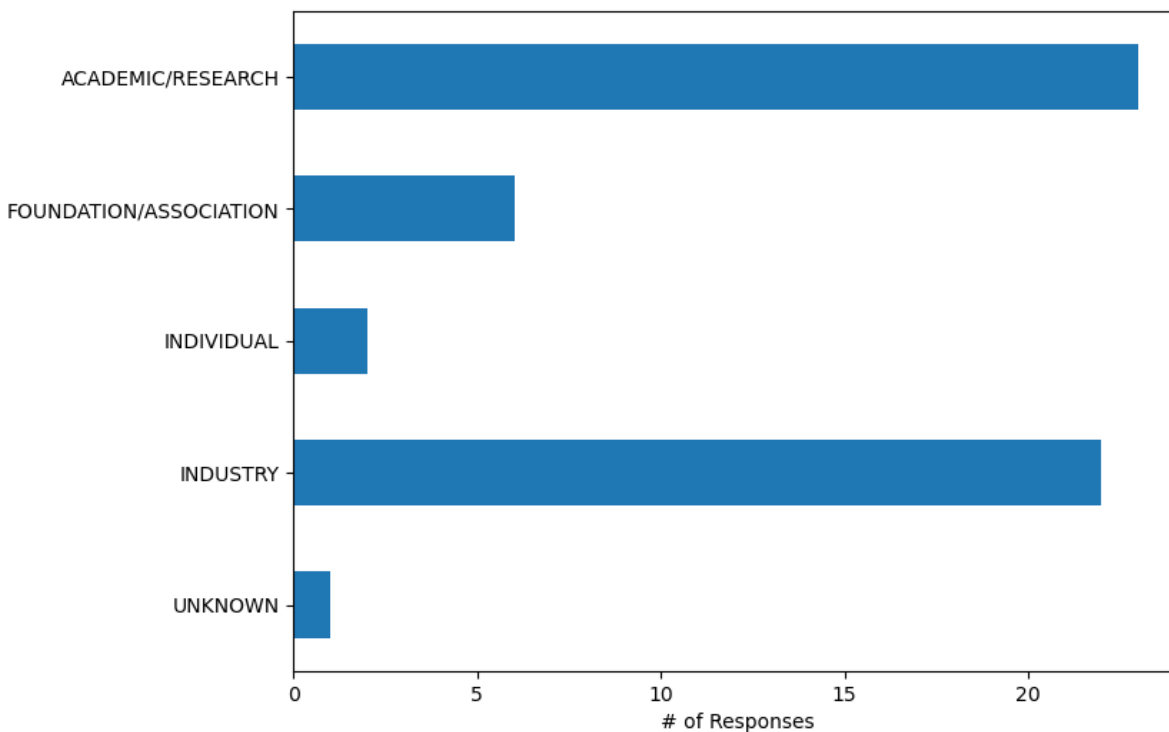
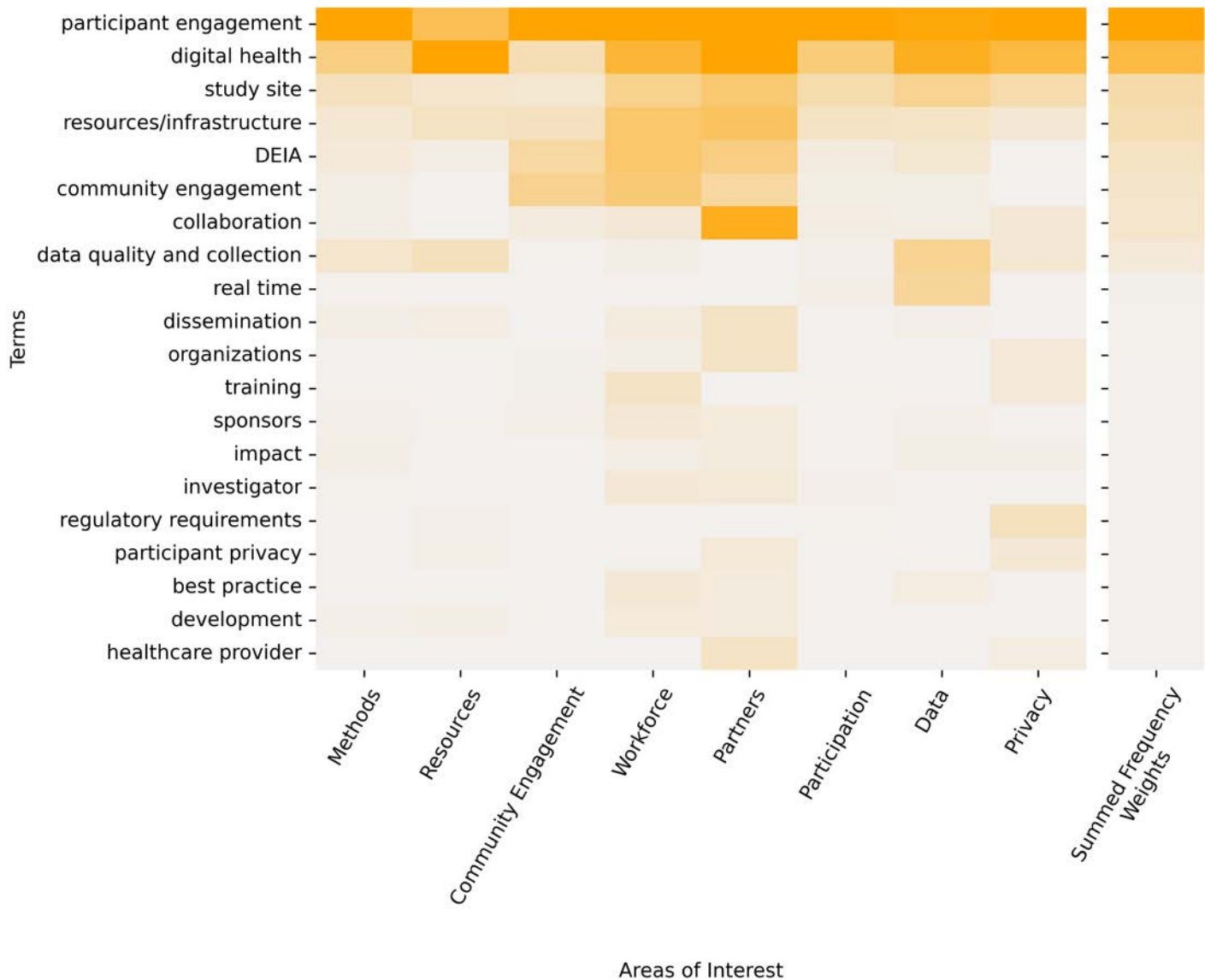


Figure 5. RFI Responses according to type of respondent by topic areas of interest/themes

ACADEMIC/RESEARCH	19	15	15	10	12	7	8	10
FOUNDATION/ASSOCIATION	4	2	4	4	3	4	1	1
INDIVIDUAL	1	1	2	2	2	2	1	1
INDUSTRY	15	15	16	10	14	13	13	9
UNKNOWN	0	1	0	0	0	0	0	0
	METHODS	RESOURCES	CE	WORKFORCE	PARTNERS	PARTICIPATION	DATA	PRIVACY

*CE Community Engagement

Figure 6. RFI response terms (vertical axis) weighted frequencies according to RFI area of interest (horizontal axis)



*Word cloud groups and combinations are further described on Appendix 3

RESPONSES BY RFI AREAS OF INTEREST/THEMES

Research Methods

Most respondents commented on the importance of research methods in the context of DCTs (Appendix 4, Figure 7). Even though the word “design” was on the lower frequency of words utilized by respondents (not shown), overall, respondents had several comments and suggestions related to the study design, including novel methods of analysis to improve the efficiency of trials under the overall framework of succeeding (or failing) fast to avoid unnecessary burden on participants, study sites and sponsors.

Many responses discussed early involvement of participants in the study design process and employing a human-centered design tailored to the needs of the participants and communities where the research is expected to have an impact on. Additional considerations included a more user-friendly and ethically appropriate mechanism(s) to obtain informed consent,

“Employing a human-centered design approach that keeps empathy with participant needs and goals at the center of the development (and design) process”

including information about future data use and data access aspects of the study and data collected. Novel clinical trial designs including adaptive designs and use of RWD were also included in several responses both to help improve the pace and impact of the study results. Additional methods were mentioned to support quality control and quality assurance efforts centrally and / or locally and avoid problematic issues with data analysis later in the research process (once data is locked).

Also, another area where there was marked interest is in the validation of digital health technologies (DHTs) for use in DCTs. Respondents stressed the importance of ensuring that DCTs with novel technologies (e.g., DHTs) have the comparable methodological rigor relative to traditional standard measurements used in clinical trials, to determine if the novel technology is equivalent or better than the established measurement or technology. This type of research could be embedded in existing trials as ancillary studies to maximize utilization of time and resources.

An area where respondents thought novel methodologies were needed was in the integration of data (sometimes disparate data) from multiple sources and in multiple formats. In particular, the need to make sure that data integration methods and tools maintain the highest standards for quality, reliability, and reproducibility without creating additional burden in data management, cleaning, and curation. In these cases, the integration of multiple data sources in one single platform could add richness and context to studies.

A cross-cutting theme between “Research Methods” and “Workforce Development” was the lack of training in novel research methodologies, such big data analyses using RWD and/or multi-modal data as well as adaptive trial designs. The multiple data sources that can be generated within DCTs was another crosscutting theme, including the utilization unique data sources, such as RWD. Respondents also stressed the importance of determining specific study data collection needs to avoid overcollection of data that could unduly add time, effort, and expenses without increasing the validity and impact of the studies. In all these cases, respondents felt that training as to the appropriate use of these tools and their respective ‘state of the art’ were needed to guide those looking to leverage them in a realistic, rigorous manner.

Resources, Infrastructure and Enabling Technologies

Several respondents commented on the importance of having adequate and equitable access to technological resources and infrastructure. This is to ensure that patients, communities, and populations not traditionally involved in clinical studies are not inadvertently excluded from participation. Issues such as broadband access, mobile device plans, mobile technologies literacy and other technology

“Research utilizing digital tools must ensure equitable access to them and consider the broadband infrastructure required to support such tools”

resources must be considered in the design and implementation of DCTs. To further highlight the importance of resources and infrastructure, 8 out of the 10 top challenges included issues related to this theme.

Data infrastructure and resources are also in high demand and this demand rapidly changes in terms of storage capacity, data privacy and security considerations. This points to a key aspect in the development and implementation of DCTs, which includes having appropriate data infrastructure for current and future study needs. Many respondents also noted that identifying currently available technologies and infrastructure that could be leveraged to develop effective and impactful DCTs is essential. For example, researchers could utilize storage capacity from existing data warehouses at institutions and expertise in data management, analysis, reporting and dissemination from existing local/regional programs, such as institutions/hubs funded through the CTSA program.

When discussing DCT-enabling technologies, respondents provided suggestion on how to make sure that when developing or refining participant-facing digital technologies, prospective participants and communities should be engaged to help inform their design and implementation while aligning with community needs. In other words, it is critical to make sure that digital health technology has the customer (participant) in mind at all stages of development.

Respondents emphasized the importance of the need to evaluate the financial burden versus the benefit of DCTs, in addition to evaluating their efficacy, effectiveness and impact.

Having sufficient analytical resources to process “big data” throughout the research process was mentioned, including early identification of problematic data issues via frequent QA/QC, locally and/or centrally. Robust analytic resources, paired with appropriate (and sometime novel) study designs are also important for the evaluation study data and dissemination of results.

Community Engagement

In terms of community engagement (CE), respondents commented on the importance of CE, not only for participant/community education and awareness campaigns, but also to include their opinions and needs within the clinical trial framework for a specific disease area or condition. Many commented on the importance of “full-circle” clinical trials where participants are involved in all aspects of the study, and have access to the results in a culturally and linguistically appropriate manner.

Several respondents reiterated the view that DCTs have the potential to bring completely new participants to research, including rural populations, low SES populations, individual with disabilities, culturally diverse populations, and those with poor access to large academic medical centers. However, respondents suggested that to ensure diverse populations are included in DCTs, a holistic approach is needed, which takes into consideration technological, infrastructural, literacy, religious, cultural, or other critical aspects.

“Identifying the needs of participants and paying particular attention to those who traditionally experience health disparities or are part of an underserved population, to participate in DCTs”

There were also crosscutting themes with “Workforce Development” and CE, where respondents found gaps in knowledge of DCTs and related digital health technologies. This includes logistical and technical issues that require additional education and training initiatives for participants and research staff to make sure everybody has adequate knowledge and understanding of the technologies to be accessed and/or utilized. These training methods need to also be culturally, linguistically, and technically appropriate for the study population. If these methods are not aligned with participant and study needs, there is a risk of overburdening participants with extraneous data entry steps, which can compromise the safety and accuracy of the information and worse, negatively impact participant adherence and study dropout rates.

Community trust was another area that respondents noted as important, especially in the current state of science and public trust. Several respondents focused on making sure the study teams gained community trust from the outset through health education and health screening programs to not only build trust but also for communities and researchers to work towards the common goal of improving health for their communities and future generations. While this is not unique to DCTs, it is particularly important for DCTs, given the remote data collection nature of this approach and their community presence.

Moreover, an area noted by respondents where the community intersected with privacy and security of the data is in understanding communities’ values and priorities when it comes to remote digital technologies, their use and the data collected. Researchers should gather information early in the design of a clinical study about the communities’ stance in terms of privacy and technology use and get their buy-in and collaboratively develop research plans that align with the community’s goals and values. This also points out the importance (noted earlier in “Research Methods”) of focusing data collection on what is strictly needed for a specific study to maximize efficiency and minimize participant, researcher, and data management burden.

Workforce Development

Identifying and developing a clinical research workforce that can adapt to research needs, including DCTs, was an area where many respondents viewed as critical for the success of DCT studies and the DCT research enterprise *writ large*.

Engaging junior faculty and trainees in the design, implementation, and dissemination of DCT-derived studies is something respondents noted to be important. This training can be in the form of structured courses in DCTs such as use of technologies, novel data methods, QA/QC aspects and strategies to improve participation and adherence through mobile technologies. Additionally, training of experts in trial designs and utilization of digital health platforms in DCTs is an area respondents felt was not being emphasized at the institutional/local, regional, and national levels.

“Workforce Development programs to engage junior faculty and trainees in decentralized clinical trials and community engaged research training primarily through structured course work”

In contrast, other respondents brought up issues as to the “over training” of investigators and research staff involved in DCTs. Related to this, there is a sense that investigators and their staff are already required to take several types of training to fulfill federal, state, institutional and sponsor requirements. Overall, respondents suggested that tailored training to fulfill training and education needs in a culturally competent way and without adding additional burden to study sites and staff would be well received. This could be in the form of short, structured courses and real case studies of how to successfully deploy DCTs embedded or attached to existing training requirements.

Also, training ‘in-the-field’ human resources, such as community health workers and community leaders according to their expertise and role in the community, may help increase the trust, participation and adherence to studies while providing a decentralized approach tailored to local community needs. These ‘culturally attuned’ human resources can also provide critical assistance in navigating community needs throughout DCTs.

Technical training on troubleshooting aspects of DCTs and related technologies was also noted to be critical. For example, several respondents pointed to the need for culturally and linguistically sensitive communication via customer/participant support. This would require that technical assistance staff supporting DCTs are well-trained to respond to a wide variety of participant needs both from a technological and participant perspective. Additional resources utilizing Large Language Models and Artificial Intelligence to help troubleshoot more simple problems or system bugs could also provide real-time, efficient support and free up time for the human-in-the-loop technical support which can focus on larger and more complex issues.

Partnerships and Collaborations

Respondents discussed the importance of developing strategic partnerships and collaborations which are essential for the success of DCTs (Figure 5). These collaborations include the traditional partnerships between government agencies, industry, non-profit organizations and/or academic institutions. But there were also calls to establish more meaningful and efficient integration with less traditional players in clinical trials including community health hospitals, primary care and community providers, local and national pharmacy chains, rural health clinics, and urban Indian Health programs. This would allow for a more diverse and inclusive research participant pool.

Furthermore, developing partnerships with home health organizations and other national retail chains (e.g., pharmacies) was suggested to provide health and research-related care in the comfort of a participant's home and for relatively lower risk research activities, such as follow ups, vital signs assessments, anthropometric measurements, and delivery of certain drugs/biologics. This exemplifies bringing the study to the patient to improve participation, adherence, and satisfaction. Positive experiences on the participant side may incentivize future clinical trials participation in non-traditional research communities.

“Establishing meaningful and efficient integration of community health hospitals, pharmacies, community providers, assisted living facilities, rural health clinics, and Urban Indian Health Programs are located where the most diverse patient populations live and receive care”

Some respondents mentioned the need to communicate research goals and subsequent results with the community through trusted sources and across trusted mediums in a culturally relevant context. This would help demystify the concept of clinical trials, including DCTs, and at the same time align with community needs.

Cross-cutting areas where collaborations were noted to be critical include improving access to digital health technologies, training participants in DCTs, and establishing standardization/validation of digital health technologies for DCTs. Finally, developing best practices for the sharing of data and results to obtain maximum benefits from DCTs will require collaborations between government, academic institutions, industry, non-profit organizations, and others to ensure the right incentives are designed to foster open and transparent sharing and communication.

Study Participation and Adherence

Over 50% of respondents suggested that “Participation and Adherence” are critical to the success of DCTs (Appendix 4, Figure 7). In addition, the words related to participant engagement and participation were among the top 3 most frequently used terms throughout all responses analyzed (Figure 6). This highlights the central role that study participation and adherence play in the clinical trials' ecosystem, including DCTs.

In terms of participation and adherence, respondents indicated that more involvement from potential clinical trial participants and communities of interest would benefit from an integrated approach. These participants and communities should be included early in the study design process to provide critical answers to ongoing and pervasive health issues that they are facing, and to assess the needs.

“Use of patient-centered design principles can help ensure that DCTs tools and platforms are intuitive and easy to use for research participants”

There were also comments related to technical support for participants, families and caregivers participating in DCTs, including troubleshooting of digital technologies related issues and technical support options for questions or issues that can't be answered through standard chatbots and/or AI powered customer/participant services and/or LLMs based technologies. Other respondents suggested the use of RWD, for example from electronic health records, would help avoid overburdening participants and families for variables that are already collected in a standardized fashion. By saving time by collecting specific data that has already been collected elsewhere (with high quality, standardization, and reliability), participants could then focus on providing critical information in support of the safety and efficacy of a clinical investigation.

This category of study participation and adherence was prevalent in the Top 10 challenges, with 6 of the top challenges. Issues included: culturally competent training of site principal investigators and staff to respond to participant needs, overburdening of

research participants with technology and data collection needs, digital literacy, digital divide, identify authentication and access to accounts for participant reporting and, privacy and confidentiality issues from data collected through DCTs.

Privacy and Security

Several responses included issues and suggestions related to privacy and security. Respondents stated that privacy, security, and confidentiality are cornerstones in the development and implementation of digital health technologies in DCTs. How to deal with data from multi-site international studies and the differences in handling of the data and regulatory landscape is considered a challenge by respondents.

“Research participants rightly have concerns about privacy risks, and these should be addressed by providing information on how data are collected, stored, shared, and used; this should include realistic assurances about data security and privacy protections”

Providing secure access to digital platforms and transmission of the information across platforms is critical to maintain the required data origin/provenance and linkages. Allowing participants to indicate their willingness for data sharing in real-time via smart phone) would be ideal for those who have this technology. Further standardized, culturally sensitive and plain language consent documentation would be of high value to driving the DCT and digital health ecosystems into the future.

Respondents also noted there is the need to maintain a balance with what is important and feasible for the participant versus the objectives of study sponsor in terms of maintaining data consent or withdrawing from a study. Voluntary withdrawal of consent from DCTs should be made close-to-real-time as possible without overburdening participants and research staff with additional operational and logistic challenges.

Technology access and user/participant authentication issues were noted to add a level of complexity that may jeopardize participation, especially of populations with lower digital literacy (e.g., very young populations, the elderly or those who are cognitively impaired). In these cases, user-friendly applications for authentication using established technologies that can be assisted by family members or caregivers with different levels of technology savviness can be developed. In addition, secure transmission of adverse events and/or serious adverse events in real-time was viewed by respondents as a key area to improve participant safety and the direct reporting of safety events by participant.

Respondents suggested that to increase public trust in DCTs and related digital technologies, it is necessary to engage diverse communities with best practices and guidelines for privacy, data use and sharing, return of results to participants, and rights for voluntary withdraw of consent.

Data

Data was the most utilized word by respondents and was also a theme across most Top 10 challenges identified (Appendix 2). Many respondents commented on the importance of high quality, reliable, accurate and reproducible data for DCTs. Comments included a variety of data challenges and possible solutions for the success of DCTs. Some respondents agreed that data storage for the expected large volume of digital health technology obtained data can be a distinct challenge. This challenge, coupled with lack of data management and analytical resources at the local level, can impede the development of DCTs more broadly. Furthermore, data validation tools using automated algorithms or AI/ML to ensure data accuracy and reliability in data obtained from digital health technologies is still a work in progress. This remains a critical issue as the data ecosystem in DCTs is expected to grow over time, with data coming from more and more sources.

Collecting data throughout a study and identifying and tracking key metrics as well as community concerns was also viewed as critical to understand participant willingness to engage in DCTs. This was viewed as particularly relevant for underrepresented and underserved communities. Having this information could help in the development of strategies to increase participant satisfaction and/or willingness to participate in DCTs.

Another aspect brought up by respondents was the implementation of standardized quality control processes both centrally and locally to assist in the evaluation and analysis throughout the DCT. Standardized QA/QC processes could also help with identification

of data outliers early in the study period, hopefully with enough time to make the necessary adjustments to avoid issues of data validity and accuracy.

Examining data integrity and the validity of information from multiple data sources, whether collected from in-home, local community hospitals (e.g., EHRs) or research sites, is necessary to maintain confidence in data collected through DCTs. To this effect, there were suggestions to perform research that confirmed consistency across these potential sources in a rigorous manner and develop best practices as to how implement DCTs that maintained integrity across them.

Availability of data collected through DCTs and related technologies was also a topic mentioned several times, including how to provide tailored access to participants to their own data and returning final results as soon as feasible. Participants and communities should reap the benefits of involvement in DCTs not simply by way of the interventions and research questions being answered, but to how they can help improve public health as to the knowledge gained by participants.

“As DCTs seek to provide study participants access to their own data and offer return of results, it may be beneficial to provide options for participants on the types of information they want to receive and community needs”

Finally, overburdening participants and research staff with large amounts of requests, visits and data points could have a detrimental effect on the quality of the data provided, as well as in the willingness of participants to provide their data. A thoughtful selection of needed and required assessments for a DCT is necessary to avoid oversaturation of participants with unnecessary requests that are not directly linked to the primary or secondary aims of a DCT. In this sense, making a straight-forward DCT into a highly complex study would defeat the purpose having research conducted at the convenience of a remote location (e.g., participant’s home).

SUMMARY

While DCTs have been utilized for many years, there has been a substantial increase in leveraging these types of trials during the COVID-19 public health emergency. This offered confirmation that the capacity of the research enterprise to adapt to highly constrained situations (social distancing, stay at home, remote work, etc.) was robust. Further, its ability to perform and complete decentralized clinical trials had matured much over the past decade. Now that the COVID-19 public health emergency has expired, it remains critical to evaluate what worked well, what needs to improve and new areas where DCTs could provide an ideal option for participants, researchers, and funders.

This RFI generated information from the public about the need for these approaches to which several critical areas of need became apparent. For example, the centrality of study adherence and participant-centered design to DCTs; robust community outreach and stakeholder engagement, a DCT-centric set of research methods and digital health technologies, as well as important data privacy and security considerations. Of these, several overarching and cross-cutting themes should be noted.

One cross-cutting theme throughout was the need to develop well-designed and robust clinical studies to critically evaluate DCT methods with a focus on for whom they were most appropriate for; what interventions and / or use cases they are best suited for; and to develop the evidence base supporting their similarity, or enhancement, to participant or translational outcomes in traditional non-DCT approaches. In essence, this highlighted the need for robust translational science to understand and generate this evidence base as well as the need for specific resources to aid the transition to these novel clinical trial designs at academic medical research institutions. As practitioners of translational science across the United States, the Clinical and Translational Science Award (CTSA) consortium of Hubs were noted as where this could occur.

Another cross-cutting theme throughout the responses, was apparent across all respondents to the RFI was the importance of community-engaged research and validated, human-centered design of the enabling tools. Often leveraged for their long-term, durable relationships with local and regional communities as well as laboratories in the development of new and innovative technologies and human-centered approaches, it was noted that the CTSA could also play a pivotal role in the implementation of

these types of studies and to further identify which enabling technologies would be ideal and where their use is not warranted. A pragmatic approach of not trying to fix what's not broken but identifying where DCTs and related technologies fit would be optimal for a more targeted and efficient strategy moving forward. Many specific solutions were also notable and mentioned in the responses.

Identifying areas of critical need by way of solid translational science for DCTs and related technologies (e.g., digital health and remote monitoring tools) to be employed was commonly offered as the first step. *Fit-for-purpose* validation of digital health technologies, for specific diseases or medical conditions, was a notable, necessary solution to make sure the technologies are validated before their deployment in larger and pivotal DCTs and other clinical trials. This provides assurance that the information obtained from DCTs and related technologies are reliable, traceable, and accurate. *Real-time* collection and transmission of information are also key features of DCTs. This could potentially provide a closer follow-up of participants and their safety in a clinical trial by providing critical information for study investigators, site staff and funders to rapidly respond to safety issues. In addition, this real-time data could also improve the QA/QC process and allow centralized and/or local monitoring of data issues, and detection of outliers early in the research process to avoid unresolvable issues later in the trial or when the data is locked. The continued development of the supporting data integration and analysis platforms was viewed as a solution and, specifically, development of platforms that were more readily accessible by academic medical research institutions.

However, also recognized by the respondents was that as DCTs become more widely used, several challenges require close consideration. This included challenges with data sharing, privacy and security, consent for use, as well as data infrastructure issues that can impact access to technologies, support, and technological literacy. Mistrust in research by participants or what is frequently called "*digital divide*" also represents key challenges for DCTs. Although the solution offered for this challenge included enforcing potential participants and their communities to be integrally involved at all stages of DCT development and implementation ensuring that, what is developed, fits their cultural and socioeconomic needs.

Ultimately it was viewed that for the field of DCTs to be a successful option in clinical investigation, these challenges must be addressed in a systematic and efficient way, early in the planning stages of DCTs. Solving these challenges to advance clinical and translational science will require a concerted and collaborative effort, guided by overall and specific unmet needs. A systematic, translational science-focused approach based on unmet needs (scientific, medical, technological, participants, community) where DCTs can help overcome *known* and *unknown* roadblocks in the development of biomedical or behavioral solutions for patients, will guarantee that we focus on what is important in an efficient and coordinated manner – for the benefit of all.

LIMITATIONS

The range of respondents, background and type of organizations do provide an overall view of the current challenges and opportunities in the development of DCTs. However, RFI responses may not reflect the needs and challenges from a broader national and international point of view. Moreover, while we received responses from various CTSA hubs, the views expressed may not represent those of the entire CTSA consortium.

ADDITIONAL RESOURCES AND TOOLS

FDA Website DCTs	https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials
FDA Guidance DCTs	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices
Duke-Margolis Center for Health Policy Mobilizing mHealth Innovation for Real-World Evidence Generation	https://healthpolicy.duke.edu/sites/default/files/2020-03/duke-margolis_mhealth_action_plan.pdf
DCT NCATS/CTSA Program RFI	https://grants.nih.gov/grants/guide/notice-files/NOT-TR-23-006.html
CTSA program	https://ncats.nih.gov/research/research-activities/ctsa

METHODS

The RFI was publicly accessible via grants.gov and responses were received until May 12, 2023. RFI responses were submitted by academia, industry representatives, not-for-profit organizations, individuals/the general public and others. Responses were submitted to an NCATS-hosted web-interface or via pdf submitted directly to an NCATS-internal email address. The web-interface provided a free-text input box for each Category in the RFI. Broad categories are included in Figure 3.

Web responses were collected via an internal database and exported into Microsoft Excel. PDF responses were converted to .txt format using the Pacific Northwest National Laboratory visual document analysis software (<https://in-spire.pnnl.gov/>). The converted web and PDF response data were subsequently processed and analyzed with custom code written with the Python programming language version 3.9.12 on a Dell Latitude 7420 running Jupyter Notebook version 6.4.8. Input text data underwent standard text cleaning using the Python wordcloud library including application of standard English language and custom stopwords and stemming using the Python Natural Language Toolkit (nltk) library.

Separately, web responses were individually extracted from the master excel spreadsheet and converted to Microsoft Word using the Python docx library. PDF highlights were imported into Python using the fitz library, converted to Word, and manually categorized into the 9 RFI areas of interest. The output word documents were randomly assigned to each of the manuscript authors. The documents were manually reviewed by the authors and salient text were highlighted to enable further processing. In this way, company advertisements or otherwise irrelevant text were filtered out.

Additionally, word term weighted frequencies were also calculated from RFI responses. For this, we utilized the python word cloud library to generate the most frequent words for each area of interest in the RFI. The resulting term frequencies were summed up and ranked by overall use in the responses. Synonymous terms were grouped into closely related uber term categories. A summary of the top 20 term groups were then analyzed according to their weighted frequency by area of interest and the total weighted frequency for all terms within all areas of interest (Figure 6).

Analysis took place from August to December 2023. Analysis included OPA RFI tool, ML data extraction, manual curation, etc. Report preparation started in January 2024 and ended in March 2024.

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APPENDIX 1. Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials Request For Information Areas for Comment

Interest Areas/Themes	Specific questions and areas to address
Methods: <i>Application of research methods in decentralized clinical trials DCTs</i>	<ul style="list-style-type: none"> a. Demonstrating how DCTs advance and accelerate the implementation of clinical trials b. Developing novel clinical trial research methods for DCTs c. Improving translational processes and workflows for study participants in DCTs d. Key factors to consider when designing and deploying a DCT
Resources: <i>Resources Infrastructure and Enabling Technologies</i>	<ul style="list-style-type: none"> a. Identifying available resources tools or technologies used or useful for DCTs and technological needs for the future as well as common operational challenges in deploying and running DCTs b. Measuring the financial burden versus benefit of DCTs and considering the areas of clinical research where they would have the most impact c. Identifying resources to collect and validate digital health technology-derived data for its use in DCTs and subsequent linking to other sources e.g. reliable public health data sources d. Identifying resources tools or technologies which may be utilized to collect and analyze large data sets during a DCT as well as post-approval indications utilizing RWE derived from RWD post-approval for RWD and RWE
CE: <i>Community Engagement</i>	<ul style="list-style-type: none"> a. Identifying the needs of participants particularly those whom traditionally experienced health disparities or in an underserved population to participate in DCTs b. Establishing support for the identified needs of participants to be engaged in DCTs c. Facilitating authentic and meaningful community driven engagement e.g. embedding clinical trials into community health care settings
WFD: <i>Workforce Development</i>	<ul style="list-style-type: none"> a. Identifying and developing a clinical research workforce with knowledge skills and abilities to administer a DCT b. Understanding the social and/or cultural nuances of communities c. Establishing knowledge and procedures to codesign studies with communities
Partners: <i>Partnerships and/or Collaborations</i>	<ul style="list-style-type: none"> a. Identifying partnerships and/or collaborations essential for DCTs to be successful inclusive of government agencies industry nonprofit organizations academia, etc. b. Developing partnerships and/or collaborations to enhance engagement with diverse or and/or underserved participants for DCTs c. Establishing meaningful and efficient integration of community health hospitals pharmacies and community providers for DCTs d. Identifying partnerships and/or collaborations needed for the dissemination and sustainability of identified technologies platforms
Participation: <i>Study Participation and Adherence</i>	<ul style="list-style-type: none"> a. Developing the methods tools resources and platforms to efficiently safely and securely screen, consent, enroll, and follow up with DCT research participants b. Identifying tools and resources to decrease the burden on the participants of clinical studies c. Identifying tools and resources to match the preferred method for targeted populations and to provide support throughout the process e.g. concierge help desk services d. Employing strategies to provide and tailor ongoing research support and technologies to stimulate participation by diverse and/or underserved populations in research
Data: <i>Data integration quality accessibility and reproducibility</i>	<ul style="list-style-type: none"> a. Maintaining data consistency and quality relative to digital health technologies and/or Bring-Your-Own-Device (BYOD) approaches in the context of a DCT b. Monitoring and acting on DCT data quality in real-time c. Providing study participants access to their own data and study information post-hoc or in real-time and granting access to de-identified data for the research community d. Analyzing and reporting disparate data generated from both the centralized and DCT results
Privacy: <i>Privacy and Regulatory Considerations</i>	<ul style="list-style-type: none"> a. Designing conducting and documenting DCTs to ensure compliance with regulatory bodies b. Fostering outreach methods for participant populations to be assured of their privacy c. Ensuring engagement by study participants to rigorously adhere to the protocols' security/safety measures and regulatory requirements
<i>Additional areas related to DCTs</i>	Other areas of interest to the DCT community

RWD: Real-world data; RWE: Real-world evidence; DCT: Decentralized Clinical Trials

APPENDIX 2. Top 10 Challenges from RFI responses

Challenges*	Methods	Resources	CE	WFD	Partners	Participation	Data	Privacy
Complex integration of data from multiple sources								
Culturally competent training for researchers and staff in DCTs								
Overburdening of participants, researchers and staff with numerous tasks, data collection, review, etc.								
Participant identity authentication issues								
Privacy and confidentiality issues of data collected through DHTs								
Digital divide and infrastructure issues								
Lack of standardization and validation for measures using DHTs in DCTs								
Digital literacy and lack of support for DCT/DHT navigation and troubleshooting								
Quality control and assurance of data from DCTs and technologies used								
Transparency and data sharing from proprietary platforms								

*In order of overall themes covered from most (top) to less (bottom) themes.

APPENDIX 3. Word cloud closely related term groupings

participant	'participant' 'research participant' 'participate' 'research participant' 'patient recruitment' 'participation' 'patient' 'patient engagement' 'participant engagement' 'participant advocacy'
resources/infrastructure	'resources' 'resource' 'support' 'infrastructure'
study site	'study site' 'medical center' 'site' 'staff'
data	'data' 'data collection' 'data quality'
community	'community' 'communities' 'community members' 'community engagement' 'community based' 'community health'
digital health	'digital health' 'technologies' 'technology' 'platform' 'digital' 'tools' 'digital health technology' 'technology'
DEIA	'DEIA' 'diversity' 'diverse' 'equity' 'inclusion' 'access' 'inclusive'
collaboration	'collaboration' 'partnership' 'team'

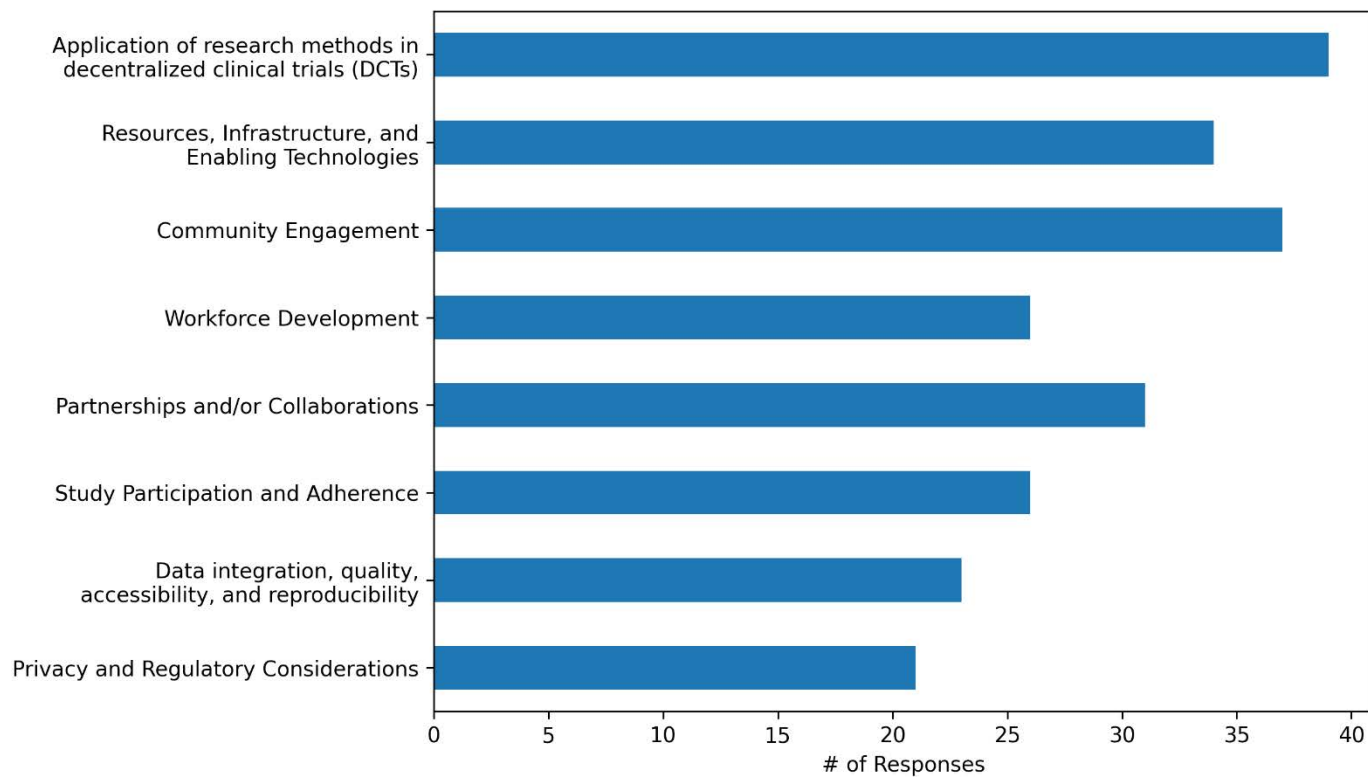
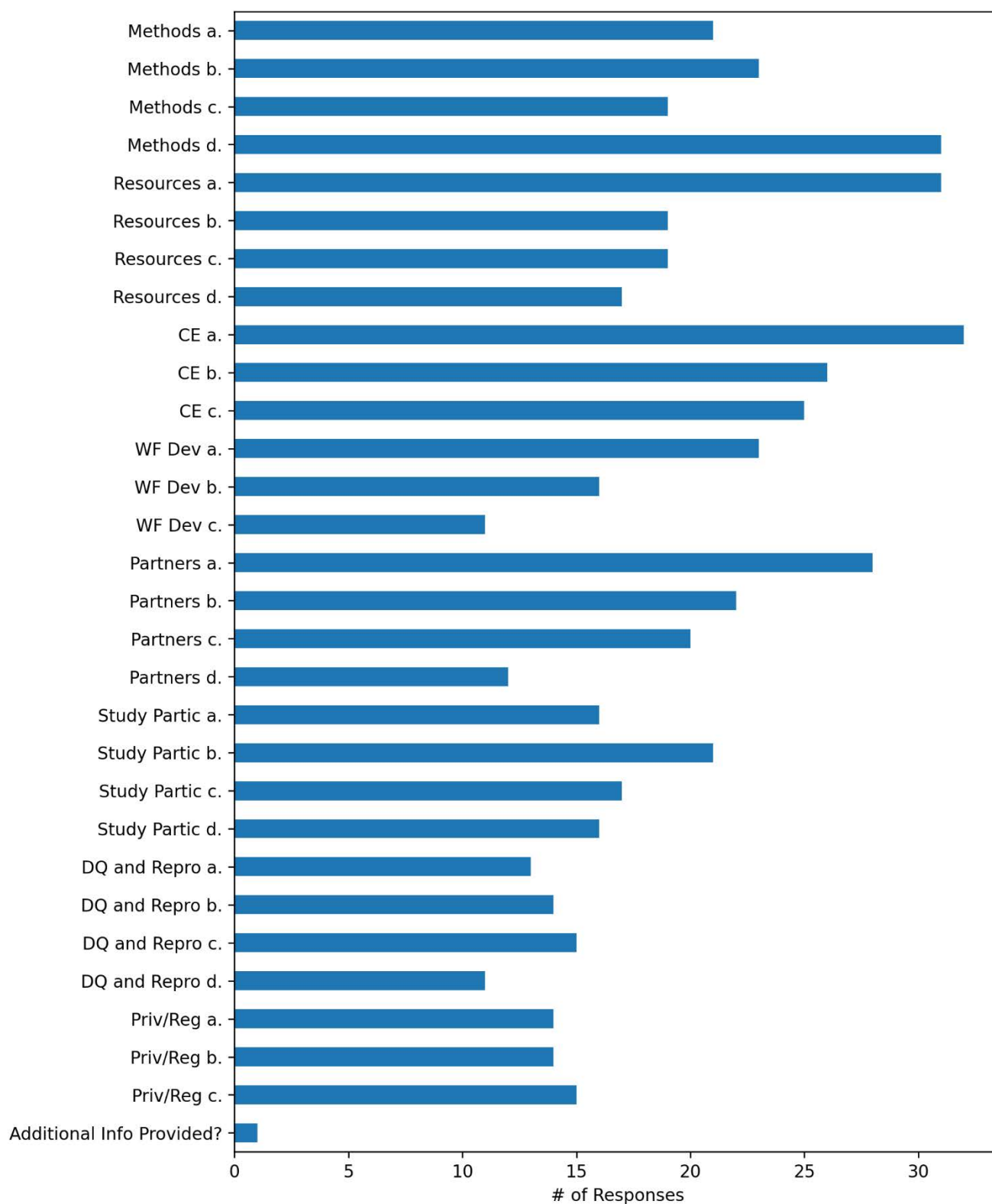
APPENDIX 4. Additional Figures**Figure 7. Areas of interest/themes and number of responses**

Figure 8. Number of Responses by Topic Areas of Interest/Themes RFI questions*

*Topic questions/specific areas by theme were included in the RFI (<https://grants.nih.gov/grants/guide/notice-files/NOT-TR-23-006.html>) and can also be found on Appendix 1 under each interest area/theme.