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Original Research

Alzheimer's Disease Clinical Trial Research Adaptation Following COVID-19 Pandemic Onset: National Sample of Alzheimer's Clinical Trial Consortium Sites

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Abstract

BACKGROUND: The COVID-19 pandemic created challenges in clinical research operations that required immediate and lasting changes.

OJBECTIVES: The purpose of this study was to explore adaptations to clinical trial research due to COVID-19 and develop a theoretical framework of emergent strategies related to pandemic mitigation in a national network of Alzheimer's disease clinical trial sites.

DESIGN: This qualitative study used a grounded theory approach including semi-structured interviews, constant comparative methods, and multi-level, iterative coding.

PARTICIPANTS: Twenty-six member sites of the Alzheimer's Clinical Trial Consortium participated with a total of 49 participants.

RESULTS: Findings demonstrate processes of adaptation following COVID-19 onset including establishing safety as priority, focus on scientific preservation, accommodations (creating policies, leadership mindset, maintaining operations, and determining research procedures), and evaluation of changes throughout the course of the pandemic. Communication and maintaining integrity were vital throughout these processes.

CONCLUSION: Processes of accommodation among clinical research sites during the pandemic provide critical insights and direction for future clinical trials development and emergent methods in Alzheimer's disease and other therapeutic areas.

Key words: Clinical trials, Alzheimer's disease, research management, COVID-19.

Introduction

The SARS-CoV-2 (COVID-19) pandemic has required numerous changes in clinical research (1). In particular, clinical research with older adults raised serious concern due to the increased susceptibility and serious consequences related to COVID-19 for this age group (2, 3). Underlying health conditions, including Alzheimer's disease (AD) and Alzheimer's disease related dementias (ADRD), added additional concerns for morbidity and mortality (4, 5). Thus, clinical trial research for ADRD was markedly impeded during 2020 and 2021 (6). Lasting implications of COVID-19 for clinical trials in ADRD research have yet to be fully identified (7).

The Alzheimer's Clinical Trial Consortium (ACTC), funded by the National Institute on Aging, is the leading academic organization in the United States supporting the design and conduct of clinical trials across the AD continuum (8, 9). The ACTC sponsors innovative clinical trials to support pharmacological and non-pharmacological clinical interventions for prevention and treatment of AD and ADRD conditions. The ACTC partners with 35 leading academic institutions (ACTC sites) throughout the United States to implement this research. ACTC sites adapted to COVID-19 calls for safety and social distancing according to their state and university requirements; adaptation to COVID-19 varied by site and by region throughout the country, as COVID-19 infection rates advanced or receded throughout 2020-2022. The heterogeneity of these adaptations by study site and by region may have long-term implications for ADRD clinical trial research design and findings.

Identification of the adaptation processes can offer a historical perspective on the effects of COVID-19 on ADRD clinical trial research. Additionally, the processes used can offer a theoretical framework to guide preparation and planning for future pandemic and emergent methods in clinical trial research. The purpose of this study was to develop a framework of emergent strategies related to pandemic mitigation in a national sample of Alzheimer's disease clinical trial sites.

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Methods

The Inclusion, Diversity, and Education in Alzheimer's disease Clinical Trials (IDEA-CT) Committee of the ACTC supports networking and mentoring among senior trialists and early and middle career colleagues within the network. An event hosted by the committee at every ACTC steering committee (held three times each year) permits networking among fellows and senior clinical trialists across ACTC sites, ACTC coordinating centers, additional collaborators, and funders. A networking event held in 2021 initiated conversation among attendees regarding accommodations related to COVID-19. Small groups discussed similarities and variation in site accommodations. Summaries of these conversations prompted the current study research question and interview guide to identify the process of accommodation employed by ACTC research sites in response to the COVID-19 pandemic.

This study utilized a qualitative, grounded theory approach to identify COVID-19 adaptation processes throughout the country. Grounded theory, originally defined by Strauss and Glasser, guides data collection methods and production of such systematic inquiry (10). The approach has evolved to become prevalent in assessing phenomena within a variety of social and medical settings. Methods of this study were designed following Charmaz' explanation; methods "begin with inductive data, invokes initiative strategies of going back and forth between data and analysis, uses comparative methods, and keeps [the researcher] involved with data and emerging analysis" (p.1) (11). This approach yields a framework illustrating the process behind the researched phenomena (12). All methods were approved through the University of Kentucky Institutional Review Board.

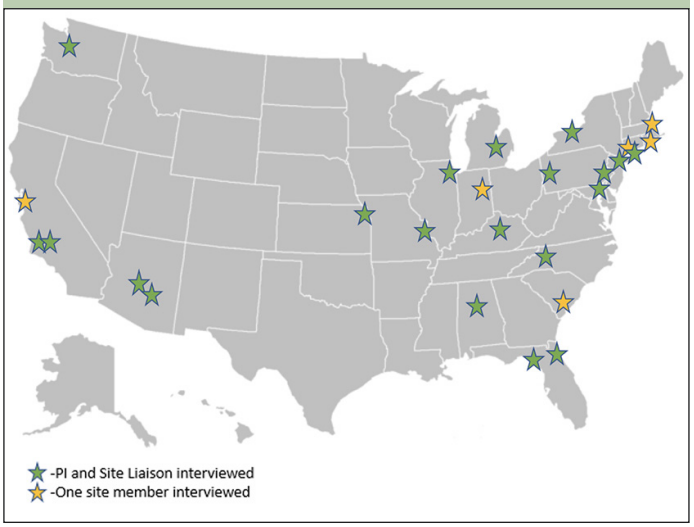
Participants

The ACTC network includes an infrastructure of experienced study sites which include senior researchers, study coordinators, and site liaisons. Site representatives maintain regular communication with ACTC via email and regular meetings. In addition, they agree to represent ACTC's interests and program development needs. All 35 ACTC sites were invited for participation. Consistent with grounded-theory approaches, purposive selective sampling was used to ensure the necessary diversity of program perspectives in the data. Emailed invitations were sent through tiered progression beginning with site Principal Investigators (PI) and associate PI (API), followed by study site liaisons. Lastly, purposeful sampling was used to include additional study site staff. Individuals included a range in ages and career stages from junior to more senior members with ACTC affiliation.

The intention was to collect data with high contrast in perspectives among senior research leadership as well as front-facing staff who managed and/or interacted with clinical trial participants. Following initial interviews, additional purposive sampling of ACTC sites that had not yet contributed served as a means for negative case exploration and validation of the developed codes and framework.

Twenty-six sites participated in this study with national representation of roughly 75% participation of eligible sites (Figure 1).

Figure 1. ACTC Sites Participation Map



A total of 37 interviews were completed (total 1103 minutes; average 42 minutes per interview). Forty-nine participants were included (see Table 1). PIs and APIs had an average length with ACTC affiliation of 7.6 years) and site liaisons and study staff represented an average length with ACTC affiliation of 7.3 years.

Table 1. Participants' gender frequency by ACTC role

ACTC Role	# Female	# Male
Principal Investigator	7	13
Associate Principal Investigator	1	3
Site Liaison	19	2
Study Staff	4	0

Data Collection and Analysis

Data collection included three phases of semi-structured interviews. Phase 1 targeted senior research leaders (PIs and APIs). Phase 2 invited study site liaisons and site staff. Interviews were completed separately when time allowed, however, some schedules required joint interviewing with the senior faculty and staff person. Phase 3 of interviewing was used for negative case exploration and member checking of the developed codes and theoretical framework. All interviews were conducted via Zoom videoconferencing with the first author as interviewer. Interviews were recorded

and transcribed verbatim using Zoom software, and subsequently assessed for accuracy by the first author. The interviewer also collected fieldnotes during and after interviews.

Using the constant comparative method of grounded theory, analyses began following the first interview. This approach allowed for concurrent data collection and analytic review of incoming data. Data analysis was initiated with line-by-line coding of verbatim transcripts to identify patterns and produce open codes. As patterns in the qualitative data emerged, they were refined by comparing new incoming data from subsequent interviews with prior identified patterns. Emergent concepts and patterns were individually described in memos, which were continually updated and refined to reflect incoming data. The iterative development of emerging patterns used three sequential levels of coding: open, axial, and thematic. Open codes generally included words, phrases, or quotes in the data which were evident, recurring, and representative of an emerging pattern. A total of 72 open codes were used. As open codes became saturated, or well-described, axial coding discovered nine broader, conceptual categories among the data, often supported by clusters of open codes. Finally, thematic coding used a comparative analytic approach to produce the grounded theory, or framework, descriptive of the primary dynamics of clinical trial adaptations to COVID-19 across the ACTC trial sites within three themes.

An audit trail was maintained within university-based protected servers that included records of data management, collection of fieldnotes during interviews, memos written for each code, bi-monthly meetings with the data analysis team, and use of HYPEResearch (13) qualitative analysis software.

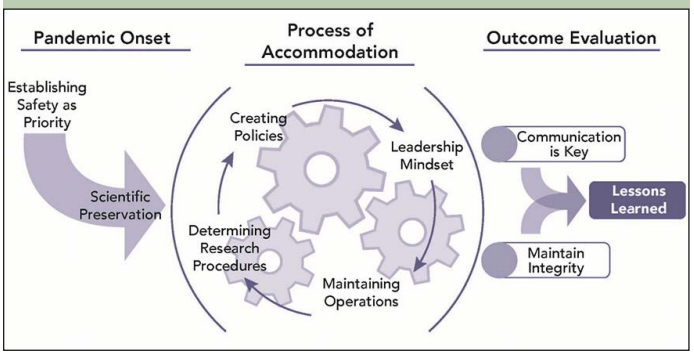
Data Credibility

The credibility of results was upheld via several procedures. Data was collected until saturation for open and axial codes. Saturation is a process whereby incoming data no longer produce new patterns or categories beyond the experiences already captured by prior established codes (14). The interviewer supplemented interview transcripts with field notes that recorded immediate impressions of the interview, as well as any recommendations to refine data collection methods. Bi-monthly communication with the data analysis team (Rhodus and Raman) were held throughout data collection/analysis to ensure consensus in code development and progression of theory emergence. If members disagreed, discussion was held until members were in consensus. Expert consultations (Rentz, Grill, Petersen), member checking, and negative case exploration were also completed during the final phases of analysis to confirm the accuracy of representation in the produced descriptive theory.

Results

Three theoretical themes describe the processes to sustain research in the ACTC sites that were related to onset of COVID-19, to accommodations to the pandemic, and to evaluation of changes throughout the course of the pandemic (Figure 2).

Figure 2. ACTC Sites' Process for Accommodations to Sustain Research During COVID-19 Pandemic



Pandemic Onset

Establishing Safety as Priority

Our county had extremely high rates of Covid infection… it wasn't safe for my staff to be engaged with [patients] when they might unknowingly be bringing a fatal disease to them and their families, so I was pretty aggressive on shutting down. (Site PI, Southeast Region, August 2021)

Onset of the COVID-19 pandemic was associated with substantial unknowns. ACTC sites across the nation recognized the safety of elderly clinical trial participants, as well as faculty and staff, as the highest priority. Risks associated with the spread of COVID-19 among elderly adults who were likely to have underlying conditions halted clinical operations for most sites. Representatives reported that shutdowns ranged from 0-8 months with an average of 3 months. Some site PIs made the decision for initial shutdown, while other sites were directed from institutional or state mandates. Upon restart of operations, implementation of social distancing, use of personal protective equipment (PPE; e.g. gloves, masks, face shields, etc.), and screening for symptoms were implemented at all sites. In the second year of the pandemic, development of vaccinations became critical for making decisions to reopen sites, however continuation of safety measures such as PPE and screening were implemented.

Scientific Preservation

All ACTC sites acknowledged the need to preserve scientific knowledge and advancement from the clinical

trials. However, upholding safety measures inadvertently impacted data collection at most sites. Alterations to data collection methods included remote assessments and data collection over the phone. Corrective analytic approaches were described as potential means to preserve data despite missing data points and altered collection methods. Researchers described a need to protect the investment and potential advances afforded by trial continuation, such as older adults' improvement from possible lifesaving medications, trialists' career-long dedication toward scientific development of interventions, and fiducial protection of sponsors' resources.

Process of Accommodation

Leadership Mindset

If [staff] could do their work remotely, that was entirely fine…so we left it to [the study] coordinators' discretion. For the most part, we kept that flexibility, and that definitely made folks more comfortable. (Site Liaison, Midwest Region, July 2021)

The mindset of leadership drove accommodations and adaptation. Site staff described trust with leadership while developing new safeguards and accommodations with trials. Willingness to adapt and flexibility were described as key elements among sites as they persevered during infectivity peaks of the pandemic. Incorporation of staff and participants' concerns and fears related to in-person visits were acknowledged as a priority during early phases of the pandemic, as well as the emotional impact of social isolation. Acknowledgement from leadership regarding staffs' lifestyle differences, such as the need to use public transportation, recovery if afflicted with COVID-19, lack of childcare, and acceptance of work-from-home provided flexibility for staffs' continued work engagement while managing personal life needs.

Maintaining Operations

Realizing every institution is different, you know, what you do there is very different than the way we operate here. (Site PI, Midwest Region, August 2021)

Site leadership verbalized an urge to understand how other sites in the nation were adjusting but recognized the limitations in that approach because community infection rates of COVID-19 varied throughout the country. Logistical and practical components of running clinical research, yet under dire circumstances for safety were recognized as varying among sites. At what point were participants contacted, by who, and how often were operational questions asked throughout the nation. Management and scheduling of staff onsite or remote work was a novel challenge without clear policies. Basic office operations including management of deliveries and medication shipment, copying, and storing protected documents, signatures for clinical documents, and use of remote work equipment (e.g., laptops, phones, web cameras, etc.) were areas of accommodation related to the pandemic. Financial support and reserve were crucial for maintaining operations during closures and limited clinical visits. Several sites reported concerns related to losing highly trained staff, while others were furloughed through closures. Sites with sufficient financial reserves did not report staggering challenges as did smaller, less well-funded institutions.

Determining Research Procedures

Let's look at our studies and tier them as to what is the most important thing that we can only do in person and can't do via the phone. Start with those drug studies, the injections or infusions, and then even for those studies…what can we do to keep the [patients] safe. (Site Liaison, Midwest Region, August 2021)

Onsite operations were paused for three months as averaged among reports from participating sites across the nation (reported pauses ranged from 0-8 months). Protocol modifications and/or halting enrollment were required at nearly every site. Recruitment and new participant enrollment experienced the most dramatic pause followed by observational studies. Interventional studies which provided potential life-saving benefits were prioritize for research resumption. Long pauses in scheduling participant visits, missed data points in allowable time frame, and the addition of more creative methods, such as remote testing or limiting time allowed onsite per participant and/or staff altered research procedures. Site leadership were tasked with determining procedures that were most suitable given the particular situation within their institution and state.

Creating Policies

To maintain cohesion within departments, leadership created policies which were often directed by state guidelines and institutional direction. However, the rapid changes related to COVID-19 safety measures required ongoing decisions among the site leadership teams. Sites described the influence of external regulations, such as institutional legal guidance on the methods to contact participants while working remotely, as well as direction from sponsors, such as methods for signing documents. Site leaders regularly categorized priorities so that all needs were met.

Outcome Evaluation

"Communication is key"

I formed a committee for disseminating information…a top-down approach [for] blasting…I would share with my research managers who would share with the coordinators while trying to share mass emails to the faculty about changes that were occurring. (Site API, Southwest Region, August 2021)

Rapid and continual changes pushed site leaders to analyze their accommodation strategies and regularly adjust. The process to determine an appropriate accommodation, subsequently analyze the success of the accommodation, and then adjust policy required continual communication. Each site described successes unique to their specific situation, but four elements were common among all sites. Communication was vital for the success of accommodation during the pandemic. Constant communication was required at multiple levels: state to institution, institution to department and/or site PIs, PIs to study coordinating teams, and study coordinators to community-based participants. The ability for teams to transition to remote work was critical for continued operations at the majority of sites. This required access to mobile technologies, such as laptops, web cameras, internet, printing, etc. ACTC sites with financial reserves described the funds as a buffer that allowed them to withstand the hardships related to shut down, remote work, and added costs related to safety measures.

"Maintain integrity"

It's been a challenging year from a site perspective. It required a tremendous amount of capital resources, finances, to continue to pay staff…we've exhausted our backup resources at this point, and that is a challenge. (Site PI, Southeast Region, July 2021)

All sites expressed challenges related to maintaining integrity of, not only the study, but logistics of site operation and participant engagement. Quite difficult to manage was the rapidly changing, and at times, contradicting recommendations for safety and operations. Limited access to supplies, such as personal protective equipment was felt nationwide, but also disruptions in the supply chain for research-related supplies. Disruptions to the workforce were also noted as challenging. Costs associated with stopping research have yet to be fully identified but presented unique challenges in how sites worked to preserve scientific progression.

Lessons Learned

Four additional themes emerged as 'lessons learned' from this experience. 1)*"Set your top priorities and then create a structure to move forward"* was echoed throughout the nation as a process for managing crises. Site leaders acknowledged the need to plan ahead for crises by establishing protocols for emergencies, as well as maintain financial reserves. 2) Implementation of hybrid work altered staffing structure but has benefits. Hybrid work enhanced communication, allowed for sustained productivity, created additional space, and strengthened teamwork. 3) The pandemic also advanced technology use to *"get the same data with less in person time"* whereby expanding opportunity for hybrid clinical trials. Continued development of statistical considerations, validation of measures, feasibility of remote cognitive testing, and confirmed e-consenting methods are underway. 4) Benefits of hybrid methods include outreach to broader geographical areas, less burden to participants, time efficiency, and more inclusivity when technology was provided to participants.

Discussion

This qualitative study offers a framework describing adaption processes of clinical research sites in the face of the COVID-19 pandemic throughout the United States. While all clinical trialists felt uncertainty during early phases of the pandemic, a process for accommodating to COVID-19 among the sites emerged from this experience. Initial onset of the pandemic nearly halted clinical research activities for the most vulnerable, older adults with underlying conditions. Trialists and their staff quickly adjusted by establishing safety as a priority and preserving scientific progression. These elements guided the process of accommodation including leadership mindset, maintaining operations, determining research procedures, and creating policies. This process became cyclical with waxing and waning of COVID-19 infection rates and has been echoed in other disciplines conducting clinical research during this time (15, 16). Finally, outcome evaluation allowed for recognition of successes such as communication, challenges related to maintaining the integrity of study data and procedures, and lessons learned which can be incorporated into future trial design. The utility of this framework may offer guidance when transferred to future clinical research planning and preparation should potential pandemics or other emergent situations arise.

ACTC member sites accommodated to COVID-19 calls for safety and social distancing according to state and university requirements. Upholding safety as a priority while maintaining scientific progression were universally expressed in clinical research during the pandemic (17). A mindset for safety and protection of vulnerable participants, as well as staff, was often reinforced by local and institutional guidelines. However, the rapid change to operations required creative exploration to maintain scientific progression of the decades-long investments toward pharmaceutical development for cures and

treatment; a phenomenon experienced across the clinical trial industry (11, 18).

The process of accommodation initially appeared linear, but as additional variants caused community infectivity surges, a cyclic pattern of accommodations was observed. For example, methods for accommodation that were used at the initial onset of COVID-19 were needed with each wave of heightened community infection rates. Factors within the cycle of accommodation allowed for ongoing success. Leadership from site PIs and APIs provided structure for operational accommodations. While determination of procedures and policies allowed for continued research success at individual sites, Hedlin and colleagues identified utility and benefits of a pragmatic, platform approach toward managing multiple studies during the pandemic (19). COVID-19 has created calls for structure and master planning among the clinical trial community to increase data integrity (20). Heightened communication was critical as sites managed ongoing changes and challenges. Communication was required at multiple levels within teams, institutions, sponsors, and other entities, to the point that one site reported hiring staff solely to manage email-based communications. The importance of retaining well-trained clinical research staff was expressed as paramount for success during rapid changes and altered participant-engagement approaches (21). Ongoing financial support provided by ACTC throughout the pandemic disruptions eased sites' ability to retain personnel despite fluctuations in trial activity. Participants of this study displayed good representation of women in PI and API leadership positions. Additionally, implementation of a hybrid approach (combination of onsite and remote work/data collection) increased inclusion and satisfaction for participants and staff. Bringing access to clinical research into community-based settings, such as through telehealth, remote medication administration, and remote monitoring were recognized as key strategies that may continue into future trial designs as they orient toward patient-centered care (17).

Overall, the lessons learned in AD and ADRD clinical trials during the COVID-19 pandemic create opportunity to enhance clinical trial design (see Table 2). 1) Identification of top priorities for the clinical trial and methods to manage crises during the pandemic provide direction for accommodation. 2) Promotion of flexible work options for highly skilled and well-trained trial staff allow for continued productivity. 3) Use of rigorous and validated methods for technology use that allow remote data collection provide avenues for continued trial activities. 4) Lastly, the benefits of hybrid methods allowing in-person and remote data collection appear to be beneficial for participant inclusivity and lessening participant burden. Key stakeholders, such as funding sources, principal investigators, statisticians, support staff, and others can develop mitigation plans that incorporate these solutions in similar-type pandemics. Further, these solutions are likely also applicable to other AD and ADRD clinical research, beyond clinical trials, such as observational and caregiver-based studies. Implications of the lessons learned as presented here offer strategic considerations for clinical trials planning that can be tested in future situations and studies.

Table 2. Future Recommendations based on Lessons Learned

1) Identification of top priorities to manage crises using a structured approach.
2) Allow flexibility with hybrid work options to sustain productivity.
3) Promote development and rigor of technology use for remote data collection.
4) Hybrid methods appear to provide benefits for participant inclusion and lessened participant burden.

Currently, two years following initial onset of COVID-19, many sites continue to grapple with issues identified in this study and are managing their long-term effects. Exploring the experiences of leaders in Alzheimer's disease clinical trials has offered a historical perspective that can be used in future investigation of the lasting consequences in clinical trials. Additionally, the processes used to accommodate for COVID-19 created a theoretical framework that can be applied and transferred among clinical research to guide design to lower disruption if future endemics should occur. The accommodations in clinical trials identified here will likely have lasting implications for trial design and implementation.

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Ethical standards: All procedures of this study were approved through the University of Kentucky Institutional Review Board. Participants provided verbal informed consent prior to all data collection as written consent was exempt from this study.

Conflict of interest: Authors do not report conflict of interest specific to this study.

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