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An approach to virtual clinical trial site visits: Lessons from the MeTeOR trial

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ABSTRACT

Objective: To provide a framework for conducting clinical trial site visits virtually over videoconference, and to report on our experience doing so during the twelve-year follow-up of the Meniscal Tear in Osteoarthritis Research (MeTeOR) trial.
Design: Using published FDA guidance and prior literature, we created a structure for virtual site visits that prioritized monitoring for protocol compliance, safety, and data integrity. We conducted site visits in three stages: preparation for the visit, the virtual meeting itself, and follow-up. The preparation phase involved a review of relevant site-specific documents and a written report on the findings prior to the visit. The virtual visit itself was focused on any questions the site staff had about the pre-visit report, observing a mock study visit, touring physical spaces, and understanding the site staff's work environment. In the follow-up phase, we wrote a post-visit report summarizing the discussion during the visit and feedback given by the coordinating site.
Results: We found that the virtual site visits conducted as part of the MeTeOR trial follow-up ran smoothly. Although we could not directly compare in-person and virtual site visits, site staff unanimously appreciated the efficiency and effectiveness of the virtual site visits. We noted that displaying physical workspaces over video-conferencing was difficult, and a notable drawback to this method.
Conclusions: To our knowledge, this is the first published framework for conducting virtual clinical trial site visits. Conducting these visits virtually confer several advantages in terms of time, money, and efficiency.

1. Introduction

Multicenter clinical trials require regular monitoring to ensure the safety of study participants and the standardized collection of high quality data [1,2]. The United States Food and Drug Administration (FDA) recommends that coordinating centers of multicenter studies conduct in-person site visits at the clinical sites with the following goals: ensure that study participants' rights and well-being are protected, observe trial operations, review the quality of data entry for accuracy and completeness in source records and case report forms, provide assurance that documentation exists, provide necessary corrections to errors observed during the visit, ensure trial conduct is in accordance with the latest protocol, and familiarize the coordinating center with all site study staff [3,4]. The SARS-CoV-2 (COVID-19) pandemic imposed strict limitations to travel and face-to-face interactions, requiring innovation in the conceptualization and implementation of site visit activities.

The Meniscal Tear in Osteoarthritis Research (MeTeOR) study, a multicenter randomized controlled trial (NCT: 00597,012), enrolled study participants from 2008 to 2011 to compare outcomes of arthroscopic partial meniscectomy and nonoperative physical therapy as treatment for meniscal tear and knee osteoarthritis [5]. During the initial funding period, site visits were conducted in-person at each MeTeOR site by the coordinating center. In 2019, the study team at Brigham and Women's Hospital (BWH) secured a grant for a twelve-year follow-up of the original MeTeOR cohort at six sites: BWH (Boston, MA), Cleveland Clinic (Cleveland, OH), Hospital for Special Surgery (New York, NY),

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Mayo Clinic (Rochester, MN), Vanderbilt University (Nashville, TN), and Washington University in St. Louis (St. Louis, MO) [6]. This follow-up required that participants be re-contacted and re-consented. Investigators at the MeTeOR coordinating center, BWH, recognized the need for site visits to ensure that the protocol was performed in a standardized fashion and to monitor data quality. These visits were originally scheduled to occur in the winter of 2021 and spring of 2022; however, the COVID-19 pandemic precluded travel and face-to-face interactions with research personnel at the clinical sites. As a solution to this problem, we developed protocols and conducted virtual site visits over videoconference in lieu of in-person visits.

Virtual site visits offer potential benefits over in-person ones. To list a few, travel from the coordinating center to clinical sites is expensive and time-consuming, and air travel contributes to carbon dioxide emissions [7–9]. To the best of our knowledge, there is little published literature addressing how to conduct a virtual site visit as a part of a multicenter clinical trial. In this report, we describe the steps we took to develop standard virtual site visits and share the benefits and drawbacks we have observed from conducting virtual visits.

2. Approach

The infeasibility of performing in-person site visits during the SARS-CoV-2 pandemic necessitated a pivot to virtual site visit platform for the MeTeOR trial. While not all elements of an in-person site visit could be transitioned naturally to a virtual format, we were able to replicate the most important aspects of the site visit virtually (protocol compliance, safety monitoring, and data quality control; Table 1). We chose to perform the site visits once each site had completed about 10% of their total MeTeOR subject study visits. This timing ensured that clinical site staff had some experience performing visits and that systematic errors were caught early, before widely affecting study data.

Each site visit consisted of three phases: Preparation, Virtual Visit, and Follow-Up. We adapted this framework from previously published guidance [2–4,10]. In the paragraphs that follow, we lay out the overall goals of each phase and report our experience conducting these elements of the virtual site visit.

2.1. Preparation (items A-C, Table 1)

2.1.1. Overview

In general, this phase should consist of a review of several items prior to the site visit to ensure that time during the visit is spent productively. These items may include completed participant-facing forms (consent forms, physical exam forms, questionnaires, or any other instruments used for data collection in the study), the site regulatory binder, the electronic data capture system, or participant images. A pre-visit written report should detail specific changes that need to be made to maintain compliance with study procedures and circulated to site personnel at least one week prior to the visit. Clear deadlines to make these changes (typically one week after the study visit) should also be included within the pre-visit document. The items being reviewed will vary for each study, and we recommend choosing ones that have a direct impact on protocol compliance and data integrity.

Table 1
Elements of in-person site visits and solutions for a virtual format (adapted from previously published guidance) [2–4, 10].

Item	In person element	Virtual solution	Advantages of virtual solution over in-person element	Limitations to virtual solution in comparison to in-person element
A	Review of paper materials in participant folders for double data entry (e.g., signed consent forms, questionnaires, physical exam forms)	Site RCs upload scanned copies of all paper materials in participant folders to secure Dropbox. Coordinating site reviews all materials and compares against data entry in electronic capture system (REDCap) prior to site visit.	Coordinating center can review all paper documents prior to the site visit and provide feedback for discussion during the site visit. This is also possible prior to an in-person study visit.	Difficult for coordinating center to see how individual participant folders are organized over videoconference. Time/effort for site research staff to scan everything.
B	Review participant radiographs and images to ensure protocol is being followed	Site RCs upload all available participant images (x-rays and MRIs) to secure Dropbox for coordinating site to review prior to site visit.	Coordinating center can review all images/sequences prior to the site visit and discuss any discrepancies during the visit.	None.
C	Regulatory binder	Site RC uploads electronic regulatory binder to secure Dropbox, coordinating center reviews prior to site visit.	Coordinating center can review the binder ahead of the site visit and discuss any discrepancies during the visit.	None.
D	Observe mock participant visit and physical exam	Site RCs conduct a mock visit with a local colleague as the study participant during the site visit, with coordinating center observing through videoconference.	None.	Difficulty viewing all aspects of the physical exam, possible to miss small departures from the protocol that could affect data collected at the site.
E	Tour of physical workspaces for participant study visits, computer/data security and storage of participant folders, and equipment	Site RCs conduct a tour of physical spaces with the coordinating site during the visit using videoconference.	None.	Walking tour on videoconference can be awkward, difficult to ascertain subtle details.
F	Discussion and assessment of site RC supervision and reporting structure	Coordinating site facilitates discussion through videoconference.	None.	None.
G	Discussion of site-specific recruitment progress and troubleshooting of issues experienced by each site	Coordinating site facilitates discussion through videoconference.	None.	None.
H	Post-site visit feedback and corrections	Coordinating site distributes detailed feedback of the documents reviewed prior to the site visit (paper documents, regulatory binder, data collection in REDCap) to site RCs the day before the scheduled visit. After the site visit is completed, coordinating site distributes feedback from the visit activities and a record of decisions made and future recommendations.	Coordinating center can provide detailed feedback in writing both before and after the site visit on issues related to quality control, team organization, adherence to protocols.	None.

RC = Research Coordinator; REDCap = Research Electronic Data Capture.

2.1.2. MeTeOR experience

In the MeTeOR 12-year follow-up, the preparation phase began two weeks before a site visit when coordinating center (CC) staff requested that all study-specific paper documents (signed consent forms, subject questionnaires, physical exam forms) from a site be scanned and/or uploaded to the secure study Dropbox. The Dropbox utilized by the CC was a business Dropbox which allowed CC study staff to share and manage study files online while remaining compliant with Mass General Brigham policies and procedures. CC research staff reviewed each of these documents carefully, compared them to electronic data records when appropriate, and documented any errors in these hard copy forms. Furthermore, this review of the paper forms allows for the assessment of responses by either site staff or the study participant and an examination of notes included in the margins. We reviewed the electronic regulatory binder, a collection of site-specific regulatory documents that site study coordinators are responsible for maintaining, and participant images available to date (in the MeTeOR study, these included knee X-rays and MRIs). We examined the images to ensure that the sites were using appropriate views and imaging sequences. If the CC staff does not possess the expertise required to interpret the images being used, the study radiologist can be consulted at this step.

The CC staff created a pre-visit report with detailed feedback including action items for remediation of potential errors. These errors may include discrepancies between a participant's answer on a hard copy questionnaire and the answer documented in the database, an outdated version of the consent form being used, missing electronic documentation of remunerating a subject for their participation in the study, or failure to use the study-approved imaging sequence. This report was distributed to the clinical sites a few business days prior to the site visit to allow site research coordinators (RCs) a chance to review and prepare to discuss the document.

The CC staff stressed that the purpose of the report as well as the visit in general was not to assign blame to individuals, but rather to identify systematic errors or misunderstandings that may compromise data quality. Before conducting site visits with sites outside of BWH, we completed an audit of internally (Items A - C, Table 1) within BWH (BWH is both a clinical site and the CC) and produced a pre-visit report identical in format to the ones we planned to use for site visits. We distributed this document to all clinical sites both to demonstrate accountability and transparency, and to set expectations for the upcoming site visits.

2.2. Virtual visit (items D-G, Table 1)

2.2.1. Overview

The time during the study visit is best used discussing any questions that the site study staff have about the results from the preparation phase, working through any site-specific issues with recruitment, reviewing the physical spaces where study staff work, conducting mock study visits/procedures, and better understanding the site working environment.

2.2.2. MeTeOR experience

Site visits for the MeTeOR trial were conducted using a videoconferencing platform (Zoom). The CC recognized that Zoom was not secure and thus did not share any study documents with participant identifiers during the virtual visits. Each site visit began with introductions and discussion of the pre-visit report (see 2.1 above).

The CC staff then observed site RCs perform the physical exam protocol for study visits either on each other or on a colleague. The CC staff provided feedback on the physical exam, noting any departures from the standardized protocols. When the CC team was unable to clearly observe the physical exams over Zoom, the site study staff was asked to reposition the video and audio and repeat the exams.

The site RC then led a tour of the physical spaces including but not limited to the location where participant folders and study equipment are stored and the rooms where participant visits take place. The CC team paid especially close attention to the security of both the cabinets where participant files are stored (if they were locked; where the key is kept) and the physical workspaces that RCs use (is the room badge access only, computers are password-protected).

The CC staff assembled data on each individual site's progress in contacting and consenting subjects and discussed these data during the visit. Given the large time gap between the 5- and 12-year follow-up visits for MeTeOR subjects, clinical site RCs were encouraged to discuss any challenges they faced with re-contacting subjects. The CC staff provided support in troubleshooting those issues.

The CC staff asked the clinical site RCs a series of questions aimed at understanding the organizational structure of the clinical site's research team. For example, the CC staff ask RCs who they consulted for day-to-day troubleshooting at their site, how often they met with the site Principal Investigator, and whether they had any unmet resource needs (e.g., space, personnel).

2.3. Follow-up (item H, Table 1)

2.3.1. Overview

The follow-up phase is an opportunity to crystallize the findings from the site visit and create concrete action items for both the CC and site study staff moving forward. This can be accomplished by writing a report detailing the recommendations made during the visit and summarizing the discussion for both those who attended and the site Principal Investigator (PI) or any other staff who could not attend.

2.3.2. MeTeOR experience

Immediately following the MeTeOR site visit, the CC staff drafted and finalized a post-visit report summarizing the main findings. The site visit report included both positive feedback and constructive suggestions to remedy problems documented in the site visit regarding the physical exam, data entry, security (computer or physical space), intra-site communication (meeting frequency with the site PI). The report concluded with a summary of decisions made during the visit and action items with set deadlines. Some specific examples of post-visit feedback include asking sites to use a chair with armrests during the physical exam for safety purposes (subjects are allowed to use armrests to help get up from sitting position) or asking site staff to keep keys to the cabinet containing participant folders in a locked drawer. If the CC staff noted significant misunderstandings of study protocols or errors in data collection, the CC staff scheduled follow up meetings to monitor these issues through to resolution. Only one virtual study visit was conducted at each MeTeOR site.

2.4. Assessment of the site visit

After the site visit, CC staff sent to the site study staff a questionnaire soliciting feedback regarding benefits and drawbacks to the virtual format. Commonly cited benefits included the flexibility to reschedule the visit if needed, the brevity of the virtual site visit, logistical simplicity (e.g., no need to book conference rooms, arrange meals, etc.), and the opportunity for more staff members from the CC and site to attend the meeting. Almost every site RC mentioned that it was awkward to show their office space and to perform the physical exam over Zoom but ultimately concluded that overall, they preferred the virtual format to in person. When asked if the feedback offered at the site visits was helpful, several site RCs stated that they were relieved to know that they had largely been implementing the study protocols correctly, made any changes the CC staff suggested immediately following the visit, and spoke with their site PI regarding what was discussed during the visit.

3. Discussion

The SARS-CoV-2 pandemic largely precluded travel to perform formal site reviews at clinical trial sites, prompting the development of a novel virtual structure. In this report, we present a framework for coordinating

virtual site visits and describe our experience implementing this framework in the MeTeOR trial. Our virtual site visit framework starts with a preparatory phase involving review of clinical site data entry and materials; a video call incorporating discussion as well as observation of secure storage spaces and mock participant visits; and a follow-up phase during which RCs at clinical sites implement quality improvements and changes based on feedback from the CC staff. Through these visits, we aim to promote accountability across sites, standardize study participant visits, ensure security of study materials, and remedy systematic errors in data collection and entry. The RCs at the CC did not work on the original MeTeOR study, and each RC had between one and two years of clinical research experience. This observation that the RCs were new additions to the MeTeOR team suggests that virtual site visits can be conducted even by inexperienced staff if the CC diligently follows our proposed framework and methodology.

To our knowledge, this is the first published framework for a comprehensive, real-time virtual site visit in place of an in-person review. Use of centralized remote data monitoring to supplement in-person visits is widespread [2], and prior research has examined specific risk-based monitoring and electronic data capture tools for this purpose [11–14]. During the COVID-19 pandemic, remote site initiation visits and monitoring became more common, with some investigators emphasizing the utility of these methods to decrease costs and increase efficiency even as pandemic restrictions ease [15–17]. Much of this literature describes trials with active pharmaceutical interventions, and some provide guidance for data quality monitoring by sponsors or contract research organizations [15,18,19].

Although we did not compare virtual and in person visits directly, our findings suggest that conducting site visits remotely may confer several advantages. Most urgently, virtual visits provided a safe option during the COVID-19 pandemic, bypassing travel and face-to-face meetings that could promote viral transmission. We envision that virtual site visits will remain beneficial post-pandemic, as they circumvent travel and lodging costs and transit time of in-person visits. Remote visits also avoid the environmental costs of long-distance air or road travel associated with in-person visits [8,9]. Finally, in comparison to in-person visits, this virtual framework grants greater flexibility in scheduling. The feedback we received from site RCs reflects these advantages, with several individuals specifically highlighting time savings from video calling and remote review of source documents prior to the call.

However, virtual visits have several limitations as well. Face-to-face meetings allow staff at disparate sites to interact as a team and build rapport, while virtual visits are less personal. Additionally, some visit components, such as the review of hard-copy participant folders and source documentation, can be unwieldy over video call. Observation of the physical exam by video is challenging, as noted by several site RCs, because the RC and the volunteer 'subjects' may move out of video and audio range during select performance tests. Similarly, a video platform offers a limited view of physical spaces, hindering assessment of aspects such as lighting and size of rooms or hallways. Finally, while our virtual site visit framework is broadly applicable, we note that we developed these virtual site visit protocols for a long-term follow-up visit to a randomized controlled trial. Because no drug or interventions are administered in the current phase of research, we did not assess randomization, concealment, blinding procedures, storage of medications or study drugs, or intervention fidelity. Some of these elements may be better assessed in person. However, our work suggests that components of this virtual framework, including the remote review of data entry and video-call based discussion, can be employed to supplement, and enrich in-person monitoring components, potentially reducing the duration and frequency of face-to-face site visits.

We anticipate this work will offer guidance to research teams who may wish to conduct virtual site visits. We provide a novel site visit structure for clinical coordinating sites for a long-term follow-up visit to a randomized clinical trial. Our framework also addresses elements of protocol adherence, participant rights and safety, and security of materials and spaces in addition to data quality monitoring. We urge other research groups to consider adapting some of the principles of virtual visits advanced in this paper and to add to this emerging literature on virtual site visits.

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Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. By signing below each author also verifies that he (she) confirms that neither this manuscript, nor one with substantially similar content, has been submitted, accepted or published elsewhere (except as an abstract). Each manuscript must be accompanied by a declaration of contributions relating to sections (1), (2) and (3) above. This declaration should also name one or more authors who take responsibility for the integrity of the work as a whole, from inception to finished article. These declarations will be included in the published manuscript.

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Declaration of competing interest

At the end of the text, under a subheading "Conflict of interest statement" all authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and research grants or other funding.

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Appendix A. Supplementary data

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