Considerations in the Conduct of Remote Clinical Research: Findings from Group Interviews

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Overview

- Objectives
- Methods
- Results
Objectives

- Describe research sponsors’ awareness and understanding of existing laws and regulations governing the conduct of remote clinical research
- Identify legal and regulatory challenges experienced or perceived by research sponsors to conducting clinical research remotely
- Identify how to clarify existing laws and regulations governing the conduct of remote clinical research
Methods

- Group interviews
- Unstructured interviewing based on topics identified in a semi-structured interview guide
  - Start with description of remote studies
  - Followed by questions on:
    - Telemedicine laws and regulations
    - Shipping and receiving
    - Delegation of PI responsibilities
    - Investigational New Drug application
    - Reimbursement
    - Ethics
    - Overall recommendations
Results

Study Population

- 9 group interviews were conducted
- 2 to 7 representatives per group, for a total of 31
- Representatives were from 7 pharmaceutical or biotech companies that sponsor clinical research
  - For one company, three separate group interviews were conducted to account for differences in time zones
Results

Representatives’ roles varied and included, for example:
- Directors
- Attorneys
- Project managers
- Clinical innovation leaders
- Business development representatives
- Regulatory representatives

Demographic data are missing from one representative.
Understand the differences in state telemedicine laws
State Telemedicine Laws: Challenges

- Sponsor groups described that—
  - Inconsistent interstate telemedicine laws made planning for or implementing clinical research with telemedicine components difficult and time consuming
  - Existing laws often do not—
    - Account for new telecommunication platforms, remote collection of patient information
    - Distinguish between prescribing approved drugs for clinical care and dispensing drugs for clinical research
State Telemedicine Laws: Challenges (continued)

- Therefore—states rely on existing legislation related to standard clinical care to interpret the legality of remote trial procedures:

  *We found that many of the state laws didn't differentiate between prescribing approved medicine and dispensing medication in a clinical trial. So, in some cases the states would apply their prescribing laws when we talked to them about this.*

- Sponsors interpreted the existing legislation to mean that the PI would need to have direct contact or supervision of patients’ care
State Telemedicine Laws: Challenges (continued)

- Variation in state laws restricted the reach of remote clinical research in terms of recruitment—i.e., the number of states in which sponsors could conduct their research.

- Ambiguity exists as to whom to speak with at the state level (e.g., state medical or pharmacy boards) and which level of government is responsible for overseeing the conduct of remote clinical research at a particular site.
We had conflicting opinions from states. In some cases, they said that the federal regulations don't apply; the state laws apply. In other cases, we had states that said, "Our laws don't apply. This would be governed by the federal regulations." So, we had some conflicting feedback there. And, not all states were favorable in terms of us conducting this. One state said they would consider it medical malpractice if the PI were to conduct the study in their state.
State Telemedicine Laws: Challenges (continued)

- Some states explicitly indicate they do not allow direct shipment of study drugs to patients.
- This variation or lack of state laws made the direct shipping of study drugs to patients, for example, extraordinarily difficult to implement.
- Interstate shipping of study drug was one of the major hurdles to conducting a “true remote” trial:

  *I think study drug shipment's probably the biggest hurdle currently… I think that's probably one of the greatest potential restrictions or hurdles to a true remote or decentralized trial, from a regulation standpoint.*
State Telemedicine Laws: Solutions

First review and understand individual state laws governing clinical trials, medical practice, distribution of drug (or study products) and telemedicine (if any are available):

So, from every angle, we had to look at it and make sure that we have covered all bases from regulatory regulations perspective, state medical board perspective, pharmacy board perspective. It's a lot of work done.
State Telemedicine Laws: Solutions (continued)

- Communicate with—
  - FDA
  - State medical and pharmacy boards
- Ask for feedback to ensure covered all regulatory bases
- Ask FDA for waivers, if appropriate
Partnering With Physicians Who Are Licensed in Multiple States
Multi-State Physician Licensure: Challenges

Some states—

- Require that a “supervising” physician be licensed to practice medicine in their state
  - Difficult to find a single PI who is licensed in multiple states to oversee multiple remote sites across different states
- Require an in-person consultation between the physician and a patient prior to initiating treatment
Multi-State Physician Licensure: Solutions

Recognize physicians with—
- Medical licenses in multiple states
- Licenses in states that allow for reciprocity in other states

Contract with a local physician in each state:

And, in most cases, we were able to...get approval from local state authorities that a physical exam conducted by a local physician and communicated to the central PI in another state would be sufficient to permit distribution of study drug to that study subject.
Drug Supply Chain of Custody
Drug Supply Chain of Custody: Challenges

- Difficult to track study drug receipt and drug accountability when drug is shipped directly to patients

- Challenges with regulatory—administering study drugs by invasive routes outside of a clinical setting because of safety concerns and lack of Medicare reimbursement for home infusion
Drug Supply Chain of Custody: Solutions

- Describe each step in the study drug supply chain
  - From dispensing the drug, distributing it to the PI, shipping it to the patient, documenting the patient’s acknowledgement of receipt, and recovering study drug
Mobile Nursing
Mobile Nursing: Benefits

- May be able to address several drug administration challenges
- Can reduce trial burden on site staff and participants
- Can broaden the reach of trials
- Can address the challenges related to shipping study drugs

We have only rarely shipped drugs directly to patients. We've done it before, but we haven't done it very often. It's not a standard practice...I think the ways that you can get around it are: if you do utilize some type of mobile nursing, have it be shipped to them, and they can then take it to the patient directly.
Mobile Nursing: Challenges

- Varying medical qualifications
- Inconsistent knowledge
  - Could pose challenges for ensuring that quality and consistent care
- Training a “vast team of mobile nurses” (that would be required to administer study drugs in remote settings) would be a “huge, huge” burden and cost
- Concerns about liability if a problem arises as a result of a mobile nurse’s interaction with a patient on behalf of the study
Mobile Nursing: Challenges (continued)

Hard to convince own study teams that engaging mobile nurses was a good idea:

But we need to get more alignment and buy-in from our protocol writers that this is a quality service that will not compromise their data. You know, it's new. It's not the way that they're used to collecting data. So they have a lot of good questions, especially in registrational studies, about whether or not this could in any way impact the ability to file the data. So we're not designing the protocols with that in mind necessarily.

Could negatively impact relationships with site teams
Mobile Nursing: Solutions

Ensuring mobile nurses:
- Have the required qualifications to conduct the study procedures
- Are licensed to conduct the specific procedures in the state

Ensuring consistent protocol training for all mobile nurses

Ensuring that vendors follow proper drug accountability procedures if study drug is being disseminated through the vendor
Mobile Nursing: Solutions (continued)

Assessing the readiness of mobile nursing in various study locations. Identify:

- Potential barriers related to the medical skills of mobile nurses in the area
- Cultural barriers to remote patient care
- Any legal or regulatory barriers to mobile nursing in those areas

Training mobile nurses to record clinical and study notes on tablets (e.g., iPads) with wireless capabilities

Training mobile nurses to document specific clinical assessments and study procedures
Privacy and Confidentiality in Remote Trials
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- Patient privacy and confidentiality were described as concerns in the conduct of trials that used mobile technologies to collect data
- See MCT Devices Project Recommendations later this year
Safety Monitoring and Remote Clinical Research
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- Engage patients’ treating physicians
- Have central sites conduct telephone follow-ups to query patients about AEs; conduct Skype visits with physicians
- Have mobile nurses collect AE data during regularly scheduled visits to the patient’s location
- Emphasize the importance of patient’s engagement in the process
- Consider using a mobile app for reporting adverse events, which will enable site staff to respond more quickly than if patients were to wait to report AEs until they physically come in to the site
Safety Monitoring and Remote Clinical Research (continued)

- Start with a product where safety is already well characterized

- Incorporate remote monitoring technology first into post-marketing studies, to track safety in larger populations
  - Then incorporate mobile tech into Phase II and III trials, where safety is not yet established, once people have gained comfort and familiarity with it
Think Creatively!
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- Recruit patients directly via the Internet → patients then “recruit” their local physician

  *I guess what we were trying to do or what the intention was to change the usual clinical trial paradigm where […] the sponsor reaches out via the Internet to patients, and the patients recruit their treating physician to support their involvements in the trial.*

- Have patients interact directly with PI via video-conferencing

- Have patients take pictures of images (related to condition) on their mobile phone, then uploaded directly to a secure study website

- Work with mailing pharmacies to ship non-investigational study drugs across state lines
Federal Regulations and State Laws
Overview

Some sponsors said…

- Few regulations exist on remote clinical trials, although there is some guidance that is helpful, particularly FDA guidance on using direct data capture tools like e-source and on the use of ePROs.
- FDA’s position on whether trials using mobile technology will be accepted is unclear.
- FDA should evolve as technology evolves and keep in step with it, rather than trailing several years behind advances in the field.
- Additional guidance is particularly helpful for the newer, smaller, and less experienced sponsors.
Allow for more reciprocity between states

I think there are perhaps mechanisms by which a doctor can have their medical license submitted in several different states. We were working with one who was licensed in seven different states. I think it's definitely an obstacle in the U.S. We don't have the same issues in Europe, where medical licensing is national, but yeah, it's an obstacle to telemedicine at a large scale.
Delegation of PI Responsibilities in Remote Clinical Research: Challenges

- Difficult to determining investigator responsibilities (PI vs. sub-PI, vs. supportive roles) and who should be on the 1572
- Define scope of PI oversight
- Need to distinguish between standard-of-care procedures and assessments, versus form 1572-type procedures
  - Challenges exists for interpreting the 1572 guidance about what “meaningful contribution to study data” means
- State laws requiring in-state PIs defeat the purpose of conducting remote trials with a single PI:
Delegation of PI Responsibilities in Remote Clinical Research: Solutions

Clarifying what activities local physicians are allowed to do without needing to be designated as an investigator would also be helpful.

- If the local physician is only asked to perform standard medical procedures that they would do regardless of whether their patient were enrolled in the study, does the physician still need to be listed as a study investigator?
Delegation of PI Responsibilities in Remote Clinical Research: Solutions

More FDA guidance about—

- Who should be included on form 1572
- Who is responsible for what in terms of delegation of responsibility in a remote trial
- What comprises standard of care versus “investigational practice”
- What point a physician should be considered a sub-investigator
Delegation of PI Responsibilities in Remote Clinical Research: **Solutions**

[Knowing whether to include a local physician as an investigator on the 1572] was a big question mark for a long time. And, by the way, that question mark persists right now in a different trial we're trying to do in a different indication that's about long-term follow-up data collection. But I would say we're struggling to provide consistent answers, even with excellent regulatory guidance. Because it's just not clear…it'd be helpful to have a little more clarity on what constitutes standard of care versus what constitutes investigational practice, and when you need to be considered a sub-investigator.
Distribution of Study Drugs in Remote Clinical Research

- Request for FDA to provide more clarity about distribution of study drugs in clinical trials
  - Current system of having to rely on sometimes inconsistent information from multiple state regulatory boards or agencies is not working well and may discourage some sponsors from conducting trials in the US
  - Opportunity for FDA to take full control of the distribution of study drugs, supplanting the current mix of federal and state control
FDA-specific Clarification

- Issues of data lineage, data integrity, and data storage, so investigators and sponsors don’t have to make assumptions on the basis of guidance designed for other types of trials.

- Safety monitoring for remote studies.

- Incorporating experimental use of mobile technology into a trial (e.g., under what circumstances can the data collected via telemedicine serve as both validation of the experimental use of telemedicine and as a primary endpoint for the purposes of the trial).
FDA-specific Clarification (continued)

- The primary and secondary clinical endpoints, captured in non-clinical settings
- Data exclusivity
- The automation of clinical studies – are there permissible automations and efficiencies that would meet FDA approval (e.g., online data entry by patients in lieu of site visits, or incorporation of real-world EMR data into Phase III trials)?
- The use of digital technology tools (e.g., what level of validation is considered acceptable, how rigorously does this need to be demonstrated, and what are requirements for standardization) need to be clarified
Overall advice
During Trial Planning—Start Planning EARLY

- Engage partners and collaborators in the very early planning of the research
- Conduct proof of concept studies
- Get aligned with company’s senior leadership, innovation group
- Build in remote aspects from the start of any clinical trial protocol
- Work closely with FDA from the beginning, to make sure that the plan involving mobile technology is going to be acceptable (as FDA is very accessible and open to reviewing and providing early feedback on exploratory or innovative clinical trial designs)
Overall Approach

- Use a patient-centered approach
- Use a problem-based design approach
  - Start with the design and build from that, rather than trying to add devices into an already-established protocol
  - Start with safer trials
- Stay focused and keep the plan simple/avoid design becoming too complicated
- Don’t be too risk averse
- Take the time to learn and work toward long-term solutions
- Use a hybrid approach—i.e., conduct a trial with both remote and traditional components
THANK YOU.