Using Telehealth to Accelerate Clinical Trials and Biomedical Discovery:
Navigating Compliance Hurdles to Maximize Potential Benefits

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The use of innovative technology and big data strategies is drastically changing the entire health care landscape. One prime example is the use of telehealth to streamline, democratize, and accelerate clinical trials and associated biomedical discovery. The many potential benefits of the use of telehealth in this context include a broadening of the geographic scope of patient access to clinical trials, improving research subject compliance, reducing subject withdrawal rates, and decreasing research-related costs. Depending on the nature of the use, however, it may be regulated by various state and federal laws. Determining whether a particular use is subject to regulation necessitates assessment of the particular facts and circumstances surrounding the service or activity, and each applicable law or regulation.

This article will explore the current uses and benefits of telehealth in clinical research, the principal associated legal and regulatory challenges, and compliance strategies for managing those challenges.

I. Role of Telehealth in Clinical Research Trials

Telehealth—the delivery of health-related services and information to individuals via telecommunications technologies—has been used for many years in the clinical research setting to test drugs, devices, and other clinical interventions. Such use has increased in recent years as a tool for recruiting and communicating with research subjects. More studies are expected in the near future to embrace mobile and web-based data capture using symptom-tracking applications or online portals to permit subjects to complete periodic self-assessments, report symptoms, submit questions, speak to the research team, and/or upload photographs for treatment purposes.

The following examples illustrate the power and potential of telehealth in the clinical research context:

- In 2011, Pfizer conducted the first randomized “virtual” clinical research trial, Research on Electronic Monitoring of Overactive-bladder Treatment Experience (REMOTE), developed in collaboration with and approved by the U.S. Food and Drug Administration.\(^1\) Prospective subjects

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\(^1\) Wayne Koberstein, Pfizer Perseveres in Pioneering Virtual Clinical Trials, CLINICAL LEADER (Nov. 29, 2012), http://www.clinicalleader.com/doc/pfizer-perseveres-in-pioneering-virtual-clinical-trials-0001; PFIZER INC., Pfizer Conducts First
completed education, qualification, and enrollment processes on the study's website; data reporting and collection were conducted using telehealth technologies (primarily a smartphone mobile application); and laboratory supplies and drugs were shipped directly to subjects' homes. In 2015, a collaboration of several major companies, including Sanofi, Mendor, eClinicalHealth, and Langland, received approval in Europe to assess the effectiveness of a 3G-enabled wireless blood glucose meter and Web-based patient-investigator communication system. The Sanofi-led virtual trial incorporates telehealth to facilitate real-time communication between the researchers and subjects, and remote monitoring devices are used to collect and analyze subjects' blood glucose levels data. In 2016, researchers with the Abramson Cancer Center at the University of Pennsylvania published a Research Letter in JAMA Oncology that sampled Twitter feeds for references to "lung cancer." Of the 1,516 random sample of tweets reviewed, 221 were related to clinical trials and one linked to a patient recruitment site. While social media may not be the primary method of trial recruitment now, the findings of this study suggest that Twitter "provides a promising and novel avenue for exploring how cancer patients conceptualize and communicate about their health, and may have the potential to promote much-needed clinical trial recruitment." 

II. Telehealth as a Potential Solution to Certain Research Challenges

The challenges associated with the recruitment and retention of subjects in clinical research trials are well documented. Prospective subjects face significant barriers to finding and securing opportunities for participation in clinical research trials, including lack of awareness of available clinical research trials, insurmountable geographical distance from academic medical centers conducting trials, and lack of time (or desire) to participate in multiple follow-up visits.

These challenges have contributed to inequities in the clinical trial opportunities that are available to patients. As noted in a 2010 Institute of Medicine report, "[s]ites for clinical trials are frequently selected on the basis of where the investigators are located, as opposed to where the eligible patients are, creating difficulties in patient recruitment." Although approximately 85 percent of cancer patients are treated at regional and community-based hospitals and cancer centers, studies for the newest targeted cancer drugs are generally offered at academic cancer centers, making it difficult for the targeted study subject populations to access the study opportunities. A compounding factor is that "[w]hen patient recruitment is impeded, the trial is delayed, sometimes by years, until the number of patients required by the study protocol can be enrolled." According to research by the Tufts Center for the Study of Drug Development at Tufts University, 11 percent of sites in a given clinical trial typically fail to enroll a single patient, 37 percent under-enroll, 39 percent meet their enrollment targets, and 13 percent exceed their targets. In some sectors, up to 80 percent of clinical trials fail to enroll subjects as planned. As leaders in fields such as oncology agree, however, access to clinical trials comprises a component of high-quality patient care. Therefore, delays can increase costs of care dramatically and defer the scientific gains that could save patient lives.

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Id.


Id.


Id.

Id.


Id.


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The use of telehealth technologies—from the traditional (e.g., Web cams and audio connections) to the innovative (e.g., interactive websites, mobile applications and wearable e-health technologies)—can help to address many of these recruitment and retention issues by enhancing awareness, access, and affordability of worthwhile clinical trials for a much larger and more geographically dispersed population, which, in turn, enhances the likelihood of the launch and successful completion of a study.

A. Recruitment and Enrollment

Researchers have shown that using technology to remotely connect with potential subjects can accelerate and enhance success in recruiting and enrolling a greater pool of potential subjects for a clinical study by removing the inconvenience, time and expense of traveling far from home to undergo screening and enrollment, particularly for time-sensitive diagnoses (such as stroke). For example, researchers successfully randomized and enrolled subjects who presented at community hospitals for treatment into an acute stroke clinical research trial using telehealth technology. The enrollment occurred within hours after symptoms began, without the need to physically transfer the subject to the tertiary facility that served as the lead site.

The use of an online process to enable prospective subjects to self-screen into a trial can also be a cost-effective way to increase the number of patients identified as eligible for the trial. The Pfizer REMOTE study noted above used an online pre-screening process for subjects interested in participating in the study. Once an interested individual clicked on a Web advertisement designed to recruit subjects, he or she was automatically linked to an online screening questionnaire that provided information about the condition and solicited information from the prospective subjects. Over 5,000 individuals began the questionnaire for the Pfizer REMOTE study, and advanced through the questionnaire until they either failed to meet essential eligibility criteria or met the criteria and were enrolled in the study. Ultimately, only a small percentage of the individuals who began the questionnaire were found eligible to participate in the Pfizer REMOTE study due, in part, to the complexity of the technological platform and participant-validation issues. However, the ability to reach out to such a large population identified the true potential for this type of process.

B. Informed Consent Processes

The Pfizer REMOTE study also successfully piloted an online informed consent process that included an interactive component that helped confirm study subjects’ understanding about the risks and benefits of a study. Subsequent studies have shown that electronic processes with an interactive interface to obtain informed consent facilitate the subject’s ability to retain and comprehend the information about the trial. A wide range of technologies has been used for this purpose, ranging from an interactive program uploaded onto a tablet that is accessed at the study site to an online program accessed in the subject’s home that includes an instructional video and quiz to verify the subject’s understanding of information provided. Furthermore, use of an online or electronic format makes it more likely that the informed consent process will be standardized across all sites.

Technologies also position the study team to rapidly notify a subject of information that is important and relevant to the individuals, and may affect the subject’s participation in the study and expedite the subject’s execution of the study informed consent form. E-mailed copies of consent forms and e-mail, text or Twitter notifications about the risks/benefits of a study and/or any adverse events that occur over the course of the study may be easier to deliver to—and more likely to be read by—subjects who change physical addresses frequently or who pay closer attention to social media or other electronic forms of communication than traditional snail-mail communications.

C. Communication with Subjects During the Research Study

In addition to remote monitoring technologies, the use of synchronous technologies, such as videoconference platforms, enables real-time, subject-researcher interaction during clinical trials. For example, researchers in the aforementioned remote stroke study were able to use existing telehealth capabilities (e.g., audio-visual conferencing with access to CT images via remote PACS system) located at participating community hospitals to connect remotely with subjects in real-time. Furthermore, the Pfizer REMOTE study was designed as a completely “virtual” study, which used Web platforms (supplemented by real-time telephone conferences) to connect with subjects for all issues (including adverse event reporting, questions about the study, etc.) and required no in-person visits by the subjects, except for some laboratory visits as necessary.

D. Collection and Analysis of Data

Telehealth technologies can also improve the accuracy of data while making it more convenient and cost-effective to collect. Through the use of remote monitoring technologies, such as wearables (e.g., heart remote patient monitoring devices) and other wireless enabled devices with sensors that collect biometric data, researchers can collect data directly from the subject in the course of his/her daily activities without the need for the subject to travel to the research site. The increased amount of information and instant access to

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such information can lead to improved outcomes, including avoidance of adverse events or identification of necessary study deviations in the event of a study subject emergency. For example, wearable technologies with biometric sensors can be used to monitor subjects for abnormalities in vital signs and provide immediate notifications to the research team and treating physicians of any subject emergencies requiring follow-up.

Many of these telehealth devices are already in the hands of subjects—rapid increases in the number and sophistication of mobile health devices demonstrate that subjects are interested in collecting these types of data to inform their own health choices. According to the Pew Center, approximately 64 percent of American adults use a wireless-enabled mobile phone or other device, and an even higher percentage of younger adults and minorities depend on their smartphone as their main source of access to the Internet. Sales of mobile fitness trackers and mobile health apps have increased annually. In the future, researchers may be able to rely on subjects to bring their own devices and apps to a clinical research trial.

In sum, real-time subject monitoring via Bluetooth-enabled sensors that track weight, temperature, blood pressure, blood glucose, oxygen saturation, and medication intake are examples of how investigators can use telehealth to decrease the need for in-person, clinic visits and to improve the flow of information from subjects to researchers.

III. Identifying Legal and Regulatory Barriers and Developing Corresponding Compliance Strategies

A. Overview of Current Telehealth Legal and Regulatory Landscape

Telehealth touches on multiple legal and regulatory issues at the state and federal levels, including professional licensure, scope of practice, informed consent, fraud and abuse, and privacy and security requirements. Existing laws, regulations, and related guidance are focused largely on the use of telehealth in traditional care delivery settings. As a result, determining whether and how these laws, regulations, and guidelines apply in the context of clinical research trials can be challenging, and legal counsel advising institutions, principal investigators (PIs) and other members of the research team, institutional review boards (IRBs), and industry sponsors need to understand the multi-faceted telehealth regulatory framework generally and how it intersects with the overall regulatory framework for clinical research, as well as 'gray areas' and associated areas of risk.

B. Professional Licensure

Most states require that a licensed health-care professional hold a license in the state where his or her patient is located at the time that the service is rendered (even if that professional never enters the patient’s state and is already licensed by another state), unless an exception applies. A small (but growing) number of states recognize licenses granted by other states or have adopted a streamlined process for the licensure or registration of telehealth providers.

While clinical research is not the practice of medicine, communicating with subjects about matters related to participation in clinical trials, in the context of discussing his/her clinical health status, and providing treatment to subjects using telecommunications technology, may constitute the provision of telehealth services, which may implicate professional licensure laws. Determining whether the activity or service falls within the scope of activities or services that require professional licensure, as well as whether an exception to the licensure requirement applies, often involves careful consideration of the applicable facts and circumstances (e.g., nature of the information exchanged between the researcher and subject, the parties participating in this exchange, the types of technology used to facilitate the exchange, the physician’s involvement in the trial, the relationship of the trial to, and/or its possible effect on the course of treatment). In short, a fact-based, state-by-state analysis is often necessary to determine whether professional licensure is required.

Given the potential for subjects to be located in multiple states, this may create the obligation for physician researchers and nurse research coordinators to hold professional licenses in multiple states. Obtaining and maintaining professional licensure (particularly medical licensure) in multiple states is expensive and time-consuming. For this reason, professional licensure requirements are frequently cited as one of the largest barriers to multi-state telehealth programs.

In an effort to create an expedited licensure process for eligible physicians that improves license portability and increases patient access to care, the Federation of State Medical Boards has formed the Interstate Medical Licensure Compact (Compact). The Compact allows physicians who are licensed in a Compact-member state to participate in a streamlined licensure process in Compact-member states. Twelve states have adopted the Compact and many other states have introduced the legislation proposing to do so. A multi-state compact that recognizes the licensure of nurses between participating compact states has been in existence for many years.

C. Liability Coverage

Research team members using telehealth to communicate with potential and existing subjects should confirm that his/her medical malpractice insurance policy and other insurance covering research activities covers telehealth services for research subjects located both within and outside the state of residence of the research team member—and whether the amount of this coverage is adequate.

D. Scope of Practice

There is a general consensus among state regulatory bodies and courts that the care provided via telehealth
must meet the same standard of care as care provided in person. However, some state professional boards do not defer to the health care professional’s independent judgment in making the determination of whether the care to be provided via telehealth meets this standard and have adopted regulations and guidelines that define the professional’s scope of practice when using telehealth to practice his/her profession.

Specifically, a number of state professional boards have adopted regulations or guidelines on the circumstances surrounding when and/or how telehealth services are provided. Similar to the professional licensure regulations, these regulations vary and can be very fact-specific. However, most states agree that an established patient-physician relationship must exist before any prescriptions are issued, which requires the performance of a physical examination of the patient, but what constitutes a valid “physical examination” varies from state to state. For example, researchers may be unable to adjust or modify the medication regime of a patient-physician relationship must exist before any prescriptions are issued, which requires the performance of a physical examination of the patient, but what constitutes a valid “physical examination” varies from state to state. For example, researchers may be unable to adjust or modify the medication regime of a subject who is located in Arkansas without first performing a physical examination of the subject, which may not always be possible. In short, consideration of how state scope-of-practice requirements apply to telehealth encounters between research team members and subjects is an essential step in any legal feasibility analysis.

E. Informed Consent

Certain states statutorily require the informed consent of patients prior to receiving care via telehealth. These informed consent requirements may apply to a specific specialty, all telehealth encounters that occur in the state, or just to the Medicaid program. States with telehealth-specific informed consent requirements often require that the patient be informed of both the risks and benefits of different treatment or procedure options, and the risks and benefits related to receiving care via telehealth, and dictate the manner in which informed consent is obtained (i.e., in writing or verbally). In addition to certain state law requirements, the FDA has adopted specific informed consent requirements. As a result, in addition to complying with the requirements specific to clinical research trials, informed consent documentation should provide the subjects with information about how telehealth will be used in the study and the potential risks associated therewith.

F. Privacy, Security and Data Management Issues

The use of telehealth in clinical research implicates state privacy and confidentiality standards, the federal requirements under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and other laws related to the preservation of the integrity and safeguarding the privacy and security of patient health information (PHI). The accumulation of subject PHI resulting from the use of telehealth technologies (e.g., remote monitoring devices and store-and-forward applications) presents special storage and management compliance challenges as the information may be in different formats (e.g., video, images, text). Accordingly, defining how PHI obtained via telehealth encounters may be used, shared, stored, and transmitted in relevant agreements (e.g., business associate agreements, confidentiality agreements) informed consents and authorizations, and policies, and integrating safeguard mechanisms and processes into existing operational procedures, is essential to achieve legal and regulatory compliance and to limit liability exposure. Active monitoring of compliance with these laws and regulations is particularly critical in the telehealth context in light of the potential volume of health information generated through telehealth mediums and how rapidly telehealth technologies are evolving.

IV. Compliance Strategies

Carefully designed, implemented and documented compliance strategies will assist institutions, industry sponsors, researchers, and IRBs to manage these legal and regulatory barriers, and minimize their individual and collective exposure to potential liability and scrutiny from state and federal regulators. Documentation includes written policies and procedures that are consistent and coordinated with existing IRB and research program policies and procedures, and the study’s protocols (to the extent appropriate).

Some of the key requirements that should be addressed and documented in policies and procedures are set forth below:

- Require the PI to consider (and document to the extent appropriate) whether the use of telehealth to communicate with potential or existing subjects is appropriate in light of the research study’s purpose, objectives, and parameters and consider this carefully in cooperation with their IRB. (The use of telehealth to communicate with potential or existing subjects may not be appropriate for every research study. Communicating with subjects via telehealth when inappropriate, such as when researcher-subject in-person visits are necessary, could jeopardize the quality of the research data and expose the subject to potential harm.)

- Require the PI to consider (and document to the extent appropriate) whether the use of telehealth to communicate with potential or existing subjects is appropriate in light of the research study’s purpose, objectives, and parameters and consider this carefully in cooperation with their IRB. (The use of telehealth to communicate with potential or existing subjects may not be appropriate for every research study. Communicating with subjects via telehealth when inappropriate, such as when researcher-subject in-person visits are necessary, could jeopardize the quality of the research data and expose the subject to potential harm.)

Require that the informed consent forms provided to and signed by subjects clearly and accurately disclose all of the material facts necessary for the subject to make an informed decision about receiving telehealth services, which may include:

- o a clear description of the telehealth process (e.g., what technologies will be used, how the researcher and subject communicate using this technology);

- o a clear description of the expected risks and benefits of telehealth services that is easy to understand.
stand (i.e., not full of undefined or complex legal and medical terms);

- information about what the subject should and what the research team will do if the telehealth equipment or technology fails; and

- direction for the subject to contact 9-1-1 and to proceed to his/her nearest emergency department for emergency conditions.

- Require consideration of the requirements applicable to electronic signatures if a subject's consent to research is obtained electronically, and require researchers to work with their IRB in creating and approving the electronic informed consent process and documentation of same.

- Require the PI to assess whether using telehealth to communicate with potential or existing subjects is allowed under the terms of the applicable research agreements, and consider whether there is an obligation (regulatory or contractual) to communicate its use to sponsors and the IRB. (For example, FDA regulations require the IRB to review the methods and materials that investigators propose to use to recruit subjects.)

- Require the research team members to receive orientation and ongoing training on how to comply with the applicable laws and regulations, and how to operate the telehealth technology. This training should advise the research team members on the types of technology used to facilitate the encounter with the potential or existing subject and how to determine if this technology is capable of fulfilling the need for which it is to be used. For example, if the researcher needs to examine certain physical characteristics of the subject to determine whether a modification of the subject’s medication regime is necessary, using secure videoconferencing technology may be more appropriate than a telephone call or e-mail exchange (which would require the subject to verbally describe his/her condition and is perhaps less reliable). Researchers should also be aware that subjects may not understand how to operate the technology (or find it difficult to use) and should build in supports and/or training to subjects as appropriate, so that there are no barriers to participation in this regard.

**Conclusion**

Telehealth complements traditional clinical research models to provide opportunities for expanding research participation; enhancing communication, data capture, and analyses; and improving the quality of care delivered to research subjects. As researchers continue to incorporate innovative technologies into clinical research studies to reap the benefits described in this article, there will likely be increased scrutiny and focus on how studies comply with the state and federal legal and regulatory requirements governing both the areas of telehealth and clinical research. As a result, it will be more important than ever for the PI and his/her research team, institutions, IRBs, and sponsors to understand and develop strategies to comply with these legal and regulatory issues.