The Role of Telehealth in Decentralized Clinical Trials

Kyle Y. Faget

Between supply chain disruptions, travel restrictions, social distancing measures, mandatory quarantine periods, and site closures, SARS–CoV-2 (COVID-19) ground clinical trials activity to a screeching halt. COVID-19 virtually upended the clinical trial industry as the virus spread across the globe. If there has been a positive aspect associated with the onset of COVID-19, it is that the virus forced the health care industry to embrace technologies that had previously and somewhat pejoratively been characterized as disruptive. In an attempt to socially distance and minimize social interactions, as much as possible, health care providers have embraced digital technologies, including the decentralized clinical trial model (also known as virtual clinical trials).

Decentralized clinical trials are clinical trials that embrace the use of digital technologies, including telehealth. There is no single brick and mortar clinical trial site, which limits enrollment to patient populations that are either native to the site's geographic area or to patients that are willing and able to travel to the site. By leveraging digital technologies, decentralized trials can recruit patients across geographies, which has the impact of making these trials widely available. This is a critical enrollment tool for clinical trials targeting rare disease populations. The strength of the model is not limited to diseases with small patient populations. Decentralized clinical trials offer trial participants, subjects, the convenience of receiving treatment in their homes or with little to no travel. Convenience offers a solution to a major issue that plagues clinical trials–no shows. Additionally, decentralized trials often include some form of remote patient monitoring that allows investigators to observe study subject status in real time and collect data from patients directly. Instant feedback allows investigators to timely intervene if a specific study subject issue arises, which leads to greater study subject protocol compliance.

With so many obvious upsides, it is hard to imagine why decentralized trials did not win favor until the onset of COVID-19. Indeed, the proof of concept was born

Kyle Y. Faget is in the Boston, Massachusetts office of Foley & Lardner, LLP and can be reached at 617/502-3292 or kfaget@foley.com.

out as early as 2011 when Pfizer conducted REMOTE, the first virtual clinical trial that allowed patient participation regardless of geography.[1] So, why has there been such resistance to adopting this clearly innovative model for conducting clinical trials? As may be readily apparent, leveraging the decentralized clinical trial model necessitates use of telehealth in many, if not most, instances, and there are a myriad of legal and regulatory obstacles to compliant use of telehealth. Of all the potential issues, compliance with licensure requirements and prescribing requirements tend to present the largest barrier to entry for use of decentralized trials. Additionally, many sponsors overlook the requirement that exists in many states with respect to telemedicine informed consent.

Licensure

The first barrier a clinical trial sponsor will face when contemplating initiating a decentralized clinical trial is the legal requirement that a health care provider be licensed in the states in which study subjects are located. If a decentralized trial is truly able to enjoy boundariless enrollment, the sponsor will need to have health care providers licensed in multiple states, if not all 50 states. Proactively identifying a potential network of health care providers across jurisdictions or working with investigators who are licensed in multiple states is one way to address this threshold issue.

Fortunately, COVID-19 catalyzed many governors across the United States to issue executive orders temporarily waiving licensure requirements. For example, in the state of Alabama, the State Board of Medical Examiners issued an emergency rule effective March 23, 2020, finding "that the need for *qualified physicians*, physician assistants, and anesthesiologists warrants the issuance of emergency certificates of qualifications to physicians licensed in other states."[2] The State Board of Medical Examiners found that physician applicants who satisfied the requirements of Ala. Admin. R. 540-X-3-.25 were eligible for emergency certificates of qualification by endorsement; physician assistant applicants who satisfied the requirements of Ala. Admin. R. 540-X-7-.69 and .70 were eligible for emergency licenses; and anesthesiologist assistant applicants who satisfied the requirements of Ala. Admin. R. 540-X-7-.71 and .72 were eligible for emergency licenses.[3] More recently, the Medical Licensure Commission of Alabama found that the state public health emergency caused by COVID-19 has not abated, that the number of persons suffering from and affected by COVID-19 has been rapidly rising, and that the rapid increase in patients requiring hospital-based care has strained the state's health care system.[4] Therefore, physicians who obtained an emergency certificate of qualification by endorsement from the State Board of Medical Examiners were eligible for an emergency medical license that expires one hundred eighty days after the effective date of the rule, when the Governor of Alabama proclaims the termination of the state's public health emergency, or when the current state of emergency expires, whichever is sooner.[5]

The waivers put in place to address COVID-19 are temporary in nature, however. When the public health emergency abates, the licensure system will likely revert to the state-by-state licensure system. The pre-pandemic system did have some built-in efficiencies, however. Some states have a telemedicine special purpose license or registration. For example, the state of Florida's telehealth statute permits an out-of-state licensed health care professional to provide health care services to a patient located in Florida if the out-of-state health care professional registers with the applicable board or the Florida Department of Health, if there is no board.[6] Importantly, however, the law prohibits an out-of-state telehealth provider from opening an office in Florida and providing in-person health care services

to patients located in Florida.[7] For the purposes of decentralized clinical trials, Florida's restrictions are not particularly problematic. If all states had a similar registration system, there would be a realistic path forward for investigators looking to enroll patients from multiple states without having to engage in the often lengthy process of obtaining multiple state medical licenses. Currently, only 12 states have implemented a telemedicine special purpose license, permit, or registration for physicians.

About half the states in the United States are members of the Interstate Medical Licensure Compact,[8] which is an agreement among participating U.S. states to work together to significantly streamline the licensing process for physicians who want to practice in multiple states. The ease with which health care providers have been able to obtain licensure, albeit temporary in most instances, has relieved an obstacle many health care providers have faced when looking to practice in multiple states, and many health care professionals and their allies are not eager to revert to the "old licensure system." For example, a bill introduced by U.S. Rep. Ted Yoho, R-Fla., would imperil funding for states that do not join the Interstate Medical Licensure Compact within three years.[9] Short of a legislative shift, licensure will remain a barrier for health care providers looking to practice in multiple states, which, in turn, will continue to be an issue for sponsors hoping to employ the decentralized clinical trial model.

Prescribing

Before prescribing approved or experimental medications, a physician must have formed a physician–patient relationship. State laws govern whether and how this relationship may be formed via telehealth. For example, in Idaho, as long as the proper standard of care is satisfied, Idaho's Telehealth Access Act allows the establishment of a valid physician–patient relationship via telemedicine.[10] Use of two-way audio or audio–visual interaction is required for forming the physician–patient relationship.[11] In addition, the applicable Idaho community standard of care must be satisfied.[12] A principal investigator looking to enroll a patient who is located in Idaho into a trial that requires prescribing will have to conform to the state's requirement that a two-way audio or audio–visual interaction is utilized, and he or she must be aware of and conform to any applicable Idaho community standard. Failure to adhere to these practice standards could lead to issues with the state's medical board.

Clinical trials that include the use of controlled substances have an even more complicated set of laws that must be considered. For example, in addition to needing to obtain a separate Drug Enforcement Administration (DEA) registration for each state in which he or she prescribes controlled substances,[13] the Ryan Haight Act and its implementing regulations require a practitioner to conduct at least one in-person medical evaluation of the patient before remote prescribing any controlled substances.[14] Once the prescribing practitioner has conducted an in-person medical evaluation of the patient, the federal regulations do not set an expiration period or a minimum requirement for subsequent annual re-examinations. While there are some exceptions to the in-person exam requirement, none apply to a direct-to-patient service where the patient is at his or her home, which is clearly the most relevant context for decentralized clinical trials.[15] The DEA is currently drafting a proposed rule (expected to be published later this year or early next year) that will create a special registration process allowing physicians to remotely prescribe controlled substances without an in-person exam, regardless of the patient's location.[16]

The DEA waived certain requirements during the declared public health emergency. Effective March 25, 2020,

DEA-registered practitioners are not required to obtain additional registration(s) with DEA in the additional state(s) where the dispensing (including prescribing and administering) occurs, for the duration of the public health emergency declared on January 31, 2020, if the physician is authorized to dispense controlled substances in both the state in which a practitioner is registered with DEA and the state in which the dispensing occurs.[17] Practitioners, in other words, must be registered with DEA in at least one state and have permission under the relevant state law to practice using controlled substances in the state where the dispensing occurs.[18]

In addition to the registration waiver, during the public health emergency, U.S. DEA-registered practitioners may issue prescriptions for schedule II–V controlled substances to patients for whom they have not conducted an in-person physical examination, provided that:

- The prescription is issued for a legitimate medical purpose by a practitioner acting in the usual course of his or her professional practice.
- The telemedicine communication is conducted using an audio–visual, real-time, two-way interactive communication system.
- The practitioner is acting in accordance with applicable federal and state laws.[19]

DEA's relaxation of the initial in-person exam requirement is a welcome change to the telemedicine community and for those interested in utilizing a decentralized clinical trial model for a trial that utilizes controlled substances either as part of the standard of care or as an experimental agent.

Federal regulation of controlled substance prescribing is only part of the legal and regulatory landscape that must be considered when contemplating use of a decentralized clinical trial that includes controlled substance prescribing. State laws also must be consulted, and some states have a more proscribed approach to controlled substance prescribing than DEA. For example, in Florida, a telehealth provider may not use telehealth to prescribe a controlled substance unless the controlled substance is prescribed for the following:

- The treatment of a psychiatric disorder;
- Inpatient treatment at a hospital licensed;
- The treatment of a patient receiving hospice services; or
- The treatment of a resident of a nursing home facility.[20]

Depending on the location of a clinical trial subject or the ailment being addressed in the clinical trial, Florida may or may not be a viable option for seeking study subjects. State laws, therefore, must be consulted before enrolling study subject for clinical trials that will include controlled substance prescribing. Additionally, sponsors and principal investigators will want to follow the action of DEA with respect to registration requirements and the traditional initial in-patient visit requirement.

Informed Consent

Most sponsors and principal investigators think about FDA regulations and 21 CFR Part 50 specifically when thinking about informed consent. Many state laws, rules, and/or medical board guidance require a telemedicine physician to obtain a patient's informed consent with respect to receiving care via telehealth. These laws and rules typically require the telehealth provider to inform the patient concerning the treatment methods and limitations of treatment using a telehealth platform and, after providing the patient with such information, to obtain the patient's consent to provide telehealth services. Moreover, some states have explicit requirements that the telehealth provider instruct the patient concerning appropriate follow-up care in the event of needed care related to the treatment.

Often, these consents must be documented in the medical record. For example, Alaska's medical board regulations

adopted by reference the Federation of State Medical Boards (FSMB), Model Policy for the Appropriate Use of Telemedicine Technologies in the Practice of Medicine, dated April 2014 (the "FSMB Policy"). The FSMB Policy provides that evidence documenting appropriate patient informed consent for the use of telemedicine technologies must be obtained and maintained. Appropriate informed consent should, as a baseline, include the following terms:

- Identification of the patient, the physician and the physician's credentials;
- Types of transmissions permitted using telemedicine technologies (*e.g.*, prescription refills, appointment scheduling, patient education, etc.);
- The patient agrees that the physician determines whether or not the condition being diagnosed and/or treated is appropriate for a telemedicine encounter;
- Details on security measures taken with the use of telemedicine technologies, such as encrypting data, password protected screen savers and data files, or utilizing other reliable authentication techniques, and potential risks to privacy, notwithstanding such measures;
- Hold harmless clause for information lost due to technical failures; and
- Requirement for express patient consent to forward patient-identifiable information to a third party.

An unsuspecting decentralized clinical trial sponsor and/or principal investigator could very easily overlook the need to provide a telehealth informed consent in addition to an informed consent that is specific to the clinical trial and the procedures therein.

Conclusion

COVID-19 ushered in a new day for health care delivery, including the ways in which clinical trials are conducted. Many of the relaxed practice standards employed for the purpose of treating COVID-19 patients have had the unintended consequence of breaking down barriers that once seemed insurmountable to those interested in utilizing decentralized clinical trials. Where we once had little data to demonstrate the efficiencies gained and the effectiveness of decentralized clinical trials, COVID-19 has allowed sponsors and principal investigators to explore this relatively novel way of conducting clinical trials. Perhaps the successes enjoyed by sponsors and investigators leveraging decentralizing clinical trials will be yet another pressure point for regulators as they consider the legal and regulatory landscape of our post-pandemic world as it relates to issues such as licensure and telehealth practice standards.

Endnotes

1. Pfizer, Pfizer Conducts First "Virtual" Clinical Trial Allowing Patients To Participate Regardless Of Geography (June 7, 2011), *www.pfizer.com/news/press-release/press-release-detail/pfizer_conducts_first_virtual_clinical_trial_allowing_patients_to_participate_regardless_of_geography*.
2. *See* Statement for Reasons for Issuing Emergency Rules Pursuant to Ala. Code § 41-22-5)b)(1), *www.alabamapublichealth.gov/legal/assets/order_emergencycert_qualification_032220.pdf*.
3. *Id*.
4. Emergency License (Dec. 12, 2020), *www.alabamaadministrativecode.state.al.us/ER/ER-JAN-21/MLIC%20545-X-2-.09%20ER.pdf*.
5. *Id*.
6. *See* Fla. Stat. § 456.47(4).
7. *Id*.
8. Interstate Medical Licensure Compact, *www.imlcc.org/*.
9. *See* HR 8723, *www.congress.gov/bill/116th-congress/house-bill/8723?s=1&r=25*.
10. *See* Idaho Code Ann. § 54-5705, which was amended by H.B. 342, effective July 1, 2020.
11. *Id*.
12. *Id*.
13. *See* 21 U.S.C. § 822(a)(2); 21 U.S.C. § 802(21), 823(f).
14. *See* 21 C.F.R. Part 1300, 1301, 1304, et al.; *see also* 74 FR 15596 (April 6, 2009); 21 C.F.R. § 1300.04(f); 21 U.S.C. § 829(e)(2)(B).
15. *See* 21 C.F.R. § 1300.04(i).
16. *See* 21 C.F.R. 1300.04(i)(5).
17. U.S. Department of Justice, DEA Registrants, *www.deadiversion.usdoj.gov/GDP/(DEA-DC-018)(DEA067)%20DEA%20state%20reciprocity%20(final)(Signed).pdf*.
18. *Id*.
19. DEA, COVID-19 Information Page, *www.deadiversion.usdoj.gov/coronavirus.html*.
20. *See* Fla. Stat. Ann. § 456.47.

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