



Call to Action: Facilitating Multi-Site, Multi-State and Decentralized Clinical Trials (DCTs)

Telehealth has provided life- and health-saving opportunities, in particular during the current pandemic. In addition to clinical opportunities, developed telehealth technologies and capabilities allowed clinical trials to continue during this same period of time. Both telehealth for health care and the use of telehealth modalities for clinical trials suffer from the arbitrary lines of state borders and the multiplicities of licensure laws, regulations, and other laws relating to informed consent, use of genetic information, etc.

Background

One of the major problems in the recent COVID-19 vaccine trials was the lack of our ability to quickly recruit and retain diverse populations in the research, highlighting the importance of a nation-wide, and inclusive approaches to multi-State trials. Addressing health equity in clinical research is an imperative for social reasons as well as to allow for representative enrollments and the ubiquity of research findings. Having a simplified approach to multi-State research trials is requisite to making progress towards equity in clinical trials, which is an important component of a future state of health equity in America.

Multi-site, multi-State and decentralized clinical trials (DCT) can address this problem, especially through the use of telehealth and other digital health technologies. However, there are a number of issues acting as regulatory roadblocks to these initiatives. Greater transparency or exemption from state and local regulations regarding variability in the informed consent process requirements, privacy variations, and the differences in distributing and dispensing of medications is needed.

A major challenge to implementing widespread DCTs and even multi-State trials is the myriad of State laws or regulations that impact the conduct of clinical trials, including variable requirements for obtaining and documenting informed consent, privacy, and limitations on drug dispensing that make it difficult for sponsors, research sites, Institutional Review Boards (IRBs), participants, and others involved to identify and track these requirements. For example:

- Regarding informed consent, 45 CFR 46.101(f) states, *“This policy does not affect any state or local laws or regulations (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects.”* 45 CFR 46.101(f) also requires that *“local”* issues be considered by the IRB, but there is no description of *“local”* in 45 CFR 46.102.
- Further, current differences in state requirements for informed consent range from age of majority (Alabama Code 26-1-1) to who can consent a patient into a trial involving an investigational product (Pennsylvania Act 135), to the California requirements for a separate California Bill of Rights for Research Participants and the separation of the HIPAA Authorization form the Informed Consent document. NOTE: While there was an amendment in 2021 to the 2017 Pennsylvania law that requires the subject’s provider to consent the subject for experimental research drugs and devices, the change in law allows the provider to delegate, but that delegation is limited to other physicians (resident/fellows), physician’s assistant, certified registered nurse practitioner, or registered nurse. This still restricts who can obtain informed consent.
- Current state differences in privacy laws and regulations range from disclosure of genetic results to laws on reporting HIV status.
- The Cooperative Research Provision in 45 CFR 46.114 requires a single IRB in multi-site trials, where practicable, and holds the IRB accountable for regulatory mistakes. This provision was enacted to improve trial start up efficiency and reduce burden on investigators. The intent was to speed up the



Health. Virtually. Everywhere.

approval process to enable trials to more quickly recruit, enroll, and find solutions to medical problems while decreasing the multiple hurdles investigators were being asked to jump over by various, often opposing, IRB viewpoints. IRBs that agree to serve as single IRBs must have a way to validate the State law information provided by local facilities, or the IRB has to attempt to search for the information and interpret it on their own to decrease their risk. This is a current burden and therefore a deterrence for single IRB review when finding State/tribal laws or regulations are not from centralized and validated sources.

Decentralized clinical trials are multi-site, multi-State projects intended to be coordinated from a single institution. According to the Code of Federal Regulations (CFR) Title 21 312.40(c), products identified by the FDA as an investigational new drugs (IND) can be shipped across state lines if the investigator receiving the drug is named on the IND application. State laws requiring in-state investigators runs counter to the purpose of DCTs. There is no such shipping provision for FDA approved drugs being used in research, such as in post-marketing studies. In these cases, many States may require registration of marketed drugs being used for post-marketing studies. In effect, state laws differ and may provide exemptions, though these laws do change over time.

State regulations also impact logistical complexity of conduct of a clinical trial, including who can receive the investigational product, whether you are engaging an institution (based on the U.S. Department of Health and Human Services (HHS) Office of Human Research Protection guidance on engagement), and how to handle invasive clinical trial procedures, such as IV infusion.

The Problem

The implementation of multi-site, multi-State clinical trials (including the District of Columbia, and US territories) is thwarted by the variation in and lack of transparency of Federal, State, and local laws. The Department of Health and Human Services' (DHHS) U.S. Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP), the two major federal institutions responsible for the policies that govern the conduct of clinical trials, are not aligned in their policies and guidance affecting multi-site, multi-State trials which causes even further confusion and regulatory risk.

A Proposed Solution

State laws vary widely regarding multiple aspects of the implementation and conduct of research trials. In order to minimize these risks, three solutions are proposed, which are not mutually exclusive:

1. Development of a Federally-created and maintained authoritative resource of State and local (including tribal) laws impacting the requirements for informed consent, HIPAA Authorizations and Waivers and other applicable regulatory requirements for the processes involved in clinical research.
2. A Federal-level exemption of multi-State clinical research from State and local (including tribal) laws impacting informed consent requirements and other applicable processes involved in clinical trials.
3. The Federally-sponsored creation of a nationally recognized set of acceptable standards under which multi-State trials can be conducted.

To fully facilitate multi-state and DCT research, and ensure more equitable participation in clinical trials, clinical research must be able to work across states with ease. This is facilitated through telehealth.

Therefore, the ATA requests that HHS consider a long-term solution of providing guidance (or a safe harbor) that allows multi-state clinical trials be exempt from particular state requirements with a federal minimum standard enacted. This would be the most efficient strategy. In the meantime, there is an urgent need to clarify applicable state and "local" laws and regulations that are relevant to multi-state clinical research.



Health. Virtually. Everywhere.

The ATA further proposes that HHS, in addition to their current international registry, create and maintain a registry of State, local and tribal laws and regulations that impact the conduct of clinical trials, for the following reasons:

1. **Precedent:** HHS has created a registry of international regulations, so a precedent has been set and a platform already in place.
2. **Clarity:** A transparent approach will clarify what actions need to be taken in which states/tribes to ensure compliance. A federal source would identify to what level “local” considerations must be included and a federally-created and maintained source will provide security to the research community.
3. **Centralization:** A registry of state, local and tribal laws impacting informed consent and other applicable procedures in clinical trials will create better security for single IRBs, help streamline other clinical trial functions, and provide timely recruitment and results for clinical trials.
4. **Risk Reduction:** One source of truth will reduce the burden on investigators, IRBs, and clinical trial organizations which decreases the risk of non-compliance.
5. **Consistency:** Establishing consistency supports an IRB’s cooperative research provision, allowing for one central place to verify state rules. This will facilitate consistency in state regulations and will shine a light on states/tribes that have burdensome or lax rules.
6. **Patient Recruitment:** Identifying burdensome state, local, and tribal laws and regulations that pose a challenge for patient recruitment and consent will enable better representation of HHS beneficiaries and create better access to underrepresented groups.

¹ McIntyre, Chelsey PharmD Regulations Regarding Interstate Shipment of Investigational Drugs
<http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.1005.2295&rep=rep1&type=pdf>

About the American Telemedicine Association

Telehealth and remote patient monitoring (RPM) will play an important role in advancing decentralized technology-driven clinical trials and eliminate existing barriers to participating in research studies. The American Telemedicine Association (ATA) has convened the Decentralized Clinical Trials Special Interest Group (SIG) to enable equal access to clinical trials by leveraging telehealth and virtual care technologies.

As the only organization completely focused on advancing telehealth, the ATA is committed to ensuring that everyone has access to safe, affordable, and appropriate care when and where they need it, enabling the system to do more good for more people. The ATA represents a broad and inclusive member network of leading health care delivery systems, academic institutions, technology solution providers and payers, as well as partner organizations and alliances, working to advance industry adoption of telehealth, promote responsible policy, advocate for government and market normalization, and provide education and resources to help integrate virtual care into emerging value-based delivery models. www.americantelemed.org