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DEMOCRATIZED CLINICAL TRIALS: REDUCING REGULATORY BURDEN AND ENSURING COVERAGE

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Summary

Clinical trials in the United States face two significant barriers that slow recruitment and limit participation, particularly among underserved populations: burdensome administrative requirements and inconsistent Medicaid coverage. This restrictive regulatory environment makes trials especially difficult to conduct outside of major academic medical centers, limiting patient access and increasing costs. Federal regulators and payors such as the Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), and Centers for Medicare & Medicaid Services (CMS) can address these challenges by streamlining investigator documentation requirements and improving Medicaid coverage for clinical trial participation across state lines.

Challenge and Opportunity

Clinical trials generate the high-quality evidence needed for regulatory decisions, physician and patient treatment selection, and the allocation of scarce healthcare system resources. Unfortunately, the current US clinical trial system inadequately serves all three of these stakeholders. Clinical trials are expensive, difficult and slow to carry out, and are not representative of the broader population. Over time, the administrative burden involved in clinical research has grown, and persistent gaps in Medicaid coverage for routine costs of care deter providers from participating in research.

The gap between routine medical care and clinical research has grown unnecessarily wide. Clinical trials require extensive documentation, specialized training, and complex oversight systems that create substantial administrative overhead. A typical trial may utilize many (20+) separate software systems for tasks like data collection, randomization, drug supply management, and safety monitoring - even though much of this information is already being collected through normal medical practice or insurance claims. This redundancy extends to personnel requirements, with extensive training needed for investigators and staff, along with multiple layers of institutional review and approval. These administrative requirements not only increase expenses but also create barriers to entry for healthcare facilities that lack dedicated research infrastructure.

Highly experienced institutions with longstanding involvement in trials continue to carry out clinical research effectively but the majority of patients do not receive care in those settings. In community hospitals and clinics, vague federal guidance leads to overly cautious implementation, while clinical staff must do double-duty as research staff—which requires training and the documentation of such training. This regulatory burden imposes disproportionate costs on less-resourced settings.

The need for more "real-world" clinical trials has been recognized at the highest levels of the FDA, with both Commissioner Califf[1] and then-Principal Deputy Commissioner Woodcock[2] publicly advocating for more trials in those settings. As a previous IFP piece has argued (reproduced below), the UK RECOVERY trial is an exemplar of such an approach:

> There are rigorous and cost-effective clinical trials that can serve as guideposts. RECOVERY[3] (Randomised Evaluation of COVID-19 Therapy) is a UK-based trial, begun in March 2020, that tested 18 different treatments for COVID-19 on 49,000 patients across 186 hospitals and found four effective therapies, at a cost of roughly $500 per patient. This is almost 80x cheaper than cost estimates of pivotal trials of new therapeutics[4], which are around $41k per patient. This was not the result of a cost advantage of repurposing old drugs: RECOVERY tested generic drugs (dexamethasone, hydroxychloroquine); repurposed drugs (tocilizumab, baricitinib); and novel unlicensed drugs (monoclonal antibodies). In addition, these were tested across "high-risk" populations that are normally difficult for trials to reach: pregnant women, neonates, the very elderly, and the immunosuppressed.
>
> What are the lessons of the RECOVERY trial?
>
> - Define the key study question(s) and focus on those things that are critical to answering the question reliably.
> - Integrate the trial into the clinical care pathway: Minimize the additional burden for front-line clinical staff and for participants (anyone can design a trial that nobody can do; the trick is to design a trial that anyone can do).
> - Take advantage of information that is already being collected as part of routine healthcare and where possible, make use of linkage to routine healthcare data (e.g. claims data, national death registry) to minimize loss-to-follow-up even when participants leave hospital or move to another medic.
>
> RECOVERY was not exclusive to the UK National Health Service (NHS) — over 1,500 participants were enrolled in Asia and Africa, with Nepal contributing nearly 1,000 patients — proving it is not necessary to have a single-payer system like the NHS to make such trials successful.

1 https://jamanetwork.com/journals/jama/article-abstract/2819603

2 https://www.nejm.org/doi/full/10.1056/NEJMp2107331

3 https://www.recoverytrial.net/

4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7295430/

A prime example of unnecessary administrative complexity is Form 1572[5], which requires investigators to document all staff involved in a clinical trial. While seemingly straightforward, the FDA estimates that completing this two-page form takes approximately 100 hours per response. The burden compounds with each protocol amendment, as training documentation must be updated, and with each addition of personnel or facilities, which requires new financial disclosures. Less experienced institutions, erring on the side of caution, often interpret these requirements expansively - documenting even routine care providers who are merely performing their usual duties. This creates a particularly heavy burden for community hospitals and clinics that lack dedicated research staff and infrastructure.

In the US context, one way to capture a more representative participant population is expanding access to trials for Medicaid recipients. The Clinical Treatment Act of 2020[6], which requires state Medicaid programs to cover routine costs for trial participants, has had some success[7], but still faces implementation challenges. Per American Society of Clinical Oncology (ASCO), as of January 2023, 47 states and DC[8] had enacted state plan amendments (SPA) that outline how each state will do so. However, significant barriers[9] remain for both providers and patients. Medicaid's state-by-state administration creates particular challenges for multi-state trials, as providers must navigate enrollment in multiple state programs. The requirements to complete Medicaid enrollment before offering trial services can delay or prevent patient participation entirely, likely deterring some research sites from accepting Medicaid patients.

Plan of Action

Recommendation One: the FDA should streamline Form 1572, which has become increasingly burdensome over time, and harmonize its language with that of OHRP.

Two recent FDA draft guidance documents, *Conducting Clinical Trials With Decentralized Elements*[10] and *Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice*[11], do move in this direction, by clearly stating that health care providers who are merely performing routine clinical care, do not need to be listed as investigators or subinvestigators. However, there are still some remaining issues, specifically relating to labs and imaging centers:

- In 2024, the American Society of Clinical Oncology (ASCO) organized a stakeholder group that specifically[12] lists three sections (Fields 3, 4, 6) as ones that unduly burden investigators and require clarification. **FDA and the Office for Human Research Protections (OHRP) should state that laboratories, and imaging centers that are providing routine medical services, no different than their usual medical practice, are not required to be listed on Form 1572.** Harmonizing Form 1572 and OHRP provisions on what qualifies as a site engaged in research would also simplify matters.
- The ASCO group also recommends **exempting laboratories from requiring registration with Form 1572**, since they are already subject to oversight by the federal government through Clinical Laboratory Improvement Amendments (CLIA). This change would allow participants to use their local hospital and lab instead of traveling hours to specific locations, reducing the burden on participants in rural areas.

5 https://www.fda.gov/media/71816/download

6 https://www.congress.gov/bill/116th-congress/house-bill/913#:~:text=This%20bill%20requires%20state%20Medicaid,or%20other%20life%2Dthreatening%20conditions.

7 https://ascopubs.org/doi/10.1200/JCO.23.01149

8 https://society.asco.org/news-initiatives/policy-news-analysis/47-states-have-implemented-clinical-treatment-act-increasing

9 https://www.manatt.com/Manatt/media/Media/PDF/trials-and-tribulations.pdf

10 https://www.fda.gov/media/167696/download

11 https://www.fda.gov/media/181871/download

12 https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.35145

Recommendations Two: CMS needs to ensure that Medicaid coverage for clinical trials is easier to access. The Clinical Treatment Act, passed in December 2020, was meant to ensure that all state Medicaid programs would cover and reimburse the routine costs of care associated with treating a Medicaid recipient who is participating in a clinical trial.

However, there are problems[13] with implementation that still hinder enrollment of Medicaid recipients in trials: 1) out-of-state providers treating Medicaid patients must enroll in multiple Medicaid state programs to receive payments for their services; 2) states require providers to complete enrollment prior to offering clinical trial services. To fix these, CMS should:

- Require state medicaid programs to implement expedited enrollment pathways for out-of-state providers.
- Require state Medicaid programs to allow providers to complete enrollment after providing clinical trial services, perhaps with a 30-day provisional authorization.

Conclusion

Reducing administrative burden and ensuring Medicaid coverage access for trial costs are essential steps toward a more efficient and representative clinical trial system in the United States. By streamlining Form 1572 requirements and removing barriers to Medicaid coverage, federal regulators and payors can help expand clinical research beyond academic medical centers into community settings where most Americans receive care.

13 https://www.manatt.com/Manatt/media/Media/PDF/trials-and-tribulations.pdf

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