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An Institutional Program to Increase Compliance with [Clinicaltrials.gov](https://clinicaltrials.gov) Requirements

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Abstract

Recent National Institutes of Health policy changes have expanded the number of research studies that must be registered in clinicaltrials.gov beyond the requirements of the Food and Drug Administration Amendments Act of 2007. The International Committee of Medical Journal Editors has also adopted a policy that requires registration of research in a public database. The goal was to increase the transparency of research by reporting the original endpoints of a study, and to discern whether primary endpoints were excluded in subsequent publications. Efforts to increase openness and accountability in clinical trials are likely to strengthen public trust. However, first investigators and study staff must be educated about the requirements, and staff must be prepared to offer support to researchers in navigating the clinicaltrials.gov system. For academic institutions, maintaining compliance requires continuous oversight so that problems can be identified centrally and addressed with investigators. At Wake Forest University Health Sciences, because researchers often did not realize they were out of compliance, we implemented a program to assist them and provide oversight. We introduced standard operating procedures, provided education and assistance to investigators, and engaged leadership about consequences of compliance, resulting in increased budget support for a full-time employee in this role. As a result of these changes, compliance increased from 22% to 92% over 4 months. These approaches may help other institutions become compliant with registration requirements more quickly.

Keywords

Registry; Outcomes reporting; Data transparency; Disclosures; [Clinicaltrials.gov](https://clinicaltrials.gov)

In September 2016, the National Institutes of Health (NIH) published the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information; at the same time, the U.S. Department of Health and Human Services issued the Clinical Trials Registration and Results Information Submission Final Rule¹. This policy expands the clinical trial

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registration requirements beyond those of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and Final Rule to include any NIH-funded study that prospectively assigns participants to an intervention with pre-specified health-related biomedical or behavioral outcomes². These changes were designed to increase transparency in how NIH research funds are spent, improve the quality of NIH-funded clinical trials, and make available the information necessary to prevent duplication of research and the accompanying risks for participants³. These aims are important for ensuring that the money and effort expended in clinical trials is tightly focused on new ideas with the potential to build on existing knowledge.

The International Committee of Medical Journal Editors (ICMJE) incentivized academic investigators to register trials with clinicaltrials.gov by requiring, as a prerequisite to manuscript publication, that clinical trials be publicly registered before the first participant is enrolled. Nonetheless, nearly one-third of clinical trials are registered more than 3 months after their start date⁴. Late registration deprives the public of an opportunity to participate in clinical trials, and may introduce doubt about the accuracy of stated outcome measures. On the other hand, benefits of prospective registration include more confidence in integrity of the results, since primary and secondary outcomes must be described before a study begins. There is consensus that no one is well served when clinical trials are registered late, or not at all.

Reporting of results in clinicaltrials.gov has been even more problematic than registration. In 2015, only 13.4% of registered trials reported their results within 12 months, and only 38.3% ever reported any results⁵. Registered trials with no outcomes data will not reduce duplicative studies, or help to protect research participants from unnecessary risks. In addition, registered clinical trials with no reported results do not honor the expectations of research participants who want their actions to contribute to medical knowledge. Ultimately, such disappointments harm public trust in health care research^{5,6}. In 2014, Guharoy wrote that:

... more stringent and strongly enforced registration requirements will likely be necessary to decrease the incidence of incomplete reports, catch retrospective changes to study results, and increase the reporting of important findings that may otherwise go unnoticed.

The final rule and new NIH Policy on Dissemination of NIH-Funded Clinical Trial Information became effective on January 18, 2017, and compliance with the Final Rule was required by April 18, 2017. In the wake of these changes, the research community also has become more aware of the risks of not complying with clinicaltrials.gov requirements. Unfortunately, institutional assistance and education on how to avoid the penalties of non-compliance has not kept pace with developments.

At Wake Forest University Health Sciences (WFUHS), we took this opportunity to re-evaluate institutional practices and reach out to investigators about the importance of clinicaltrials.gov registration and reporting. When we reviewed our compliance with clinicaltrials.gov requirements at the end of 2016, we found 529 records in the registry from WFUHS components. Our total compliance with the FDAAA was low (22%), and 98% of

records had some sort of problem. Problems ranged from never-released records, those without reported results, and records with comments from clinicaltrials.gov reviewers that required a response. Another challenge was that WFUHS activities were captured in four separate accounts within clinicaltrials.gov. To begin the process of developing our navigation program, first we created an overarching WFUHS account encompassing the four separate ones.

We then calculated the financial risk WFUHS faced from non-compliance. By educating institutional leaders about the risk of monetary penalties that noncompliance brings, we received support to add a full-time staff member focused completely on clinicaltrials.gov. We also enlisted the support of the Vice-President for Research Administration and Operations, the Institutional Review Board, and the Office of Clinical Research to help educate researchers on the new regulations and the importance of ensuring that records were updated and correct.

Next, we created a new standard operating procedure (SOP) to explain to investigators how they can manage their own clinicaltrials.gov records, and how to get assistance with registration and updates. We also sent individual emails and made phone calls to investigators whose records were not compliant, and offered help resolve issues. As a result of these combined efforts, we reached 92% compliance with the Food and Drug Administration Amendments Act (FDAAA) within 4 months (Figure 1).

As we worked with investigators, we learned that most thought they were in compliance, even when they were not. Some were unaware of steps they needed to take to release records; others did so, but were unaware of any additional requirements.

Because of frequent changes in the status of records as clinical trials begin, reach various milestones, and end, institutional compliance levels must be monitored continuously. The academic community has an interest in supporting the goal of clinicaltrials.gov to allow scientists to focus on areas of promise and avoid wasteful repetition of unsuccessful research³.

Enforcement of outcomes data reporting in clinicaltrials.gov could increase public trust by reducing biased reports and publications of results^{7,8}. Allowing comparisons of published results with endpoints in clinicaltrials.gov introduces more accountability and encourages greater overall transparency. Outcomes data reporting also helps to reduce the knowledge gap caused by results that are never published^{9,10}. Finally, reporting opens up new possibilities in scientific discovery. For example, text mining of adverse events in clinicaltrials.gov for potential new uses of existing drugs or other ways to improve public health is a future way to use the valuable data in clinicaltrials.gov¹¹.

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Figure 1.
Compliance with FDAAA shown as % of complete records in clinicaltrials.gov.