Research paper

Overcoming non-compliance with clinical trial registration and results reporting: One Institution's approach

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ABSTRACT

ClinicalTrials.gov is a web-based resource which provides the general public, healthcare professionals, patients, and caregivers access to privately and publicly supported clinical trials and trial results. The web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) (ClinicalTrials.gov Background, 2018). The penalties for non-compliance with the legal obligations under FDAAA 801 (Food and Drug Administration Amendments Act of 2007) and the NIH requirements for registering and reporting results on studies within certain timeframes can result in large monetary fines and the withholding of federal funds (ClinicalTrials.gov FDAAA 801 and the Final Rule, 2019). Years following, in 2016, the Final Rule expanded upon the requirement with additional data elements for both registration and result submission records in accordance of FDAAA 801 (ClinicalTrials.gov FDAAA 801 and the Final Rule, 2019).

The Medical University of South Carolina (MUSC), along with the institution's Office of Clinical Research and Regulatory Knowledge & Support group, identified issues affecting their own compliance rate with FDAAA 801 and the NIH and implemented several processes to overcome these challenges. In short, these processes included hiring a designated full-time ClinicalTrials.gov coordinator, implementing a workflow that identifies trials early in the IRB approval process requiring registration (without effecting study start up timelines), assisting researchers when navigating the registration and results reporting process through one-on-one consultations, Lunch and Learns, and disseminating new training tools as they become available.

Over the next 12 months the results of this approach demonstrated a marked increase to 98% overall compliance with these federal regulations which may provide valuable guidance for other institutions working toward improved compliance rates.

1. Introduction

ClinicalTrials.gov is a web-based resource managed by the National Institutes of Health (NIH) and the National Library of Medicine. This public website, originally launched in 2000, provides the general public, healthcare professionals, patients, and care givers access to privately and publicly supported clinical trials [1]. The registry was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA 113), a law passed by Congress that required the NIH to create a public information resource on trials regulated by the FDA including those which involved Investigational New Drug trials for serious or life threatening diseases. The intent of FDAMA 113 was to provide more transparency of research conducted, as well as providing accessibility to the public ClinicalTrials.gov [2]. Adoption of these obligations was slow; a mere 1255 trials were registered within the first year after launch of the website in 2000 [3].

The number of trials registered in ClinicalTrials.gov markedly increased in 2005 after the implementation of the International Committee of Medical Journal Editors (ICMJE) policy that required studies to be registered in order to be considered for publication [4]. In addition, Congress passed FDAAA (Food and Drug Administration Amendments ACT) in 2007, which ultimately expanded the types of studies requiring registration, and the submission of a results record [5].

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Reported compliance with the mandate has been generally poor [6] and when results reporting requirements are fulfilled, they are oftentimes not done so within mandated timeframes [7]. The definition of compliance varies as there are several obligations and timing requirements for both registration, ongoing record maintenance and results reporting. A recent analysis of registered clinical trials reported only 13% compliance with timely reporting of data (Anderson et al., 2015). Failure to meet the obligations of the FDAAA prevents achievement of the overall goal of the mandate, to improve transparency regarding clinical trials, but also risks substantial financial penalty, up to $12,103 per day [8] and loss of NIH funding [9].

The Medical University of South Carolina (MUSC), along with the institution’s Office of Clinical Research and Regulatory Knowledge & Support group established a goal of full adherence to the registration and reporting obligations of FDAAA and the requirements of the NIH Policy on the Dissemination of NIH funded Clinical Trials. Having the infrastructure in place to educate our researchers and provide the tools needed to ensure compliance with ClinicalTrials.gov is in alignment with the mission and objectives of the site’s Clinical & Translation Science Award (CTSA) award. The CTSA program is intended to develop innovative solutions that will improve the efficiency, quality and impact of research [10]. Historically, our institution entrusted compliance with these requirements to the individual investigator, but it has since recognized that additional support is necessary to achieve and maintain compliance. Through strategic planning, our intent was to develop and implement multiple workflows for the various facets of entering data into ClinicalTrials.gov, including study registration, record maintenance and results reporting to achieve this goal. Here, we describe the ClinicalTrials.gov Compliance Assessment Process, a mechanism that identifies studies requiring registration under our institution’s Protocol Registration System (PRS) account, as well as other services implemented to improve compliance with the study registration and results reporting.

2. Methods

2.1. Assembling the team

The Regulatory Knowledge & Support (RKS) program of the South Carolina Clinical & Translational Research Institute (SCTR), with an academic home at the Medical University of South Carolina (MUSC), developed and implemented a plan to resolve our institution’s low compliance rate in reporting. The process began with an audit of all of MUSC’s ClinicalTrials.gov records performed by the RKS core under the direction of the Associate Provost for Research Compliance and Regulatory Affairs. A full-time ClinicalTrials.gov coordinator was identified who was designated as the institution’s primary PRS administrator and tasked with overseeing institutional efforts to achieve and maintain compliance. Multiple avenues of training including utilization of online resources and attendance at an in-person 2-day comprehensive Train the Trainer workshop conducted at the NIH. Within six months, the coordinator was able to demonstrate sufficient mastery of the process and began managing the PRS and conducting consultations independently. In addition, our site participated in monthly meetings with the ClinicalTrials.gov Taskforce, a nationwide network of CTSA members, universities, medical centers, and nonprofit organizations that collaborate and share processes and approaches regarding ClinicalTrials.gov and the Protocol Registration System (PRS) [11].

2.2. Phase 1: identifying noncompliant trials

We performed an audit of our institution’s baseline compliance with reporting of data for registered trials using both the public-facing interface and internal PRS accounts. We identified duplicate studies, as well as studies entered in error, which were administratively withdrawn after consultation with ClinicalTrials.gov reviewers. The investigators of several trials had left the institution without delegating responsibility to another to assume record maintenance or results-reporting duties; these responsibilities were then assigned to the respective department chairs. In-depth review of records yielded issues that could have been prevented at the start of record registration, such as the description of outcome measures in a way that could not be understood during the results submission process, thus resulting in more PRS reviewer comments. We categorized studies according to their non-compliant status and established priorities based on the type of problem record and time elapsed relative to the reporting requirement. Our highest priority was to address completed studies with results more than one year past due followed by those that had not been updated in 12 months, or had an anticipated start date in the past.

2.3. Phase 2: implementing the ClinicalTrials.gov compliance assessment process

Following the compliance audit, a memo from the Associate Provost was sent via email to the entire research community at MUSC reiterating the importance of ClinicalTrials.gov compliance and informing that a project to improve the institution’s compliance was underway. Investigators with studies deemed out of reporting compliance (Phase 1) were then sent a customized email identifying specific studies requiring attention, how to address the outstanding issues, and where to find the resources if assistance was needed. All correspondence was signed by leadership (Associate Provost), with copies sent to the respective department chairs. Investigators could request a consultation for advice and assistance with ClinicalTrials.gov navigation through SPARRequest®, an open-source research services request and tracking system developed at MUSC [12]. SPARRequest® also serves as a repository for shared relevant study documents (protocol, informed consent documents) and a centralized system for communicating with study teams. We provided additional training to the research community through a variety of formats, including Lunch and Learns and one-on-one consultations.

The MUSC ClinicalTrials.gov coordinator position served as the primary resource for investigator training and consultation and developed standard operating procedures. This position was housed in MUSC’s Office of Clinical Research (OCR), facilitating collaboration with the various research support departments within the OCR. To reduce investigator burden, ensure review of all clinical research studies, and minimize the impact on study start-up, the ClinicalTrials.gov compliance assessment process was incorporated into the established study billing compliance review for all human subject research studies at MUSC.

During the ClinicalTrials.gov compliance assessment, the ClinicalTrials.gov coordinator reviewed study documents to determine the Responsible Party. The Responsible Party is the entity that registers the study, and submits results information. It could be either the sponsor of the trial, or the principal investigator designated by the sponsor, grantee, contractor, or awardee [13]. When it was determined that the MUSC or the MUSC Primary Investigator was the Responsible Party the ClinicalTrials.gov coordinator would notify the study team of potential registering requirements. A REDCap® database was developed to document the review, indicating whether the MUSC primary investigator or another institution was responsible for registering. Voluntary registration was sometimes encouraged because it could be necessary for publication purposes. For study teams needing further assistance with the registration process, the ClinicalTrials.gov coordinator initiated a record in ClinicalTrials.gov with basic study information, such as the unique protocol ID #, official study title, and study type. However, it was the responsibility of primary investigator to complete the record, maintain it through the life of the study, and report results as required by federal law.
2.4. Training and consultative resources

When it was determined the responsible party of the study was an MUSC investigator and ClinicalTrials.gov registration was necessary, investigators were offered one-on-one consultations. The ClinicalTrials.gov coordinator provided a brief background of the process, issued logins for new users attending the consult, and navigated through the various required sections of a record while entering study-specific information.

Consultative services are offered as a result of the compliance assessment but also to study team members who have been taking on the responsibility of record maintenance and the task of results reporting.

2.5. Escalation procedures

The ClinicalTrials.gov coordinator communicates regularly with study teams when updates are required within a specific record, in particular when a results record due date is approaching. If a study team is non-responsive, the ClinicalTrials.gov coordinator will include the Associate Provost for Research Compliance and Regulatory Affairs on email communications for additional support. If needed, the department chair will be included in all correspondence until the record update has been completed.

3. Results

Phase 1: The compliance audit was conducted in January 2018. MUSC was deemed the responsible party for 493 study records. Results revealed 403/493 (81.74%) noncompliant records led by investigators across various departments at MUSC, who were then notified of their obligations and encouraged to consult with the ClinicalTrials.gov coordinator. The remaining 90/493 records were identified as currently compliant, and 36/493 registered studies were administratively withdrawn because of duplication or error. Of the investigators with non-compliant records, 23 sought consultation. Anecdotally, post-consultation feedback was generally favorable. Investigators indicated that they valued the assistance as they struggled with the website used for the registration and reporting [14]. The compliance rate improved rapidly (Fig. 1), and within 15 months, resulted in an overall compliance rate of 98.6%, an increase from the 18.26% compliance rate identified before the audit began.

Phase 2: With compliance of registered studies well underway, focus then shifted to implementing the ClinicalTrials.gov Compliance Assessment workflow with the purpose of reviewing and identifying those trials requiring initial registration. Since integrating our parallel process along with the OCR billing compliance review, 367 trials have undergone a ClinicalTrials.gov compliance assessment and 31/367 trials (8.45%) were MUSC Investigator Initiated and required registration under the MUSC PRS account. Of those requiring initial registration nearly half (45%) of primary investigators or their designee utilized the training and consultative services that we provide.

As routine record maintenance was continuously performed, the escalation procedures were found to be helpful when problem records were identified. When leadership, or a department chair was included in correspondence, we found study teams responded quickly and the record was brought back into compliance.

4. Discussion

The research community has an inherent, ethical responsibility to ensure transparency with the public. This is important not only to facilitate access of clinical trial information for the public for study enrollment, but also to make available accurate and complete study results, be it positive, negative or inconclusive results. Consistent with what has been reported elsewhere, our investigators found meeting the requirements of ClinicalTrials.gov reporting to be challenging, resulting in a low overall baseline compliance rate. Nonetheless, adherence to the federal regulations is also critical. Failing to do so may not only result in civil and/or financial penalty, but may also impact grant funding as well as hamper the ability to publish findings. With an efficient workflow in place, we are not only fulfilling our responsibility to the public, but we are also providing the research community at MUSC the resources needed necessary while they are conducting research at our institution and beyond.

We recognized that investigators would need more than a reminder of their obligations, and together with our Regulatory Knowledge and Support Program, developed a highly collaborative consultation and support service that was ultimately integrated within the existing OCR workflow. Prior to reaching out to investigators, we systematically planned an approach to clearly identify the non-compliant records and establish priorities to achieve our goal of total compliance as efficiently as possible. Email communication from leadership was an effective approach. While we strived for 100% compliance, we could not foresee the individual challenges of each problem record. We then sought to advise and support the study teams accordingly. As a result of this strategy, the number of problem records under the MUSC PRS began to decrease.

Moving studies that were delinquent in reporting into compliance was the first major task, but our long-term aim is to sustain this level of compliance through continued monitoring and outreach by proactively identifying the studies requiring registration and working with the study teams to complete the records in an accurate and timely manner. Incorporating the ClinicalTrials.gov compliance assessment process into the established OCR workflow ensures that all human

![Fig. 1.](image-url)
subject studies at MUSC receive review without negatively affecting study start-up times. Offering consultations and consistent communication with the research community will also help us meet our long-term goal of maintaining high compliance. Promoting awareness of these processes is an important aspect of the program. We now track studies and send reporting notifications 90, 60, and 30 days before applicable due dates, escalating via research leadership when necessary. The notifications include links to training information and resources.

In conclusion, multiple lessons have been learned from this effort that may be instructive to other institutions who struggle with this same issue. First, a centralized, institutional approach was the most efficient manner for MUSC to ensure success with ClinicalTrials.gov registration and reporting requirements. Second, it is a vital to have a workflow in place to determine if a study needs to be registered by an MUSC investigator before the study begins enrollment in order to meet federal requirements, publishing expectations. Additionally, this ensures the public has informational access to clinical trials conducted at our site. Third, investigators have benefited from specific consultation, particularly related to best practice recommendations to cite clear and concise outcome measures required for registration to minimize later results reporting complications. Overall this multi-faceted, practical approach can be effective when ensuring compliance with trial reporting and results submissions, and ultimately achieves the overarching purpose of transparency and ethical obligations assumed by the research community.

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References

[1] ClinicalTrials.gov Background, Retrieved February 3, 2020, from (n.d.). https://clinicaltrials.gov/ct2/about-site/background.
[2] History, Policies, and Laws, Retrieved February 3, 2020, from (n.d.). https://clinicaltrials.gov/ct2/about-site/history.
[3] R. Williams, Celebrating 20 Years of ClinicalTrials.gov and looking to the future, NLM Musings from the Mezzanine, 2020, January 7 Retrieved February 3, 2020, from https://nlmdirctor.nlm.nih.gov/2020/01/07/celebrating-20-years-of-clinicaltrials.gov-and-looking-to-the-future/.
[4] n.d.Clinical Trials Registration, Retrieved February 10, 2020, from (n.d.). http://www.icmje.org/about/icmje/faqs/clinical-trials-registration/.
[5] Food and Drug Administration, Amendments Act of 2007. (Public Law No. 110-85 § 801, 2007.
[6] D.A. Zarin, T. Tse, R.J. Williams, R.M. Califf, N.C. Ide, The ClinicalTrials.gov results database – update and key issues, N. Engl. J. Med. 364 (2011) 852–860.
[7] A.P. Frayle, M.N. Hurley, A.R. Smyth, Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study, BMJ 344 (2012) d373-d373.
[8] Annual Civil Monetary Penalties Inflation Adjustment, Civil Monetary Penalty Authorities Administered by HHS Agencies and Penalty Amounts, 84, 2019 214 Reg. 59550/October 29, 2019 (to be codified at 45 CFR pts 102).
[9] (n.d.)NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, Retrieved February 8, 2020, from (n.d.). https://grants.nih.gov/policyclinical-trials/reporting/understanding/nih-policy.htm.
[10] n.d.PAR-18-940: Clinical and Translational Science Award (U54 Clinical Trial Optional), Retrieved February 8, 2020, from (n.d.). https://grants.nih.gov/grants/guide/pa-files/PAR-18-940.html.
[11] n.d.Mission, Retrieved September 17, 2019, from (n.d.). https://cttrtaskforce.org/mission.
[12] He, W., Sampson, R., Obieid, J., Hutson, K., Knosp, B., LaSalle, B. … Brady, K. (n. d.). Dissemination and continuous improvement of a CTSA-based software platform, SPARCRequest®, using an open source governance model. J. Clin. Transl. Sci., 1-7. doi:10.1017/cjts.2019.403.
[13] FDAAA 801 and the Final Rule, Retrieved March 1, 2020, from (n.d.). https://clinicaltrials.gov/ct2/manage-recs/fdaaa.
[14] A. Kent, Retrieved September 17, 2019 from (n.d.). https://scholarlykitchen.sphinx.org/2016/03/15/why-is-clinicaltrials.gov-still-struggling/.