

Understanding and Improving Clinical Trial Compliance

Mr Anthony Keyes

UNDERSTANDING AND IMPROVING CLINICAL TRIAL COMPLIANCE

Clinical trials are a cornerstone of modern medicine. Before drugs and other interventions can be prescribed to patients, their safety and efficacy must be established through rigorous, tightly regulated studies. **Mr Anthony Keyes** and a team of administrators from Johns Hopkins University have designed and implemented programmes and checklists to improve the regulatory compliance of trials at their institution. They have shared these resources through publications, national presentations and via the Clinical Trials Registration and Results Reporting Taskforce (Taskforce).

The Necessity of Clinical Trials

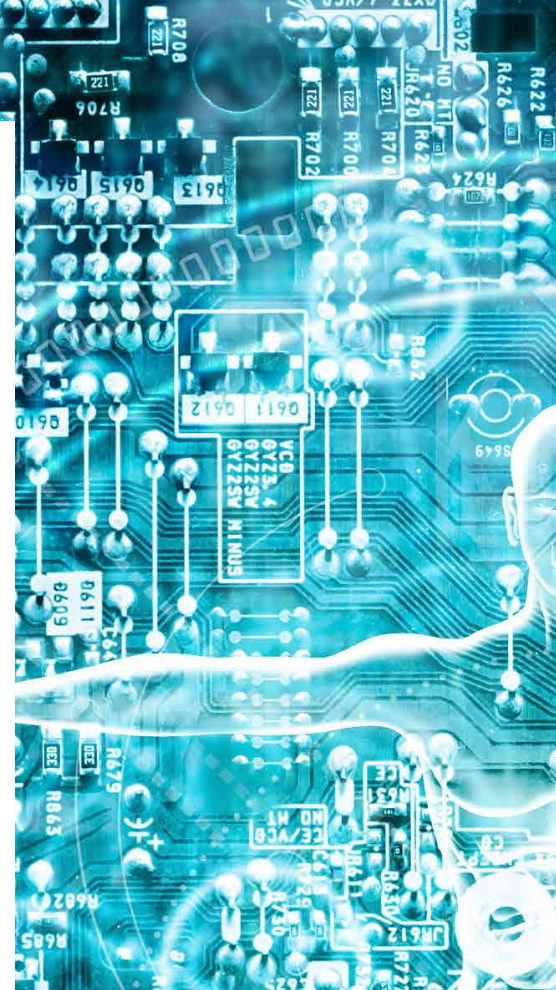
Clinical trials are medical research studies in which new treatments or interventions (e.g., drugs, behavioural interventions, devices) are tested and established to be safe and effective, and therefore, appropriate for patient use. Clinical trials can also determine if a new treatment is more effective or has fewer side effects than the current options. Due to their importance in influencing treatment, patient care and patient outcomes, clinical trials must be conducted to high and clearly defined standards.

There are three main stages of clinical trials, each with specific aims. Phase one trials involve a small number of healthy volunteers and focus on the treatment's safety. Phase two trials recruit more participants, including those with the condition targeted by the treatment, and have the goal of evaluating treatment efficacy as well as safety. Phase three trials are much larger and involve participants in multiple locations to obtain data on efficacy, side effects, and also compare the effects of the new product against existing

intervention(s) or placebo. To ensure clinical trials adhere to the highest standards of patient safety and ethical conduct, they are overseen by regulatory authorities and review boards. Mr Anthony Keyes leads the Johns Hopkins University ClinicalTrials.gov Program, dedicated to clinical trial transparency and maintaining a high compliance level with ClinicalTrials.gov requirements, and has also created resources to help other institutions improve efficiency and compliance.

Keeping Clinical Trials Safe

The US Food and Drug Administration (FDA) Modernization Act of 1997 led to the establishment of a registry of clinical trial information from both federally and privately funded trials for serious or life-threatening diseases. This led to the formation of ClinicalTrials.gov – an online registry and results database for clinical trial data. This platform shares information about all trials (including those considered 'failed', which are not typically published). By sharing information on negative outcomes, researchers can learn from the already 'tried and tested' avenues.



The FDA Amendments Act 2007 (FDAAA) subsequently required that all applicable clinical trials be registered within 21 days of patients being enrolled and that results be reported to the system within a year of the trial finishing. Low compliance with some of this legislation led to the implementation of the 'Final Rule' in 2017, which expanded on and clarified previous legislation. Under this, the FDA can issue civil monetary penalties for non-compliant trials up to 13,237 USD per study, per day.

A Survey of Clinical Trial Administration Support

Mr Keyes and a team from the Taskforce conducted a survey of standards in clinical trials reporting in America spanning from 2016 to 2017, before the Final Rule came into place. At this point, little was known about how academic organisations supported trial registration and reporting, and this was the largest and most comprehensive survey of organisations registering and reporting clinical trials on ClinicalTrials.gov.



The team identified 783 eligible accounts from universities and medical centres, which together contained over 47,000 clinical trial records (the median number of records per account was 7, although some accounts contained up to 1,563 records). Of these 783 accounts, 366 participated (47%) and provided enough information to be included in the survey analysis, representing 85% of all records.

Questions explored organisation characteristics, registration and results policies and practices, and staff and resources. Skip logic was used so participants only saw relevant questions based on their previous answers. The responses were automatically saved, and participants could return to the survey at any point – allowing them to discuss their answers with colleagues before submitting them to obtain a full and accurate response. Of the 366 accounts, 43% had a registration policy and 35% had a reporting policy. The team found that principal investigators were most often responsible for registering the trial. The survey highlighted that few accounts (19%) used computer software to manage their records. While 74% of people providing clinical trials administration had graduate degrees, the average number of full-time equivalent staff dedicated to managing clinical trial records was 0.08. Only 10% of respondents were planning to hire more staff for this.

The team was aware of direct and indirect participation bias in their study, which means their results might have overestimated the support available for trial registration and reporting at academic organisations. Participation may have been related to organisation resources – institutions with dedicated administrative staff would have had the capacity to take part, and those without the survey invitation may have been missed.

At the time, key findings were that most organisations assign the responsibility for trial registration and reporting to individual investigators and provide little oversight or support for this. The team suggests that organisations could take steps, including education, institutional procedures, provision of compliance software, and specific consequences for not cooperating to improve trial registration and reporting.

Further analysis and more recent data have revealed much has changed. Organisation policies are keeping up with changing guidelines, and there are statistically significant correlations between staffing size and the number of records. A follow-up survey has been launched, with plans to publish in early 2024.

Clinical Trial Support at Johns Hopkins University

The team's previous work highlights a lack of support for the registration and reporting of clinical trials at academic organisations. In early 2014, a principal investigator associated with the Johns Hopkins University School of Medicine received a notice of FDAAA non-compliance. Investigation into this by the institution, conducted by Mr Keyes, revealed over 300 other trials which were also potentially FDAAA non-compliant and could have resulted in institutional penalties of \$1 million per day.

From this point, Mr Keyes established a formal programme to support investigators in complying with clinical trial requirements. Mr Keyes joined the Clinical Trials Registration and Reporting Taskforce to communicate with peer organisations and access policies and resources. With University support, a clinical research compliance specialist was hired, and a programme to support clinical trial administration was implemented.



Credit: Anthony Keyes

This programme aimed to develop institutional ClinicalTrials.gov policies, develop a process for communication with investigators, identify and reduce problem records, and train investigators across the institution to meet registration and reporting requirements. At the beginning of the programme, 44% of trials at the institution were potentially non-compliant. The team revised existing policies to ensure they met the Final Rule and created standard operating procedures for staff to follow when registering and reporting to ensure standards were not only met but consistent across the institution.

A significant focus of the team's work was on communicating requirements to investigators. A system was set up to notify them by email if there was a compliance issue and included steps to remedy it. If the problem was not addressed, a further email was sent with the department director copied in. Phone calls and in-person visits were also made when necessary.

The team saw that investigators often required additional support to understand and meet the standards required, and worked to provide registration and results support at no additional cost to help bring the institution to standard. The team also offers voluntary in-person training sessions to help study teams maintain compliance and avoid penalties.

The programme has been incredibly successful, with FDAAA compliance rates going from 56% to 98% in five years. The team continues to focus on maintaining excellent standards at Johns Hopkins University and actively shares these resources and strategies with other institutions through the Taskforce to contribute to national best practices.

The Taskforce is an active consortium of members from academic medical centres, universities, hospitals and not-for-profit organisations who work together to maintain the highest possible standards of clinical trial transparency and compliance. They meet regularly to share resources such as educational materials and provide informal peer-to-peer education.

Mr Keyes co-leads the Taskforce along with Sarah White, Executive Director of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard.

After Results are Reported

Clinical trial results are reported to ClinicalTrials.gov, where other researchers can access them for guidance with future work and trial participants, and the public can view the data. After investigators submit their results, the National Library of Medicine performs a quality control review of the submission and requests responses to quality control issues. Results are posted within 30 days whether they meet quality control review or not.

The JHU team analysed over 200 trial submissions from 2017–2019 and found the National Institutes of Health took more than 30 days to comment on most (93%) clinical trial results, with multiple review and submission cycles delaying the posting of results. To help researchers, the team then created a checklist to help make sure the results contained all the necessary quality control information. Use of the checklist has substantially improved the success rate and reduced the review time of Johns Hopkins University trials. Thus, the team have published their checklist, which is now being used by other institutions to improve the quality of their submissions.

Mr Keyes' work in understanding and improving the regulation of clinical trials at Johns Hopkins University has improved compliance and allowed the Johns Hopkins University ClinicalTrials.gov Program to retain its high success rate. By sharing his work and resources through presentations, publications and the Taskforce, the programme honours research participants while promoting clinical trial transparency and responsible stewardship through effective management and maintenance of ClinicalTrials.gov study records.



Meet the Researcher

Mr Anthony Keyes

The Johns Hopkins University School of Medicine
Baltimore, MD
USA

Anthony Keyes obtained a Bachelor of Science degree from the University of Maryland in 2003 and an MBA in Healthcare Management from Johns Hopkins Business School in 2016. He is also a certified Project Management Professional (PMP). He has nearly 20 years of experience in clinical trial management and is now the Program Administrator of Clinical Research Operations at the Johns Hopkins University School of Medicine Institute for Clinical and Translational Sciences. He is an expert in managing research teams to produce the highest quality clinical trial data and has experience supporting all phases of clinical trials. He has led teams in developing, planning, and implementing institution-wide research improvement initiatives to enhance efficiency and compliance using project management approaches. Alongside his management role, Mr Keyes is also a part of several professional and healthcare membership societies, including the Society of Clinical Research Associates and the Project Management Institute. He also co-leads the Clinical Trials Registration and Results Reporting Taskforce and the Clinical Research Professional Taskforce.

CONTACT

E: registerclinicaltrials@jhmi.edu

W: <https://ictr.johnshopkins.edu/service/study-conduct/rcss/staff/>
<https://ictr.johnshopkins.edu/service/regulatory/ct-gov/>
<https://ctrtaskforce.org/>

KEY COLLABORATORS

Daniel Ford, MD
Kim Hill, MS
Oswald Tetteh, MD, MPH
Prince Nuamah, MD, MPH
Aliya Lalji, MD
Nidhi Atri, MD
Sarah White, MPH, MRCT Center Executive Director
Jesse Reynolds, MS, Yale School of Public Health, Statistician 3

FUNDING

This publication was made possible by the Johns Hopkins Institute for Clinical and Translational Research (ICTR), which is funded in part by Grant Number UL1 TR003098 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Johns Hopkins ICTR, NCATS or NIH.

FURTHER READING

A Keyes, E Mayo-Wilson, P Nuamah, et al., [Creating a Program to Support Registering and Reporting Clinical Trials at Johns Hopkins University](#), *Academic Medicine*, 2021, 96(4), 529–533. DOI: <https://doi.org/10.1097/ACM.0000000000003806>

A Keyes, E Mayo-Wilson, N Atri, et al., [Time From Submission of Johns Hopkins University Trial Results to Posting on ClinicalTrials.gov](#), *JAMA Internal Medicine*, 2020, 180(2), 317–319. DOI: <https://doi.org/10.1001/jamainternmed.2019.4710>

O Tetteh, P Nuamah, A Keyes, [Addressing the quality of submissions to ClinicalTrials.gov for registration and results posting: The use of a checklist](#), *Clinical Trials*, 2020, 17(6), 717–722. DOI: <https://doi.org/10.1177/1740774520942746>

E Mayo-Wilson, J Heyward, A Keyes, et al., [Clinical trial registration and reporting: a survey of academic organizations in the United States](#), *BMC Medicine*, 2018, 16(1), 60. DOI: <https://doi.org/10.1186/s12916-018-1042-6>