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Central Monitoring in a randomized, open-label, controlled phase 3 clinical trial for a treatment-shortening regimen for pulmonary tuberculosis

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Ethics approval and consent to participate

This study is approved by the institutional review board of the US CDC. Additionally, each site follows local review policies and procedures. All adult study participants provide written informed consent. For adolescents, written parental permission is obtained from the parent/legal guardian, and written assent is obtained from the adolescent.

Competing interests

The authorship team members have declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Sanofi commercial interests did not influence the study design; the collection, analysis, or interpretation of data; the preparation of this manuscript; or the decision to submit this manuscript for publication. A Sanofi technical expert served on the protocol team.

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Abstract

Introduction: With the growing use of online study management systems and rapid availability of data, timely data review and quality assessments are necessary to ensure proper clinical trial implementation. In this report we describe central monitoring used to ensure protocol compliance and accurate data reporting, implemented during a large phase 3 clinical trial.

Material and methods: The Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) study A5349 (S31) is an international, multi-site, randomized, open-label, controlled, non-inferiority phase 3 clinical trial comparing two four-month regimens to a standard six month regimen for treatment of drug-susceptible tuberculosis (TB) among adolescents and adults with a sample size of 2,500 participants.

Results: Central monitoring utilized primary study data in a five-tiered approach, including (1) real-time data checks & topic-specific intervention reports, (2) missing forms reports, (3) quality assurance metrics, (4) critical data reports and (5) protocol deviation identification, aimed to detect and resolve quality challenges. Over the course of the study, two hundred and forty data checks and reports were programed across the five tiers used.

Discussion: This use of primary study data to identify issues rapidly allowed the study sponsor to focus quality assurance and data cleaning activities on prioritized data, related to protocol compliance and accurate reporting of study results. Our approach enabled us to become more efficient and effective as we informed sites about deviations, resolved missing or inconsistent data, provided targeted guidance, and gained a deeper understanding of challenges experienced at clinical trial sites.

Trial registration: This trial was registered with ClinicalTrials.gov (Identifier: NCT02410772) on April 8, 2015.

Keywords

Tuberculosis; Clinical Trial; Central Monitoring; Clinical Trial Quality Assurance

INTRODUCTION

High-quality data support good decision-making in trial management and are necessary to answer key questions of clinical studies [1]. Quality assurance (QA) helps ensure that Good Clinical Practice (GCP) standards and regulatory requirements are met. Prevention of errors in data submission and study implementation saves time and resources; if errors do occur, timely identification and rapid resolution are desirable.

Centralized monitoring involves review and evaluation of study data by persons at a location other than the clinical research sites conducting a trial [2]. The US Food and Drug Administration (FDA) encourages the use of centralized monitoring when various features are present, including the sponsor's use of electronic systems, central access to study data,

timeliness of data entry, and rapid communication with the study sites [3]. Several clinical trials have discussed their central monitoring methods since immediate online data capture became feasible. Comparisons between traditional on-site and central monitoring have been made, with a focus on risk-based monitoring (RBM). “The purpose of centralized RBM is ultimately to increase data quality and trial integrity while ensuring patient safety and reducing resources needed for on-site visits” [5]. Venet, et. al. used a statistical approach to central monitoring to identify centers that were performing differently than others on various measures. Using this method they found “that central statistical monitoring can reveal data issues that had remained undiscovered after careful source data verification (SDV) and on-site checks” [4]. Agrafiotis et al. found “strong evidence that their RBM methodology can significantly improve the clinical oversight process” at a lower cost by focusing “resources to the sites that need the most attention” [5]. Engen et al. conducted a cluster randomized study, nested within the Strategic Timing of AntiRetroviral Treatment (START) trial, to compare centralized and on-site monitoring. This study found it was “unlikely on-site monitoring had a major impact on identifying START primary events that would have led to a biased treatment difference.” Similar outcomes were found at sites with only central monitoring compared to those with both central and on-site monitoring [6]. These trials showed the potential value of central monitoring, despite some variation in the processes used to monitor sites.

Our trials consortium, the Tuberculosis Trials Consortium (TBTC), has previously described the quality assurance methods used in earlier TBTC studies, prior to the creation of our current study management system [7]. In this report we describe the updated central monitoring processes that we implemented during a recent large phase 3 clinical trial of tuberculosis treatment [8]. Our approach encompassed the quality control, quality assurance, and monitoring of real-time data and enabled us to quickly develop interventions to improve study conduct and strengthen study quality. For the purposes of this report, “real-time data” refers to data which are available to the central monitor as soon as they are captured in the study management system. Although data can be seen immediately after they are captured in the study management system, full trial datasets are downloaded from the system once daily for report creation and analyses.

MATERIALS AND METHODS

Study setting

TBTC Study 31/ ACTG study A5349 is an international, multi-site, randomized, open-label, controlled, non-inferiority phase 3 clinical trial comparing two four-month regimens to a standard six-month regimen for treatment of drug-susceptible tuberculosis (TB) among adolescents and adults, with a sample size of 2,500 participants (Table 1). Recruitment sites were in Brazil, Haiti, Hong Kong, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the United States, Vietnam, and Zimbabwe. Study design and objectives are published [8]. Supported by the United States Centers for Disease Control and Prevention (CDC), the TBTC network collaborated on this trial with the AIDS Clinical Trials Group (ACTG) network, supported by the UnitedStates National Institutes of Health. The trial was performed under an investigational new drug application (IND). Human subjects protection

and ethical approvals were provided by the CDC Institutional Review Board (IRB), and by each participating institution's local IRB or ethics committee. The study was registered with ClinicalTrials.gov (NCT02410772).

The TBTC Data and Coordinating Center (DCC), which is housed within CDC's Division of Tuberculosis Elimination, Clinical Research Branch, conducted central monitoring for this trial, and provided oversight of study operations and data management for all research sites. To gain approval to enroll, trial sites from both networks completed start-up requirements defined by the DCC; this included submission of detailed plans and procedures for direct observation of trial therapy (DOT), local quality management, and mycobacteriology laboratory testing. The operational components of the site-specific Quality Management Plans (QMPs) were quality control, quality assurance, and quality improvement. In their plans, sites included quality control processes implemented to ensure that protocol-required procedures were followed. Described quality assurance processes included methods used by the site to ensure the protocol-required procedures were conducted effectively, as intended by the study protocol, and efficiently, in a well-organized and competent way. The quality improvement portion of the plan included the site's methods for evaluating and improving their study performance and their efficiency at implementing the study protocol. Site-specific QMPs also included detailed site procedures for:

- Obtaining, documenting and monitoring regulatory and essential documents, including IRB correspondence and approvals, CDC correspondence and approvals, institutional committee correspondence and approvals, FDA form 1572 (documenting site investigator agreement to comply with FDA regulations and Good Clinical Practice), site research personnel documents, and reports of monitoring site visits, audits, and inspections;
- Informed consent process and training, including the consent process for special populations, designation of persons authorized to conduct the consent process, processes for ensuring the correct consent documents are used, and training of personnel to perform informed consent at the site;
- Competency assessments and monitoring processes to prevent, or to identify and correct, data collection and submission errors, including the site's methods for ensuring that relevant staff complete trainings on Human Subjects Protections and Good Clinical Practice, Dangerous Goods Shipping, TBTC Study 31/ ACTG A5349 Study Specific Trainings, and Orientation and Competency Assessments of new staff.

Submitted quality management plans were reviewed and approved by a DCC workgroup comprised of a senior study coordinator, a Contract Research Organization (CRO) representative, and the DCC QA lead. For ACTG sites only, previously approved quality management plans were submitted for TBTC review; if any components of the plan were not clear, then the workgroup requested additional information. Continued approval to enroll was contingent on resolution of any issues of concern.

Data reporting and storage

Working with software developers at Northrop Grumman, we developed a custom web-based data capture and study management system, called TBTC2, solely for TBTC studies. Within this system, local site staff can complete electronic case report forms (eCRFs), access study updates, submit study drug requests, and review data quality reports provided by the TBTC DCC. Twenty-four unique eCRFs were designed and programmed for study data collection in this trial. Collected data included a total of 647 data elements stored in 34 Clinical Data Acquisition Standards Harmonization (CDASH) [9] standardized format domains. These domains and data elements were exported into 34 Statistical Analysis Software (SAS v9.4, Cary, NC) datasets. Over 100 SAS programs were written by four DCC team members to address specific quality assurance issues such as consistency and completeness of adverse event reporting, longitudinal laboratory results, and study drug dose reporting.

User-facing data entry rules and validation checks were programmed into the eCRFs. These checks were active at the time of data entry, prohibited submission of missing or illegal data and ensured that submitted data were complete, logical, and internally consistent. Examples of these rules include:

- date of birth cannot be a future date;
- date of birth must be consistent with participant being aged 12 years or older, as defined by the protocol;
- dates must be valid dates (e.g., no month 13 or day 32);
- a pregnancy test result cannot be entered for male participants.

Additionally, the user received warning messages when height and weight measurements were extremely high or low. Hundreds of such rules were programmed to minimize data entry errors.

Quality Management

Monitoring of Study TBTC S31 / ACTG A5349 was performed at three levels: On-site, Local, and Central (Figure 1). Monitoring was used to ensure study sites followed their quality control, assurance and improvement processes. On-site quality monitoring was performed independently for each collaborating network (TBTC and ACTG) by Clinical Research Associates employed by two different contract research organizations (CRO). Local monitoring involved implementation of each site’s QMP, overseen by local site leadership. TBTC DCC staff developed a central monitoring framework that capitalized on the data submission efficiencies of TBTC2, and that leveraged and complemented local and on-site monitoring activities.

RESULTS

Data System Efficiencies

Development of the Study 31/A5349-related components of TBTC2 was an iterative process completed by a multidisciplinary team of ten staff over 12 months. As a result of the

implemented user-facing data entry checks described above, central study staff and on-site monitors spentlittle time on queries for empty data fields or illogical data; the rules and validation checks largely prevent erroneous data from ever entering the dataset. Rather than manually reviewing the submitted data, we used analytical methods in SAS to code the data, analyze them, and prepare periodic reports for all involved.

Central Monitoring Framework

A novel, five-tiered framework methodology (Figure 1) was used to perform quality management at the central level; it included:

1. Performance of "real-time" data checks on submitted data, and development of topic-specific intervention reports;
2. Production of site-specific missing forms reports based on the expected study schedule for each participant at the site;
3. Evaluation of protocol compliance according to study-specific quality assurance metrics;
4. Production of critical data reports; and
5. Identification and notification of protocol deviations.

This progressive five-tiered approach (Table 2) aimed to detect and address quality challenges at the first tier (realtime data checks), long before they reach the fifth tier (a protocol deviation). Each level of the tiered approach aids sites in identifying different levels of risk to data quality. As the tier number increases, the risks to proper study implementation and to data quality also increase. With this approach, the central monitoring team could first identify data entry errors and missing data, which provided assurance the inconsistencies actually occurred. The first and second tiers are thus the top line effort to ensure that accurate and complete data are submitted in a timely manner. The third tier, evaluation of submitted data according to study-specific quality assurance metrics, allowed the site and the central monitor to recognize areas where the site had failed to satisfy a significant protocol requirement. The fourth tier, critical data reports, identified missed data points necessary for determining study endpoints or important study events. The logic behind production of critical data reports is analogous to the rationale for risk-based monitoring (RBM); both focus on identifying areas that pose a risk to participant safety or to the collection of sufficient data to permit the precise and reliable determination of outcomes. The fifth tier detected situations when the site failed to comply with protocol requirements despite application of the prior steps.

Types of Quality Management Activities

Tier 1: Real-time data checks and topic-specific intervention reports: Real-time data checks and topic-specific intervention reports were site-specific reports that showed inconsistencies in the submitted data (Table 3), such as a possible missed Adverse Event based on the lab values submitted. These reports were created by a multidisciplinary team of data management and subject-matter experts in relevant areas. Throughout the study, 80 real-time data checks or topic-specific intervention reports were created to review data accuracy

compared to other data submitted from the site related to each participant. The reports were coded with SAS, then generated by the SAS program automated process and posted on TBTC2 daily. Our automated programs reviewed all captured study data from each trial site every day.

Two steps were taken to implement real-time data checks for Study 31. User-facing data entry checks were built underneath each data field, which identified and required correction of data entry errors at the time of data entry, else the data could not be submitted. The purpose of real-time data check reports was to list possible data entry errors or data entered with values outside of the normal limits for a specific measure that should be reviewed. Topic-specific Intervention Reports were also created for each study site. These reports encompassed data cleaning tasks, such as checking data reliability or accuracy across different fields/forms; evaluated participant's eligibility; or identified Adverse Events (AE) or Possible Poor Treatment Response (PPTR) situations, based on the participants' laboratory and mycobacteriology values. Site staff were responsible for logging into TBTC2, reviewing the reports and correcting the issues listed on the report. If the site did not understand the issue in the data, they contacted the central monitoring team for additional guidance.

Tier 2: Missing forms reports: Missing forms reports (MFR) were site-specific reports listing any of the 24 eCRFs that were late, based on the form submission deadlines listed in the S31 Manual of Operating Procedures (MOOP) (Table 4). The deadlines were chosen to respect regulatory requirements, and otherwise to allow ample time for submission (e.g., 48 hours for Serious Adverse Events, 45 days for Adverse Event follow-up, and 300 days for follow-up of reported pregnancies). These reports were created with SAS coding and were based on procedures expected at a given visit, as indicated by the site on the Treatment Evaluation (TX) or Follow-up Evaluation (FU) forms. Forms listed on the report needed to be submitted to the online TBTC2 system. Once submitted, the missing forms would be automatically removed from the MFR. MFRs were posted on TBTC2 and updated every day.

Tier 3: Quality assurance metrics: In TBTC2, quality assurance (QA) metrics reports were posted and updated daily. The QA metrics report content, format, and wording were developed by TBTC's QA Working Group (WG), based on 30 overarching areas focused required procedures listed in the study protocol (Table 5). Created using SAS coding, the reports served to identify areas where the site was deficient compared to expected study implementation. Tables in the QA reports displayed a score for each measure for each site, as well as an average score for the entire study. Each site's report included a line list of individual participants not meeting each specific measure. Reports were re-run each day and were available on the TBTC2 website for review by site staff; each site determined its own review schedule to assess study management and data quality. We prepared formal QA Performance Measure (PM) reports twice per year (9). We asked site staff to review their QA PM Reports, to comment on areas where the site was deficient and to specify actions to prevent deficiencies in the future. Each site submitted a response to the QA WG co-leads, the senior study coordinator and the DCC QA lead, using a Site Evaluation Report Form

(SERF). QA WG co-leads reviewed the SERF responses, and (importantly) provided timely feedback to site staff.

Tier 4: Critical Data Report (highlighting key data elements): Critical data reports are site-specific reports assessing completeness of 14 critical data elements necessary for determining study endpoints. Accuracy and completeness of these data elements are integral to outcome determination. Participants who are missing critical data at a key visit are deemed to have experienced an unfavorable outcome. Thus, elements were considered top priority and additional interventions were focused on them.

The primary trial endpoint was TB disease-free survival at twelve months after study treatment assignment.

Secondary endpoints included:

- TB disease-free survival at eighteen months after study treatment assignment; and
- Proportion of participants who were culture negative at completion of eight weeks of treatment (solid and liquid media considered separately).

The Critical Data reports highlighted participants missing (or at risk of missing, as determined by missing the schedule visit but still in the visit window for these key data elements necessary for determining outcomes, such as unevaluable sputum culture results or missing study visits at months 12 and 18 (Table 6). These reports were also posted to TBTC2 and updated daily.

Tier 5: Protocol deviations: DCC staff identified 59 specific S31 protocol deviations that could be detected through SAS coding. We used SAS code to populate the CDASH Deviations domain (DV) from primary study data and created a deviations dataset without requiring a deviation CRF. The large majority of deviations identified through SAS coding were considered to be minor.

In a few instances, protocol deviations were not captured solely from primary study data but were designated as “important,” because they might affect the completeness, accuracy or reliability of the data, or might affect a participant’s rights, safety or well-being. Generally, we became aware of these deviations through direct reporting by the site, and then communicated with the site to obtain the information needed for reporting to the IRB and study leadership.

Based on the populated DV domain, queries were emailed to sites to confirm the deviation or resolve data deficiencies. In some cases, sites were not aware of the deviation or had not reported the deviation to the Sponsor (CDC). When what appeared to be a deviation was actually a data entry error, sites were able to correct these promptly, instead of waiting for exhaustive data cleaning during preparation for data analysis, thereby improving data accuracy. If a deviation was seen frequently, specific directions were provided during study conference calls and meetings, or memos (eight in total), related to these issues were sent to study sites to provide additional guidance.

Timeframe for report development

We used SAS to develop reports for all QA activities. Over several months, we wrote and refined the code, drawing on quality assurance findings to ensure identification of the correct participants for data checks and deviations for the various reports. Once the study was underway, additional queries and checks were added to all reports as concerns arose. If the DCC identified an area of concern, we developed queries to address the matter. The majority of data reports were updated and made available daily. However, the protocol deviation queries were initially run on a bi-weekly basis, and later on a monthly basis as the trial progressed. Nonetheless, these queries captured 99% of all deviations identified during the trial. Deviations not captured through this automated method were reported to the Sponsor via email and tracked manually. Given that all QA activities were occurring rapidly, data cleaning and quality analysis were ongoing throughout the trial. Final data analysis of all study data and endpoints will occur after study completion, with reduced data cleaning required as data have been cleaned during the course of the study. Due to the cleaning measures taken during the study, the time from analytic database creation to primary analysis results was only three weeks.

DISCUSSION

This use of primary study data to identify data issues promptly allowed CDC, as the study sponsor, to focus quality assurance and data cleaning activities on prioritized data related to protocol compliance and accurate determination of study endpoints. Our approach enabled us to inform sites about deviations, resolve missing or inconsistent data, and gain a deeper understanding of challenges experienced at clinical trial sites. As our processes relied on automated SAS programs with ongoing feedback to sites, site staff received timely information to assist in modifying local procedures to minimize future deviations, queries, and data inconsistencies. Additionally, we used knowledge gained during communication with trial sites about deviations and performance measures to tailor guidance messages, creating a cycle of quality improvement. Frequent communication with sites was a necessary part of this approach, as providing the data to “those who need to know them is the basis of achieving effective action” [10]. Focused training sessions incorporating knowledge gained from working with the quality assurance data and discussions with site staff were delivered to clinical sites at semi-annual/annual network meetings with guidance on best practices for data submission to improve site processes. Thus, clinical trial site staff could devote more time to the many other required study procedures. Our central monitoring and QA efforts were all designed to ensure that quality, accurate data were submitted; we have not sought to to quantify how many errors occurred or were prevented, but could seek to do so if this appeared useful.

The majority of these quality management methods were applied in reports that were updated daily, allowing us to improve the quality of the data received from trial sites throughout the trial. The initial review of the quality management plans and discussion with sites ensured that methods for quality control were in place. As an additional method of quality control, protocol deviation checks and QA Performance measures confirmed that sites followed the protocol and investigational plan during the trial. When study procedures

were not followed, sites became aware daily, by reviewing their online reports, or weekly, by receiving emailed reports, about the issue. To ensure sites were conducting activities effectively and efficiently, we ran the programs for missing forms reports, real-time data checks, and topic-specific intervention reports to check for missing or incorrect data daily. These reports verified that data were entered when required, correctly and consistently. The data management process improved the quality of the data received and the performance at the trial sites. The process included communication with sites via email, phone, and in-person training. Formal quality assurance reviews allowed sites to consider ways to improve performance to eliminate future deficiencies. Critical data reports pointed out key areas for sites to monitor to improve performance, especially in areas that affected our ability to assess trial outcomes. When errors were seen across multiple sites, DCC staff developed site-wide memos or training, to provide additional guidance and to enhance performance and efficiency in these areas. As seen in other studies, we found central monitoring to be "effective for ensuring consistency of data, range checks, and ensuring the completion of documented processes" [11].

There are some limitations to the use of real-time data. These reports are based on the data available in the system; sites must submit data in a timely manner for accurate reporting. If data were not submitted in a timely manner, reports might list queries simply because the data were not available, creating the appearance that procedures were not done. This might serve as an incentive for some sites, as many of our sites did not like to see queries on their reports and would work to submit data quickly to decrease the queries received. One limitation of our deviation reporting was that our SAS program identified only deviations for which primary data were reported. There were infrequent deviations that required manual reporting, such as unnecessary blood draws, which were not collected in the primary study data but reported by the site to the sponsor. Based on discussions with sites, an important protocol deviation CRF is being developed for sites to report these instances in future studies. When important protocol deviations occur, extensive reporting is required, necessitating frequent communication with the site. Based on the knowledge gained from Study 31, the CRF is being created to harmonize reporting in these special situations. This should decrease the burden of work for this reporting process in the future.

The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use recommends a *quality-by-design* approach in clinical research, wherein the researcher "sets out to ensure that the quality of the study is driven proactively by designing quality into the study protocol and process" [1]. We will continue to build upon the central monitoring process in future studies, with a focus on these approaches. According to the ICH, it is important to "focus effort on activities that are essential to the reliability and meaningfulness of study outcomes for patients, and the safe, ethical conduct of the study for study subjects" [1]. Given the large size of our clinical trial databases, strategies to tailor review critical study data are an essential component. When looking at risk-based monitoring in the academic setting, Niederhausern et. al. stated they "envision the future monitor to be an on-site partner to the study team, supported by centralized data checks adaptable to the risk of a trial, considering the experience of and the management at the site itself" [12]. Bhagat, et. al. discussed the importance of considering potential risks and strategies in the pre-phase of clinical trials [13]. "Development of an

effective risk monitoring and management strategy requires both scientific and organizational support" [13] and should be discussed frequently in the trial planning process. We found this to be true in our setting as well. In the future, these practices can be incorporated into all studies in the pre-phase steps by building them into the protocol development process.

Trial status

Recruitment began at the first study site in January 2016. The last participant was enrolled in October 2018. Participant follow up was completed in May 2020.

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Study Participants

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CDC Leadership

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Participating Sites (not listed individually)

We would like to acknowledge all site study staff members who implemented the clinical trial (please see full list of site staff in [8].

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REFERENCES

[1]. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Humane Use, "FDA Guidance Documents," 8 May 2019. [Online]. Available: https://www.fda.gov/media/129527/download.

[2]. Ghone A, "Applied Clinical Trials," 01 October 2015. [Online]. Available: http://www.appliedclinicaltrialsonline.com/centralized-monitoring-smart-reliable-approach.

[3]. US Food & Drug Administration, "Guidance for Industry: Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring," August 2013. [Online]. Available: https://www.fda.gov/media/116754/download.

[4]. Venet D, Doffagne E, Burzykowski T, Beckers F, Tellier Y, Genevois-Marlin E, Becker U, Bee V, Wilson V, Legrand C and Buyse M, "A statistical approach to central monitoring of data quality in clinical trials," Clinical Trials, vol. 9, pp. 705–713, 2012. [PubMed: 22684241]

[5]. Agrafiotis D, Lobanov VS, Farnum MA, Yang E, Ciervo J, Walega M, Baumgart A and Mackey AJ, "Risk-based Monitoring of Clinical Trials: An Integrative Approach," Clinical Therapeutics, vol.40, no. 7, pp. 1204–1212, 2018. [PubMed: 30100201]

[6]. Engen NW, Hullsiek KH, Belloso WH, Finley E, Hudson F, Denning E, Carey C, Pearson M and Kagan J, "A randomized evaluation of on-site monitoring nested in a multinational randomized trial," Clinical Trials, vol. 17, no. 1, pp. 3–14, 2020. [PubMed: 31647325]

[7]. Sandman L, Mosher A, Khan A, Tapy J, Condos R, Ferrell S, Vernon A and t. T. T. Consortium, "Quality assurance in a large clinical trials consortium: The experience of the Tuberculosis Trials Consortium," Contemporary Clinical Trials, vol. 27, pp. 554–560, 2006. [PubMed: 16876488]

[8]. Dorman S, Nahid P, EV K, Goldberg S, Bozeman L, WJ B, Chang K, Chen M, Cotton M, Dooley K, Engle M, Feng P, Fletcher C, Ha P, Heilig C, Johnson J, Lessem E, Metchock B, Miro J, Nhung N, Pettit A and Phillips P, "High-dose rifapentine with or without moxifloxacin for shortening treatment of pulmonary tuberculosis: Study protocol for TBTC study 31/ACTG A5349 phase 3 clinical trial," Contemporary Clinical Trials, pp. 1–11, 3 2020.

[9]. Clinical Data Interchange Standards Consortium, "Clinical Data Interchange Standards Consortium," 2019. [Online]. Available: https://www.cdisc.org/standards/foundational/cdash.

[10]. Langmuir AD, "The Surveillane of Communicable Diseases of National Importance," The New England Journal of Medicine, vol. 268, no. 4, p. 182, 1963. [PubMed: 13928666]

[11]. Bertolet M, Brooks MM and Carson JL, "Commentary on Egen et al: Risk-based, dynamic, process-oriented monitoring strategies and their burden," Clinical Trials, vol. 17, no. 1, pp. 15–17, 2020. [PubMed: 31647327]

[12]. Niederhäusern B. v., Orleth A, Schädelin S, Rawi N, Velkopolszky M, Becherer C, Benkert P, Satalkar P, Briel M and Pauli-Magnus C, "Generating evidence on a risk-based monitoring approach in the academic setting - lessons learned," BMC Medical Research Methodology, vol. 17, p. 26, 2017. [PubMed: 28193170]

[13]. Bhagat S, Kapatkar VK, Mourya M, Roy S, Jha S, Reddy R, Kadhe G, Mane A and Sawant S, "Potential Risks and Mitigation Strategies Before the Conduct of a Clinical Trial: An Industry Perspective," Reviews on Recent Clinical Trials, vol. 11, pp. 47–55, 2016. [PubMed: 26435140]

Highlights

- Informed sites about deviations and resolved missing or inconsistent data.
- Minimized future deviations, queries, and data inconsistencies.
- Tailored training messages, creating a cycle of quality improvement.

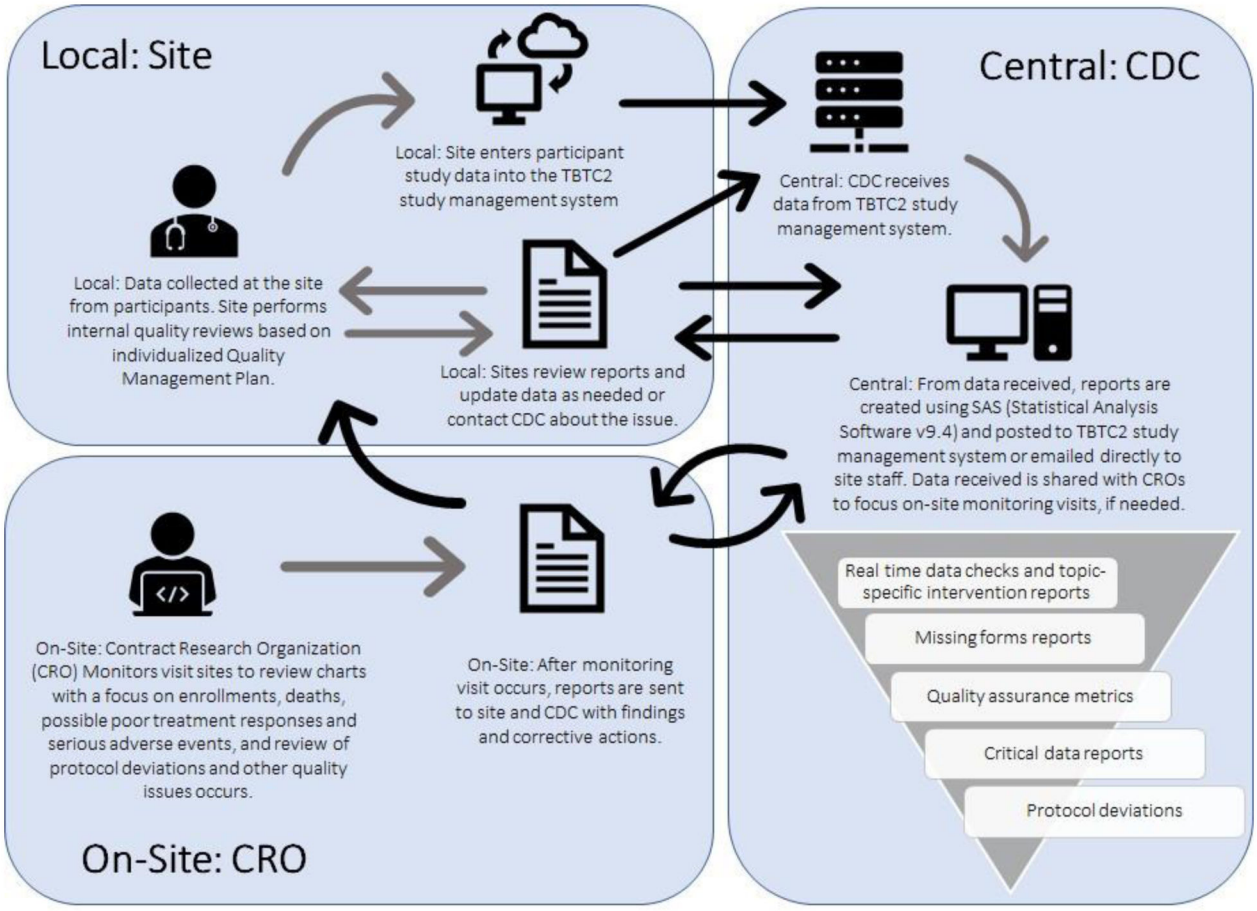

Figure 1.
Quality Monitoring Map for Study TBTC S31 / ACTG A5349

Table 1.

PROTOCOL SYNOPSIS: STUDY 31

<table>
<tr><td>Protocol Title:</td><td>Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial</td></tr>
<tr><td>Treatment Indication:</td><td>Pulmonary Tuberculosis (TB)</td></tr>
<tr><td>Trial Objective:</td><td>• To evaluate the efficacy of a rifapentine-containing regimen to determine whether the single substitution of rifapentine for rifampin makes it possible to reduce to seventeen weeks the duration of treatment for drug-susceptible pulmonary tuberculosis
• To evaluate the efficacy of a rifapentine-containing regimen that in addition substitutes moxifloxacin for ethambutol and continues moxifloxacin during the continuation phase to determine whether it is possible to reduce to seventeen weeks the duration of treatment for drug-susceptible pulmonary tuberculosis</td></tr>
<tr><td>Trial Design:</td><td>This is an international, multicenter, randomized, controlled, open-label, 3-arm, phase 3 non-inferiority trial. Previously untreated individuals with active drug-susceptible pulmonary tuberculosis were randomly assigned in a 1:1:1 ratio to the study arms, 2RHZE/4RH, 2PHZE/2PH, or 2PHZM/2PHM (see Treatment Arms, below). Patients received 17 weeks of experimental treatment or 24 weeks of standard treatment. Randomization was stratified by site, by the presence of cavitation on chest radiograph at baseline (since cavitation is associated with a decreased rate of microbiological response to TB treatment), and by HIV status (HIV-uninfected vs. HIV-infected). Participant safety was maximized, and risks were minimized by frequent study visits for safety assessments, intensive microbiological monitoring for TB treatment failure and relapse, and periodic review of unfavorable outcome rates by a Data and Safety Monitoring Board.</td></tr>
<tr><td>Patient Population:</td><td>This is a multisite international study. Male and female participants who are age 12 or older and suspected to have pulmonary tuberculosis will be enrolled into the study.
Target enrollment was 2500 participants. Pregnant or breast-feeding women were excluded from the study because of uncertainties about the safety of rifapentine, moxifloxacin, and pyrazinamide in these groups. The sex, ethnicity, and socioeconomic background of study participants were expected to mirror those of the populations served by local tuberculosis clinics and the populations most affected by tuberculosis worldwide.</td></tr>
<tr><td>Treatment arms:</td><td>Study participants will be randomized 1:1:1 to receive one of the following:

<table>
<tr><th>Regimen</th><th>Weeks 0–8</th><th>Weeks 9–17</th><th>Weeks 18–26</th></tr>
<tr><td>1 (control regimen)</td><td>2RHZE</td><td>4RH</td><td>4RH</td></tr>
<tr><td>2</td><td>2PHZE</td><td>2PH</td><td>No treatment</td></tr>
<tr><td>3</td><td>2PHZM</td><td>2PHM</td><td>No treatment</td></tr>
</table>

<table>
<tr><th>Drug</th><th>Dose</th></tr>
<tr><td>Isoniazid (H)</td><td>300 mg</td></tr>
<tr><td>Vitamin B6</td><td>25 or 50 mg</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Pyrazinamide (Z)</td><td></td></tr>
<tr><td>< 55 kg</td><td>1000 mg</td></tr>
<tr><td>≥ 55–75 kg</td><td>1500 mg</td></tr>
<tr><td>> 75 kg</td><td>2000 mg</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Ethambutol (E)</td><td></td></tr>
<tr><td>< 55 kg</td><td>800 mg</td></tr>
<tr><td>≥ 55–75 kg</td><td>1200 mg</td></tr>
<tr><td>> 75 kg</td><td>1600 mg</td></tr>
<tr><td></td><td></td></tr>
</table>
</td></tr>
</table>

Drug	Dose
Rifampin (R)	600 mg
Rifapentine (P)	1200 mg
Moxifloxacin (M)	400 mg

Criteria for evaluation:
Primary Endpoints:

- Efficacy: TB disease-free survival at twelve months after study treatment assignment.
- Safety: Proportion of participants with grade 3 or higher adverse events during study drug treatment

Secondary Endpoints:

- TB disease-free survival at eighteen months after study treatment assignment
- Time to stable sputum culture conversion (solid and liquid media considered separately)
- Speed of decline of sputum viable bacilli by automated liquid MGIT culture days to detection
- Proportion of participants who are culture negative at completion of eight weeks of treatment (solid and liquid media considered separately)
- Sensitivity analyses assuming all participants classified as ‘not assessable’ have a favorable outcome
- Discontinuation of assigned treatment for a reason other than microbiological ineligibility
- Estimated steady state efavirenz PK parameters including mid-dosing interval concentration

Study sites:
Multiple international and U.S. sites of the Tuberculosis Trials Consortium and the AIDS Clinical Trials Group (34 sites).

Study duration:
Duration of study: Duration per participant is approximately 18 months.

Table 2.

Five-tiered methodology for quality management

Tier	Measure	Method	Data Impact	Trial Impact
1	Real time data checks and topic-specific intervention reports	**1** User-facing data entry checks prevent illogical entry errors at site **2** Daily automated SAS reports denote illogical entries	Identifies inconsistencies in submitted data, automated data cleaning	Prevents missing data fields, illogical data, or data entry errors
2	Missing forms reports	Daily automated SAS reports identifies case report forms not submitted by predetermined deadlines	Prevents loss of data and ensures data for all time points and participants	Identifies possible issues with data management, team communication, or implementation
3	Quality assurance metrics	Daily automated and formally review biannually, SAS reports to evaluate established performance measures per site	Identifies issues with sites meeting protocol requirements	Identifies sites needing additional training, monitoring, or clarification
4	Critical data reports	Daily automated SAS reports	Identifies participants with risk for missing data points required for study endpoints	Prevents exclusion of participant data for endpoint analysis and erosion of statistical power
5	Protocol deviations	Automated SAS reports, direct notification to site staff	Identifies deviations from the protocol for real-time correction, when possible	Prevents systemic problems leading to protocol deviations, identifies areas where further training/clarification is needed, prevents some participant data exclusion

Table 3.

Real-time data check and topic-specific intervention reports

<table>
<tr><th>Short name</th><th>Description of data check</th></tr>
<tr><td>Possible missing Adverse Event (AE) form-due to Lab results (except potential hepatotoxicity)</td><td>Line list of participants whose chemistry or Complete Blood Count (CBC) result should trigger an AE report requirement but who are missing an AE form (when the lab result is normal at baseline); includes the following checks:
1 Alkaline phosphate > 5xUpper Limit Normal (ULN)
2 Creatinine > 3xULN
3 Glucose > 250 mg/dl or 13.9 micro mol/L
4 Hemoglobin < 8.0 g/dl or <80 g/L
5 Platelets < $50\times10^{3}/mm^{3}$ (10^{9}/L)
6 White Blood Cell (WBC) > $100.0\times10^{3}/mm^{3}$ (10^{9}/L)
7 Absolute Neutrophil Count (ANC) < 1000 cells/mm^{3}
8 Positive pregnancy test</td></tr>
<tr><td>Missing diabetes diagnosis: Hemoglobin A1C (A1C) check</td><td>If participant is not reported as a diabetic (Type I or Type II) on History and has A1C % > 6.5%, flag as potential new diabetes diagnosis</td></tr>
<tr><td>Missing Possible poor treatment response (PR): Positive culture at or after week 17</td><td>Among persons for whom follow-up continues (excluding participants who are late exclusions):
The result of a single sputum specimen collected on or after the week 17 treatment evaluation is reported to be positive for Mycobacterium tuberculosis (MTB), but missing PR form</td></tr>
<tr><td>Missing Possible poor treatment response (PR): Positive smear at or after week 17</td><td>Among persons for whom follow-up continues (excluding participants who are late exclusions):
The result of a single sputum specimen collected on or after the week 17 treatment evaluation is reported to be smear positive for acid fast bacilli.</td></tr>
<tr><td>Missed Doses</td><td>Check to create a line list of participants with more than two consecutive missed doses</td></tr>
<tr><td>Weight Grade</td><td>Line list of participants that have a change in weight grade, but not a change in dosage for Pyrazinamide or Ethambutol
Doses of study medications will be determined by body weight, as follows:
<table>
<tr><th>Drug</th><th>Dose</th></tr>
<tr><td>Pyrazinamide</td><td></td></tr>
<tr><td>< 55 kg</td><td>1000 mg</td></tr>
<tr><td>≥ 55–75 kg</td><td>1500 mg</td></tr>
<tr><td>> 75 kg</td><td>2000 mg</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Ethambutol</td><td></td></tr>
<tr><td>< 55 kg</td><td>800 mg</td></tr>
<tr><td>≥ 55–75 kg</td><td>1200 mg</td></tr>
<tr><td>> 75 kg</td><td>1600 mg</td></tr>
</table></td></tr>
<tr><td>Resistance</td><td>Baseline/week 2 mycobateriology (MB) form reporting resistance to any one or more of the following: rifampin, isoniazid, pyrazinamide, ethambutol or fluoroquinolones; If Yes, then query site about patient eligibility or missing MB forms</td></tr>
</table>

Table 4.

S31 electronic Case Report Form (CRF) Submission Timelines

CRF Submission Timelines			
CRF Name	**CRF Abbreviation**	**Maximum allowable submission timeline**	**Included on data query or missing forms report**
Adverse Event	AE	Within 48 hours of site notification for Serious Adverse Events 5 days after site notification for other events	Yes for some events
Adverse Event Follow-Up	AF	45 days after AE onset 300 days after AE onset for pregnancies	Yes
Clinical Evaluation	CE	Associated with HX:7 days after enrollment date Associated with TX, FU, AE or PR: ame day as associated form is submitted	Yes, if associated with HX, TX, FU or PR
Concomitant Medication	CM	Data entry is on-going for this CRF as long as the participant is on study. All medications reported at a study visit, 3 days after initial report of the medication.	No
Notification of Death	DE	45 days after report of death on an AE or AF form	Yes
Dose Record	DR	Data entry is on-going for this CRF as long as the participant is on TB treatment. All doses administered in a 2 week period should be reported 3 days after the associated TX form is submitted.	Yes
Efavirenz PK Sampling	EPK	10 days after associated TX form is submitted	Yes
Efavirenz PK Shipping	EPKS	7 days after efavirenz PK sample is shipped	No
Follow-Up Completion	FC	18 months after last dose of TB treatment or 5 days after date of discontinuation of study follow-up	Yes
Follow-Up Evaluation	FU	6 days after scheduled visit date for week 22 10 days after scheduled visit date for week 26, and months 9, 12, and 15 17 days after scheduled visit date for month 18	Yes
History	HX	7 days after enrollment date	Yes
Laboratory Evaluation	LB	Associated with HX: 7 days after enrollment date Associated with TX, FU, AE or PR: 3 days after associated form is submitted	Yes, if associated with HX, TX or FU
Mycobacteriology	MB	Associated with HX: 75 days after enrollment date Associated with TX, FU, AE or PR: 75 days after associated visit	Yes, if associated with HX, TX, FU, or PR
Pharmacogenomic Blood Sampling	PG	10 days after associated TX form is submitted	Yes
Pharmacogenomic Shipping	PGS	7 days after pharmacogenomic sample is shipped	No
Possible Poor Treatment Response	PR	As soon as possible after site notification	Yes
Signs & Symptoms	SS	Associated with HX: 7 days after enrollment date Associated with TX, FU, AE or PR: same day as associated form is submitted	Yes, if associated with HX, TX or FU
Treatment Completion	TC	5 days after participant has completed or discontinued TB treatment	Yes
TB Drug Sparse PK	TSPK	10 days after associated TX form is submitted	Pending
Rifapentine/Rifampin PK Shipping	RPKS PPKS	7 days after PK sample is shipped	No
Treatment Evaluation	TX	6 days after scheduled visit date for weeks 2, 4, 8, 12, 17, and 22 10 days after scheduled visit date for week 26	Yes

Table 5.

Quality Assurance Metrics Sections and Overarching Performance Measures

TBTC QUALITY ASSURANCE PROGRAM SITE EVALUATION REPORT- Study 31 **Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial**		
Section	**Performance Measure**	**Goal**
I. Enrollment	Ineligible	0% Maximum 0%
II. Study Phase	1. On time visit rates during treatment phase	>95% Minimum 95%
	2. On time visit rates during follow-up phase	>95% Minimum 95%
	3. Treatment completion rate	100% Minimum 100%
	4.a. Correct # Directly Observed Therapy (DOT) doses, current treatment	100% Minimum 100%
	4.b Correct # DOT doses, completed treatment	100% Minimum 100%
III. Data Quality	1. Cavitation reported concordance	100% Minimum 100%
	2. HIV status reported concordance	100% Minimum 100%
	3. Timely Electronic Case Report Form (eCRF) submission at Baseline	100% Minimum 100%
	4. Timely eCRF submission during treatment	100% Minimum 100%
	5. Timely eCRF submission during follow-up phase	100% Minimum 100%
IV. Blood Specimens	1. Obtained scheduled chemistry labs	100% Minimum 100%
	2. Obtained scheduled CBC	100% Minimum 100%
	3. Obtained screening CD4 cell count/HIV viral	100% Minimum 100%
	4. Obtained scheduled HIV viral load during EFV (Efavirenz) PK (Pharmacokinetics)	100% Minimum 100%
V. Sputum Specimens	1. Obtained screening and baseline sputum	100% Minimum 100%
	2. Obtained sputum during treatment phase	100% Minimum 100%
	3. Obtained sputum during follow-up phase	100% Minimum 100%
VI. Physical and Physiological Measurements	1. Weight obtained	100% Minimum 100%
	2. Visual acuity testing	100% Minimum 100%
	3. Color perception test	100% Minimum 100%
VII. Other	1. Ethambutol dose change when participant weight moves from one weight band to another during Intensive Phase (IP) treatment	100% Minimum 100%

TBTC QUALITY ASSURANCE PROGRAM SITE EVALUATION REPORT- Studv 31 **Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial**		
Section	**Performance Measure**	**Goal**
	2. Pyrazinamide dose change when participant weight moves from one weight band to another during IP treatment	100% Minimum 100%
VIII. PK Specimens	1. TB drug sparse PK specimens obtained during IP treatment	100% Minimum 100%
	2. TB drug sparse PK specimens obtained within specified times in Regimen 2 & 3	100% Minimum 100%
	3. TB drug sparse PK specimens obtained within specified times in Regimen 1	100% Minimum 100%
	4. Obtained scheduled EFV1 PK specimens	100% Minimum 100%
	5. Obtained scheduled EFV2.A PK specimens	100% Minimum 100%
	6. Obtained scheduled EFV2.B PK specimens	100% Minimum 100%
	7. Obtained scheduled EFV2.C PK specimens	100% Minimum 100%

A goal was set for each measure which was the number sites should attempt to achieve. The minimum goal was the lowest expected result for the measure.

Table 6.

Critical Data Report Structure

Data Table:	**Explanation of Table:**
Mycobacteriology: Unevaluable results by study visit	Table showing the percentage of unevaluable culture results collected at each study visit at the site
Mycobacteriology: Participants with unevaluable results	Line list of participants with unevaluable culture results, with reason results are unevaluable
Mycobacteriology: Participants with unevaluable results at month 12 visit	Line list of participants with unevaluable results at the month 12 visit and whether the participant is still in the month 12 analysis window
ALERT LIST: Participants who missed their month 12 visit but are still in the month 12 analysis window	Line list of participants who missed their scheduled month 12 visit, but are still in the analysis window to perform an unscheduled visit to replace the missed scheduled month 12 visit
ALERT LIST: Participants who missed their month 18 visit	Line list of participants who missed their scheduled month 18 visit, but are still in the analysis window to perform an unscheduled visit to replace the missed scheduled month 18 visit
Retention: Missed treatment visits	Percentage of on-time visits during treatment phase for the site
Retention: Line list of participants with missed treatment visits	Line list of participants with missed treatment visits including the visit missed
Retention: Trends in missed treatment visits	Table displaying the number of visits missed per participant, including participants with one missed visit, two missed visits up to five+ missed visits during treatment phase
Retention: Missed follow-up visits	Percentage of on-time visits during follow-up phase for the site
Retention: Line list of participants with missed follow-up visits	Line list of participants with missed follow-up visits including the visit missed
Retention: Trends in missed follow-up visits	Table displaying the number of visits missed per participant, including participants with one missed visit, two missed visits up to five missed visits during follow-up phase
Retention: Missed visits by Phase	Study visits missed in each phase by percentage, displaying which visit is missed most frequently in each study phase
Retention: Missed and completed visits by visit week	Bar graph of completed and missed visits by visit week

Note: All reports are site specific