TREAT TB | Technology, Research, Education and Technical Assistance for Tuberculosis

PRACTICAL RECOMMENDATIONS
FROM THE STREAM CLINICAL TRIAL

Implementing Clincial Trials

USAID FROM THE AMERICAN PEOPLE

Vital Strategies

The Union

About this guide

STREAM is a multi-country clinical trial evaluating shorter, more tolerable multidrug-resistant tuberculosis (MDR-TB) regimens, carried out over more than 10 years.

The trial offered an exceptional opportunity to evaluate key issues related to implementing clinical trials and this guide presents eight practical recommendations designed to improve future clinical trials.

Companion documents covering community engagement and pharmacy and clinical supplies can be found here.

LEFT

Study team members at King Dinuzulu Hospital review trial requirements in the STREAM protocol

Background

STREAM is the first large-scale, multi-country clinical trial to examine shortened regimens for MDR-TB. It is also the first phase III trial to test the efficacy and safety of bedaquiline in a shorter regimen. STREAM began in 2012 as an academic non-registration trial (Stage 1) funded by the United States Agency for International Development (USAID) and the UK Department for International Development (DFID) through their grant to the UK Medical Research Council Clinical Trials Unit at University College London (MRC CTU at UCL).

STREAM Stage 1 compared a 9–11-month MDR-TB regimen to the locally-used regimen in line with 2011 World Health Organization (WHO) guidance (approximately 20 months). Stage 2 (which added two bedaquiline-containing arms) resulted in additional funding from Janssen Pharmaceuticals and STREAM becoming a US Food and Drug Administration (FDA) regulated registration trial. The two stages of the trial recruited more than 1,000 participants at sites in Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, Uganda, and Vietnam, making STREAM the world's largest recruited clinical trial for MDR-TB.

Results from Stage 1 were published in the *New England Journal of Medicine* and demonstrated that favorable outcomes for participants on the control (approximately 20 months) and intervention (9–11 months) regimens were very similar under trial conditions. The STREAM Stage 1 results, which also showed that the shorter regimen can reduce costs to the health system and patients, as published in the *Bulletin of the World Health Organization*, played a key role in the development of the WHO recommendations on the use of shorter regimens to treat MDR-TB.

STREAM Stage 2, which is ongoing, is evaluating an all oral, bedaquiline-containing regimen that is potentially as effective as and more tolerable than the injectable-containing regimens currently in use. It is also evaluating the comparative cost of the two regimens, for both the patient and the health system. Stage 2 is expected to contribute important evidence for future policy decisions about injectable-free MDR-TB regimens. Recruitment to Stage 2 of the trial was completed in January 2020 and results are expected in 2022.

There are a number of key implementing partners involved in the trial, including the MRC CTU at UCL who oversees overall trial implementation, technical partners for microbiology, health economics and community engagement, a central safety lab, and a contract research organization for onsite monitoring.

THE PRINCIPAL IMPLEMENTING PARTNERS AND THEIR ROLES FOR THE STREAM TRIAL ARE:

TECHNICAL PARTNERS

Medical Research Council Clinical Trials Unit at University College London is responsible for overall trial implementation, including trial design, statistical analysis, clinical oversight of sites, and data management.

Institute for Tropical Medicine Antwerp (ITM) is responsible for all microbiology-related aspects of the trial, including initial site assessments and ongoing site monitoring. Additionally, ITM is the central microbiology laboratory for the trial.

Liverpool School of Tropical Medicine (LSTM) is responsible for all aspects of the health economics study for the trial.

CONTRACT RESEARCH ORGANIZATION

IQVIA is the clinical research organization (CRO) contracted in Stage 2 to oversee onsite monitoring at all sites and coordination of submissions to some local ethics committees and regulatory authorities.

CENTRAL SAFETY ASSESSMENTS

Q2 Solutions and **QCSS** are contracted in Stage 2 to provide central laboratory testing and central ECG reviews for participant safety assessments in the trial.

COMMUNITY ENGAGEMENT

REDE-TB is an advocacy expert that provides technical assistance for STREAM community engagement, as detailed in the companion practical recommendations guide.

"The highest quality evidence the WHO looks [for] is from randomized clinical trials... They are the number one approach for making new guideline recommendations, and results from clinical trials like STREAM help to ensure WHO recommendations... are as strong as possible."

THE WORLD HEALTH ORGANIZATION

Implementing Clinical Trials

Designing and implementing an MDR-TB clinical trial is complex and requires team members (centrally and locally) with a unique combination of skills and training. Beyond the obvious clinical, laboratory and statistical expertise required, successful trial implementation requires deep regulatory knowledge and strong project management skills to address the wide variety of implementation challenges that inevitably arise in multi-site trials. Key aspects to address range from site selection and training, to regulatory compliance, procurement, logistics, and community engagement. When added to the complex partner relationships typical for regulatory trials, this breadth of implementation issues demands careful site and study team selection, targeted capacity building, systematization of key trial processes, and structured and continuous stakeholder communication and coordination.

Deep local knowledge and relationships

PAGE 5

Systematic site assessments

PAGE 6

Diverse range of skills and experience

PAGE 7

Risk-based monitoring strategy

PAGE 8

Standard processes at sites

PAGE 9

Site-level input into trial design

PAGE 10

Clear roles and responsibilities

PAGE 11

Well-designed data flows

PAGE 12

Deep local knowledge and relationships

Deep local knowledge and stakeholder relationships are essential for successful trial implementation

There were 15 STREAM trial sites from eight countries in Africa, Asia and Europe – all with very different local contexts. It was essential to the success of the trial to understand local variations and effectively adapt implementation in response.

One example was MDR-TB patient referral patterns. Only by building support for the trial at frontline health facilities where patients are diagnosed with MDR-TB can potential trial participants be referred to trial sites for trial enrolment.

When STREAM began in India, diagnosis and treatment of MDR-TB was centralized at centers that were shortlisted for the STREAM trial, but decentralization was expected to occur. To address this challenge, the trial Sponsor appointed a local expert with close connections to the national TB program (NTP) and deep knowledge of MDR-TB management in the country. This enabled the trial to understand the decentralization strategy of the NTP, to prepare trial sites for expected changes to referral patterns, and to conduct outreach to the frontline units that would ultimately refer participants to the trial. As a consequence, the India trial sites were able to meet their recruitment objectives, even after decentralization.

There were also significant variations in local regulatory environments, and deep local knowledge and relationships were crucial to navigating them. Regulatory requirements can be difficult to understand without access to local experts because clinical trial regulations are not always available publicly or easy to interpret, and practices of regulatory agencies may be unwritten. Gaps in local regulations can also exist, making it essential to work collaboratively with regulatory bodies to resolve questions during the course of a trial. In China, initiation of STREAM was ultimately abandoned when it became clear the country's clinical trial regulations, which only recognized industry sponsors, were incompatible with an NGO sponsor like Vital Strategies. The trial's absence of experienced local regulatory contacts contributed to a delay in reaching that conclusion. In contrast, in Mongolia, where STREAM was the country's first international clinical trial of such scope and complexity, the study team's strong relationship with the Ministry of Health and the national ethics committee enabled them to work collaboratively to address novel issues in the context of the trial.

"At the beginning of the trial, it was challenging for [the] trial clinic team at our site to work with TB program's district MDR-TB staff because discharged patients were followed by the district TB staff. Once discharged, the trial staff at [our site] had no connection or communication with the patients. Now, different teams at [our site] as well in the district TB programs work very closely and share the responsibility of looking after the patients."

SITE COORDINATOR,
STREAM TRIAL

RECOMMENDED BEST PRACTICES

Build and maintain in-depth local knowledge and relationships through the following measures:

- Identify local "champions" with excellent connections to the NTP and key regulatory bodies
- Meet early with the NTP, regulatory bodies (where feasible – e.g., the Indian regulator DCGI has recently made 'advance consultations' possible), and other key stakeholders to discuss the trial and obtain their buy-in
- Develop a thorough understanding of the NTP's network, patient referral pathways and treatment model
- Develop a thorough understanding of the clinical trial regulations in each potential trial location
- Implement a continuous communications plan with key stakeholders

Systematic site assessments

Sponsors should systematically assess potential sites and develop a targeted response to identified weaknesses

A robust site selection process is required to ensure appropriate sites are selected and equipped to manage a clinical trial. The process should consider patient population (recruitment potential), clinical expertise (ability to manage participant care), microbiology expertise, non-clinical expertise (for example project management and regulatory knowledge and experience) and the adequacy of physical infrastructure (such as that of lab, pharmacy, and information technology).

In STREAM, site selection began with a desk-top analysis of recruitment potential based on burden of disease and competing trials at the site. For potentially eligible sites, the Sponsor approached the NTP to determine their support for the trial. MRC CTU at UCL, ITM and Sponsor pharmacists then visited the site to assess its facilities and expertise. While these visits were quite good at confirming clinical expertise and identifying required changes to infrastructure, they were less effective at assessing non-clinical capabilities. As a consequence, there were sometimes delays in identifying gaps and weaknesses related to aspects such as project management, logistics and regulatory expertise. For example, a trial site in India had significant experience with the primary trial regulator (the DCGI), but less experience with secondary regulatory requirements under the country's biodiversity legislation applicable to the export of trial samples. A more thorough upfront assessment of expertise by the Sponsor could have identified and addressed this gap through additional staff hiring or by contracting local consultants or experts.

In most cases, however, the STREAM site selection process worked very well to ensure trial sites were well-equipped to conduct the trial. Excellent sites were selected, and the assessment process effectively identified gaps and weaknesses. At many sites, assessment visits successfully identified infrastructure improvements needed for storing trial medicines in appropriately controlled environments. In Mongolia, the initial assessment concluded that STREAM was among the most complex clinical trials ever conducted in the country and, therefore, would necessarily raise novel regulatory issues for the national ethics committee to consider. In response, trial timelines and resources were adjusted to account for the extensive interactions required with the ethics committee and regulators to ensure their concerns and questions regarding the trial were adequately addressed by the Sponsor and the site. In India, some sites received more intensive GCP training to address their limited experience with phase III FDA-regulated clinical trials. Site assessments also helped identify laboratories where ITM conducted pre-initiation trainings on trial-specific techniques for staining and culturing of *Mycobacterium tuberculosis*.

"Careful review of all regulatory components as part of the site assessment, such as import/export requirements, can help mitigate delays and other challenges in trial implementation."

VITAL STRATEGIES,
STREAM SPONSOR

RECOMMENDED BEST PRACTICES

Ensure clinical trial sites are equipped to successfully manage the trial through the following measures:

- Implement a systematic site evaluation and selection process that assesses the full range of criteria relevant to successful implementation of the trial and includes clear selection criteria
- Clearly document site assessments and targeted responses to identified weaknesses
- Implement responses to identified weaknesses, including infrastructure improvements and capacity building at site as well as systems level
- Share information about site readiness with sponsors of future trials to simplify site selection

Diverse range of skills and experience

Site staff must have a broad range of skills and experience to effectively implement a phase III clinical trial

Good clinicians are essential for successful trial implementation, but a wide range of other skills are needed, including project management skills, ethics and regulatory expertise, and data management experience. Sponsors should ensure the breadth of trial requirements is clear to participating trial sites so that appropriate staff are available and trained. This is particularly the case in the two areas outlined below – project management and regulatory expertise.

Project management is especially important in clinical trials, with a strong need to coordinate diverse activity streams – for example, clinical care, laboratory assessments, regulatory compliance, and financial compliance (among others). Equally, a focal point for communication with the trial sponsor is essential. Therefore, every site should aim to have a very strong trial coordinator.

Ideally, given the range of issues they need to manage, trial coordinators will be as comfortable in high-level meetings with regulators as they are managing the details of procurement. In addition, trial coordinators should be good communicators who can "translate" clinical concepts for non-clinical staff and vice versa, as well as communicate with the sponsor (which often requires English fluency). In STREAM, sites that had trial coordinators with strong communication skills whose role was defined as overall trial implementation and management, rather than only clinical care, performed very well.

In-depth regulatory expertise is also important, and critical to navigating initial approval of the study by local ethics committees and regulators, as well as ongoing regulatory compliance. Where STREAM study teams did not have significant regulatory expertise, the trial experienced delays in approvals for the initial submission as well as subsequent amendments and the trial was forced to rely on external parties (CRO or local consultants) to understand and comply with regulatory requirements. Access to regulatory expertise was especially important in locations with more complex or less-developed regulatory regimes, for example India and Mongolia.

Ideally, sites will recruit staff that have the diverse experience and expertise required by the trial. However, where that is not possible, Sponsors will need to identify local consultants to fill gaps and/or provide appropriate training and support to build expertise in existing staff.

"At first, we thought the study coordinator should be chosen based on their excellent patient management skills. Soon into the trial, we understood that the role should be more focused on the overall coordination and administration of the trial."

SITE PRINCIPAL INVESTIGATOR, STREAM TRIAL

RECOMMENDED BEST PRACTICES

Ensure sites are equipped to manage the broad range of issues that arise in connection with clinical trials through the following measures:

- Provide sites with standard Terms of Reference for key positions to inform hiring decisions
- Invest in key non-clinical staff positions, including a trial coordinator with strong project management and communication skills and a regulatory lead with the experience required to navigate local and international requirements
- Work with sites to identify local consultants to fill gaps in staff experience/expertise
- Support capacity building for site staff throughout the trial, especially on non-clinical aspects such as project management, operations, and financial management.

Risk-based monitoring strategy
Implement a well-designed, risk-based monitoring strategy

Oversight of a clinical trial requires a well-designed, risk-based monitoring strategy that is flexible enough to account for the different experience/expertise levels of trial sites. While much of the oversight can be conducted remotely, onsite visits are required to build personal relationships, effectively carry out capacity building, review sensitive participant records and observe site facilities and activities. In STREAM, the trial's main implementation partner, MRC CTU at UCL, made in-person monitoring site visits in response to identified issues, but generally oversaw the trial remotely. In Stage 2, in recognition of the need for further onsite oversight, the frequency and scope of onsite monitoring increased and included regular onsite visits by a contract research organization (typically one visit/site/month), the trial's microbiology lead (typically one visit/site/year) and the trial's pharmacists (typically one visit/site/year).

At sites with prior experience of running multi-site trials (e.g., some of the South African sites), this approach worked well because they had experienced principal investigators and clinical trial/research units to support less-experienced trial team members and understood when to escalate issues to the sponsor/partners.

However, some less experienced sites initially reported more serious protocol deviations – including some related to the informed consent process and reporting of safety events – indicating that a more comprehensive monitoring approach was needed for inexperienced sites.

As issues were identified, monitoring strategies were adjusted to incorporate more intensive onsite monitoring (particularly in the early stages of participant recruitment), additional site audits, and development of corrective action and prevention (CAPA) plans. At the less-experienced India sites, a New Delhi-based sponsor representative made frequent onsite visits to identify challenges and provide support. In addition, later in the trial, CRO visits were timed to ensure an initial visit just after the first few participants were recruited in order to confirm site compliance with the informed consent process and participant eligibility requirements. This helped control major protocol deviations and identify training and/or process changes required at sites.

"The role of the local country based monitor is very important in bridging the gaps of understanding context at a site level between sponsors and site staff. Site visits from the sponsor could have been more frequent and if not possible, skype calls or regular feedback sessions on study progression to address concerns as they came up would have been very useful for new sites."

SITE PRINCIPAL INVESTIGATOR, STREAM TRIAL

RECOMMENDED BEST PRACTICES

Identify and respond to quality issues through the following measures:

- Develop a clear, risk-based monitoring system that accounts for differing experience levels at trial sites
- Implement more intensive and in-person monitoring during the initial recruitment period to identify and resolve major quality issues
- Develop and implement a risk-based audit plan that prioritizes higher-risk sites (e.g., inexperienced or high recruiting sites)
- Ensure frequent and regular communication channel between sponsor and site team

Standard processes at sites

Sites should develop and document standard processes (SOPs) in line with the trial protocol for key aspects of trial implementation

Regulated clinical trials must meet the highest standards related to participant safety and data integrity. To do so, key trial requirements are set out in the trial protocol, with details of implementation typically left to sites so that local conditions can be considered in site-level processes. Too little site-level systematization of processes can mean key aspects of the trial are not implemented in accordance with the trial's requirements (per the protocol, lab manual, etc.).

In STREAM, more systematized implementation at sites would have improved trial performance related to central laboratory testing. All of the trial's safety testing and some microbiology analyses were conducted by central laboratories. A complex supply chain was required to permit the import of lab kits and the export of samples to central labs in Singapore, Belgium, South Africa and the UK. Sites were required to manage various aspects of the supply chain, including import and export licenses, customs/duties clearance and kit inventory management, but were not required to document their processes for managing these issues (although some elected to do so). In some cases, that resulted in high levels of kit wastage, kit stock-outs, and/or delays in sample shipment; these could have been avoided if site-level processes for inventory and shipment management had been developed.

In contrast, the trial's response to the COVID-19 pandemic demonstrated the impact of well-developed processes. Early in the pandemic, the Sponsor developed a strategy for ensuring continuity of care for participants and minimizing loss of trial data. This strategy prioritized continuity of treatment first, then protocol-mandated safety assessments for those still on treatment and finally minimization of data loss. This was communicated to sites and rapidly implemented by site PIs. While the principles were developed centrally, each site developed processes adapted to local circumstances – for example, where participants were unable to travel to the trial site due to lockdown restrictions, study teams made home visits; where participant travel was permitted, participants were transported to/from trial sites for key visits in a private vehicle to reduce exposure risk. Because sites developed clear processes to manage these issues, all trial treatment doses were properly dispensed to participants, even during COVID-19 lockdown restrictions.

"When we learned the trial would require central lab testing with imported bespoke kits, we knew we needed to put in place a process to make sure we didn't run out of kits and didn't order too many. So, we decided that we would keep strict records of the kits, with information about visit and expiry date. When we place an order, we make sure to consider the number of visits during the period, the type of visit, and which kits will be needed depending on the structure of the visit according to the protocol."

SITE PRINCIPAL INVESTIGATOR, STREAM TRIAL

RECOMMENDED BEST PRACTICES

Systematize key site-level processes through the following measures:

- Require sites to develop a minimum set of site-specific SOPs that cover key implementation issues, including informed consent processes (including documentation of inclusion and exclusion criteria), drug dispensing frequency and logistics to directly observed therapy (DOT) centers, trial visit scheduling, local and central laboratory testing logistics, onward reporting of protocol deviations and safety events to local ethics committees and regulatory authorities
- Provide sites with template site-level SOPs for key processes that can be adapted to local conditions
- Develop flow charts and job aids for sites around key trial processes, such as eligibility assessments and inclusion/exclusion criteria
- Review metrics around key site processes including but not limited to protocol deviations, regulatory non-compliances, kit wastage, failed tests, delays in sample shipments in order to revise and improve site-specific SOPs as required

Site-level input into trial design

Sponsors should seek and consider local input on trial design before finalization with central regulators

Trial design and implementation are improved when informed by the local context at participating sites. Despite this, it can be challenging to incorporate local input on major trial design issues in the context of multi-site, international regulatory trials. Often a protocol for the trial is submitted and approved by central regulators (for example, the US FDA or the European Medicines Agency (EMA)) before sites for the trial are selected. And even when a trial protocol is amended after sites are selected, it may not be practical for the Sponsor to consult with all trial sites due to timing constraints and/or where the central regulator's requirements are clear and overriding. Nevertheless, Sponsors should aim to maximize site-level consultation on major trial decisions, especially around trial regimens, sample exports and safety assessments. Although this could delay central approvals, it might also significantly improve implementation by avoiding decisions that will be unacceptable to country regulators and inappropriate in the local context of trial sites.

The importance of local consultation was evident on a number of occasions during STREAM. When version 8.0 of the protocol was introduced, it included significant changes related to treatment regimens and trial design that sites and local committees had not reviewed prior to finalization with the US FDA. In one country, the local regulator did not approve the change – resulting in prolonged recruitment to a secondary arm of the trial and extending overall recruitment timelines for the trial. Understanding the local regulator's views prior to engaging central regulators (USFDA/EMA) could have influenced proposals made and the ultimate decisions reached with the central regulators. In addition, even if the Sponsor had been unable to accommodate changes to account for local requirements/ context, prior consultation may have improved buy-in to the centrally-approved design changes.

A second aspect of the STREAM trial design that would have benefitted from prior local consultation was the requirement for central laboratory safety testing. It is a common requirement in multi-site, phase III trials to require central lab testing to ensure consistency of results across sites in multiple countries. However, this requirement can be misunderstood by sites and regulators, who sometimes interpret the requirement as a lack of confidence in local capacity, rather than being driven by the need for consistent results. Sponsor consultation with local partners on this issue before site selection could have improved interactions with local regulators and enhanced buy-in or – where local regulators were unwilling to permit central safety testing – informed the Sponsor's site selection.

"[I recommend that sites] ... participate in the Protocol development (to ensure local regulator's concerns regarding patient management and treatment regimens are accounted for) and ensuring that the clinical management guides (that also address issues raised locally) are in place."

STUDY COORDINATOR, STREAM TRIAL

RECOMMENDED BEST PRACTICES

Sponsor should maximize site-level consultation on major trial design issues through the following measures:

- Develop a standardized list of proposed trial characteristics (e.g., use of a central lab, import of supplies available locally, benefit sharing requirements arising from biodiversity laws, storing samples for future research, etc.) that might be controversial for local regulators
- (Using the standardized list) consult with site-level stakeholders on key aspects of trial design before finalization with central regulators
- Seek out opportunities to meet with local regulators to understand their requirements and align them better with requirements of international regulated trials

Clear roles and responsibilities

Clear roles and responsibilities must be agreed to avoid inefficiency in trial implementation

Implementation of phase III registration trials typically involves multiple partners, creating the risks that key activities are not completed or that partners duplicate efforts. It is therefore essential to clearly delineate roles and responsibilities at the start of the trial, and systematically oversee partner activities.

In STREAM, the trial Sponsor retained responsibility for oversight of investigational medicinal product but delegated most other activities to partners - MRC CTU at UCL for overall trial coordination and management, clinical oversight, data management, and statistical analysis; a CRO for regular onsite monitoring and source data verification; a central laboratory for safety testing; and ITM for central microbiology assessments and local monitoring.

There were a number of examples when the roles and responsibilities of partners were not clear, leading to inefficiencies in implementation. For example, at the start of Stage 2 of the trial, roles and responsibilities between MRC CTU at UCL and the CRO were not well-documented, making it unclear who had ultimate responsibility (and therefore decision-making power) for overall site management. This arose in part because the "typical" CRO role in industry-sponsored trials would have been more expansive than its role in STREAM. Until those roles were clearly delineated and documented, sites sometimes received conflicting instructions from MRC CTU at UCL and the CRO, which was inefficient and time consuming to manage.

Roles and responsibilities with respect to oversight of ITM were also unclear as between the sponsor and MRC CTU at UCL at the start of the trial. When the issue was identified, a microbiology sub-committee – made up of members from Vital Strategies, MRC CTU at UCL, and ITM – was formed. The committee regularly reviews a range of microbiology topics, including quality issues at site-level laboratories, sample tracking (to ensure samples were arriving at ITM), and technical issues related to ITM's central laboratory testing. The committee also developed and tracked key performance metrics to systematically assess progress on the trial. Because this subcommittee included members with responsibility for project management, vendor management and technical matters, it was an excellent model for ensuring coordinated oversight of a key trial activity.

"We would definitely focus more on writing down the roles and responsibilities of key partners/vendors before our next phase III trial. Creating a RACI matrix really helped define where our work stopped and the CRO's work started."

MRC CTU AT UCL, STREAM IMPLEMENTATION PARTNER

RECOMMENDED BEST PRACTICES

Avoid inefficiency and gaps in trial implementation through the following measures:

- Ensure overall roles are clearly defined in terms of both implementation and oversight and appropriate mechanisms are in place at the outset of the trial
- Develop a roles and responsibilities (RACI) matrix that covers all key aspects of trial implementation
- Clearly communicate agreed roles and responsibilities to sites
- Develop and regularly review key performance indicators to monitor partner performance and identify potential bottlenecks
- Regularly update RACI and Key Performance Indicator documents to adapt them to trial changes

Well-designed data flows

Document and implement well-designed data flows

The ultimate aim of clinical trials is to generate new knowledge based on accurate trial data. This often requires integration of data from multiple sources, including clinical data, lab data, and health economics data. These data will be generated at different locations and times, as well as different formats that may change over time. This makes robust, flexible and locally-appropriate data management systems and processes important, and well-qualified data management staff essential.

The main STREAM trial database was developed in-house by MRC CTU at UCL, which has a dedicated programming team. This was important for STREAM, as the programmers could make database changes quickly to address protocol amendments, modifications in data formats and new case report forms (CRFs). In addition, the database was built with robust internal checks to ensure validity and reliability of data being entered at site-level. Having a dedicated data management team to develop and document efficient data flows was also essential. For example, STREAM microbiology data transfers were required bi-directionally – from MRC CTU at UCL to ITM (information on randomized patients, follow-up visits, and local cultures) and from ITM to MRC CTU at UCL (DST and sequencing results). These transfers required close coordination and communication between data management teams at MRC CTU and ITM to ensure data could be linked to trial outcomes and were consistent in content and format.

STREAM's data management systems also needed to cater to conditions at trial sites. For example, STREAM used paper, rather than electronic CRFs to collect data because some STREAM sites experienced unreliable internet access and might have struggled with an internet-based e-CRF system. Appropriate staffing at trial sites was also a key component in efficient site-level data management. Site Data Managers not only input data, but also manage and resolve data queries raised at the central level. The STREAM experience indicates that – to fulfill these requirements – the ideal Data Manager will have clinical or clinical trial experience and English-language proficiency, as well as data entry skills. This enables them to understand and resolve data queries, interacting with the Sponsor and clinicians, where necessary.

"Ensure the data entry system has capacity to detect errors in real time to minimize the number of queries to resolve later."

SITE-LEVEL DATA ENTRY OPERATOR, STREAM TRIAL

RECOMMENDED BEST PRACTICES

Design and manage efficient and accurate data systems and flows through the following measures:

- Clearly map all data sources prior to trial initiation and documenting data transfers in data transfer agreements
- Where possible, maintain a dedicated database programming and data management team at Sponsor level
- Pilot data transfers/flows from different origins to help anticipate and identify issues
- Ensure sites understand the roles, responsibilities and skills/qualification required for site-level data managers so that appropriately qualified staff are hired
- Hold regular meetings of data management and clinical teams at trial sites to improve communication and coordination and site-level data management, especially query resolution

CASE STUDY

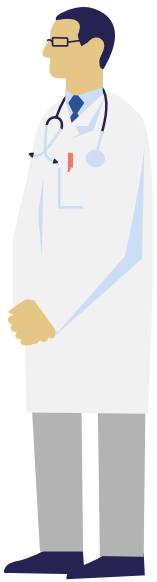
Trial implementation in Mongolia: Collaboration for successful clinical trials

In 2013, when the National Center for Communicable Diseases (NCCD) was approached to participate in STREAM, it was the first international trial of such scope and complexity implemented in Mongolia. Despite this, the site was keen to conduct the trial, given the burden of MDR-TB in the country. The site has now participated in both stages of STREAM, recruiting more than 160 participants, and is well-placed to conduct future regulatory TB trials. This was only possible because the site envisioned the trial as a collaboration among stakeholders.

The site's commitment to collaboration applied well before participant enrollment began, with initial approvals requiring the site to build understanding and support for the trial across stakeholders. The trial allocated adequate time for this work (about seven months) so sensitization meetings with all key stakeholders could be held, including the Ministry of Health (MoH), the national ethics committee, directors of the NCCD, decentralized health facilities, front line health workers, non-profit organizations supporting TB patients, and donors supporting the national TB program (NTP). The trial team's long-standing relationships with the MoH and the NTP were essential to the success of those initial meetings and achieving buy-in for the trial.

As the site moved closer to enrolling participants, study team members collaborated amongst themselves to ensure they understood each other's roles and responsibilities, and were thoroughly familiar with the protocol, as well as logistics and regulatory requirements for the trial. Study team members participated in internal role plays that covered key trial processes like screening and enrollment of participants in line with the protocol, randomization to the trial, packaging and dispensing trial medications, ECG and audiometry assessments, and completing case reporting forms. The study team also trained directly observed therapy (DOT) volunteers, who would play an important role in supporting participants during the trial. This upfront investment to clarify roles and responsibilities and to train the study team helped ensure efficient trial implementation and a positive experience for trial participants.

Collaboration between the trial team and the NTP was important at nearly every stage. Site study staff were drawn from the NTP, helping ensure the trial fully understood patient referral patterns and designed effective recruitment processes. Cooperation was also important for patient management – in particular, arranging DOT options for trial participants that met their needs. The study's experience with clinical aspects of the shorter regimen, community-based support for participants and retention were shared regularly with NTP colleagues. This conscious focus on knowledge sharing strengthened the relationship between the study and the NTP and helped improve coordinated patient management.



The site took a similar approach to managing regulatory issues collaboratively. Given the country's history with clinical trials, Mongolia's regulatory institutions had limited experience with oversight of clinical trials like STREAM. In response, the site invested in regular communications with the ethics committee and regulators to strengthen their working relationship. Regulators were invited to visit the trial site for regular updates and the study team often presented protocol amendments in person to facilitate Q&A. The trial protocol has now been amended five times and regulatory approvals have always been obtained in adequate time to permit uninterrupted trial implementation.

Perhaps the most important collaboration in the trial has been between the study team, and trial participants and family members. For example, the study worked closely with participants to adapt follow up options to participants' needs. Instead of requiring participants to return to district TB dispensaries for all treatment, participants were offered different options for DOT (at home, at lunch breaks, at family health centers and (in some cases) using video-DOT). The study team credits this flexible approach with ensuring high participant retention at the site.

> *"The [NTP] appreciates the STREAM trial not only because we contributed to the shorter MDR-TB regimen, but also STREAM's capacity building initiative has helped to ensure all staff are well-situated to work on other large-scale clinical trials."*
>
> STREAM SITE COORDINATOR

The final collaboration was between the trial site and the community. With the support of the trial, a community advisory board (CAB) was formed as a coordinating mechanism. The CAB – whose members included people affected by TB and a diverse range of representatives from NGOs and community-based organizations – served as an important bridge between the study and the community. Through the CAB's work, the study remained aware of the community's concerns and questions about STREAM, and the community was informed about study progress. This helped build the community's trust in both the STREAM trial and clinical research generally.

More than seven years after joining STREAM, Mongolia has gained important experience and strengthened critical relationships needed to participate in future clinical trials. This underscores the gains that can be made when stakeholders collaborate with a common purpose.

TREAT TB | Technology, Research, Education and Technical Assistance for Tuberculosis

ACKNOWLEDGMENTS

This report is made possible by the generous support of the American people through the USAID TREAT TB Cooperative Agreement No. GHN-A-00-08-00004. The contents are the responsibility of Vital Strategies and do not necessarily reflect the views of USAID or the United States Government.

This report was developed by Vital Strategies (trial sponsor) with input from MRC CTU at UCL, ITM and trial sites.

STREAM was conceived by The Union and key partners, including Vital Strategies, the Medical Research Council Clinical Trials Unit at University College London (main implementing partner), the Institute of Tropical Medicine (microbiology lead) and Liverpool School of Tropical Medicine (health economics lead). STREAM Stage 1 was funded by The United States Agency for International Development (USAID), with additional support from the United Kingdom Medical Research Council (MRC) and the United Kingdom Department for International Development (DFID) under the MRC/DFID Concordat agreement. STREAM Stage 2 is being funded by USAID and Janssen Pharmaceuticals, the maker of bedaquiline, with additional support from MRC and DFID.

USAID FROM THE AMERICAN PEOPLE · Vital Strategies · The Union · MRC Clinical Trials Unit · UCL · LSTM · Institute of Tropical Medicine Antwerp