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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart Lung and Blood Institute (NHLBI) or the National Institute of Allergy and Infectious Diseases, the National Institutes of Health (NIH), or the Department of Health and Human Services.

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The importance of methods for site performance evaluation in REPRIEVE, a longitudinal, global, multicenter trial

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2022.107035.

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Abstract

Background: REPRIEVE, the Randomized Trial to Prevent Vascular Events in HIV, is a multicenter, primary prevention trial evaluating whether a statin can prevent major cardiovascular events in people with HIV. REPRIEVE is conducted at >100 clinical research sites (CRSs) globally. Detailed, comprehensive, and novel methods for evaluating and communicating CRS performance are required to ensure trial integrity and data quality. In this analysis we describe a comprehensive multidimensional methodology for evaluating CRS performance.

Methods: The REPRIEVE Data Coordinating and Clinical Coordinating Centers developed a robust system for evaluation of and communication with CRSs, designed to identify potential issues and obstacles to performance, provide real-time technical support, and make recommendations for process improvements to facilitate efficient trial execution. We describe these systems and evaluate their impact on participant retention, data management, and specimen management from 2019 to 2022, corresponding to the period from end of recruitment to present. This evaluation was based on pre-defined metrics, regular reviews, and bidirectional communication.

Results: Participant retention, data management, and specimen management all remained steady over the three-year period, although metrics varied by country of enrollment. Targeted messaging relating to certain performance metrics was effective.

Conclusion: Site performance is vital to ensure trial integrity and achievement of key trial goals. This analysis demonstrates that utilization of a comprehensive approach allows for a thorough evaluation of CRS performance, facilitates data and specimen management, and enhances participant retention. Our approach may serve as a guidepost for maximizing future large-scale clinical trials' operational success and scientific rigor.

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Keywords

Site performance; Clinical trial management; Participant retention; Data management

1. Introduction

Multicenter randomized controlled trials are complex undertakings. Developing and evaluating clinical research site (CRS) performance for the efficacy and quality of trial conduct is important to carry out during trial start-up, enrollment, and follow-up phases

to ensure scientific integrity. Site performance evaluation is also important for key stakeholders. Excellent trial conduct is a key factor in the scientific success of multicenter trials and is a measure dependent on how well CRSs meet goals established for participant retention and collection of high-quality data in a timely manner. Developing operating procedures that generate easily accessible data relevant to the performance of CRSs and streamlined processes for review and dissemination of this data has the potential to improve the efficiency and success of trials. Ideally, such performance metrics should provide information that quickly identifies potential problems so they can be mitigated or avoided, hence minimizing their impact, and improving the efficiency and robustness of trial conduct. Herein we describe a system and process of CRS performance evaluation and quality improvement developed for a large-scale, longitudinal, multicenter international trial utilizing novel metrics, reports, and interventions to ensure trial integrity and data quality. To evaluate the utility of site performance metrics we analyzed site performance data from April 2019, when study enrollment was nearing completion, to April 2022, when the current analysis was performed. Specifically, we looked at three categories of performance: retention of participants, data management, and specimen management. These metrics capture performance relating to key trial outcomes as already described [1]. Notably, this trial was initiated prior to but extended into the period of COVID-19 pandemic. The methods we describe were helpful to maintain key trial metrics within expected thresholds despite these difficult circumstances.

2. Study background

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is a randomized, double-blind, placebo-controlled phase III trial evaluating pitavastatin calcium as a prevention strategy for major adverse cardiovascular events (MACE) among people with HIV (PWH) on antiretroviral therapy (ART), with low-to-moderate traditional cardiovascular disease (CVD) risk. The trial is supported by the National Heart Lung and Blood Institute (NHLBI) and National Institute of Allergy and Infectious Diseases (NIAID), with additional support from Kowa Pharmaceuticals America Inc., Gilead Sciences Inc., and ViiV Healthcare. Between March 2015 and July 2019, REPRIEVE enrolled 7769 participants at over 100 CRSs in 12 countries. Follow-up is to continue until the study reaches its target number of MACE endpoints with the duration of follow-up anticipated to be between 6 and 10 years depending on when participants enrolled in the trial. Additional details on trial design, recruitment methods, and detailed inclusion and exclusion criteria have been described elsewhere [1,2].

3. Methods

3.1. Role of the clinical coordinating center in CRS performance evaluation

The Clinical Coordinating Center (CCC) for REPRIEVE, located at Massachusetts General Hospital (MGH), is responsible for the clinical conduct of the trial. Critical functional components of the CCC include trial execution, clinical operations, site management and performance, protocol training, and development of study materials and communications. The CCC liaises with various stakeholders to ensure operational control over protocol

execution and coordination of sites and communication. The Site Selection, Performance, and Close Out Committee (SSPCC), the committee responsible for CRS performance evaluation, is under the oversight of the CCC.

3.2. Role of the data coordinating center in CRS performance evaluation

The Data Coordinating Center (DCC) provides methodological and logistical support for the collection, quality control, and analysis of data including rigorous, timely, and independent adjudication of potential MACE events. Furthermore, the DCC remains responsible for statistical design and analysis, assistance in protocol development, data management and is responsible for development and distribution of site performance summary reports internally, including Site Score Cards, Retention Summaries, Site Summary Reports, and Specimen Availability Reports. The DCC includes the Center for Biostatistics in AIDS Research (CBAR) at Harvard T.H. Chan School of Public Health, the clinical data managers and laboratory data managers at Frontier Science (FSTRF), and the MGH Imaging Trials Center. The reports are organized by site and include summary statistics of overall performance. Importantly, the DCC has built programs to automate the process of data extraction and report creation. The CRS performance summary reports are distributed monthly to the SSPCC.

3.3. The site selection, performance, and closeout committee

The SSPCC is responsible for CRS performance evaluation and as such is the committee charged with communication with CRSs regarding any concerns related to participant retention, data management, or specimen management. This committee was constituted during the start-up phase of REPRIEVE and is under the oversight of the CCC. The committee was established to evaluate and initially select sites and assist with site activation. As recruitment began, the SSPCC developed processes to: (1) evaluate each CRS based on predetermined performance metrics; and (2) communicate performance evaluations with each CRS. To properly carry out site performance evaluation, the SSPCC critically depends on the DCC for accurate and timely data regarding performance and actionable reports. The SSPCC draws insight and expertise from a membership that encompasses REPRIEVE site investigators, study coordinators, as well as laboratory and pharmacy representatives (see Supplemental Material 1 for a description of roles and responsibilities of SSPCC members). A key principle of trial oversight is to engage and involve the site investigators and staff in the evaluation of CRS performance methods and communication about performance with CRSs.

3.4. Site performance plan

Evaluation of site performance is a collaborative effort between the DCC and CCC. A Site Performance Plan (SPP) was developed by trial leadership with input from stakeholders as a document to guide the evaluation and assessment of CRS performance. The SPP was developed through adaptation of the AIDS Clinical Trials Group (ACTG) Performance and Evaluation Committee's site performance plan to meet the needs of REPRIEVE CRS performance evaluation. The SPP explains each area of performance evaluated (i.e. retention, data management), the standard expected, and the outcome if not meeting the

standard. All CRSs have access to the SPP on REPRIEVE's protocol-specific webpage (Supplemental Material 1).

3.5. Formal site performance evaluation

Because of the large number of CRSs (>100) participating in REPRIEVE, CRSs are assigned to one of four "Teams" for the purposes of performance evaluation review. The Team assignment determines the cycle of CRS performance evaluation, conducted biannually (twice yearly) (Table 1). For example, all CRSs in Team 1 receive their biannual performance evaluation in January and July each year and the SSPCC meeting is focused on performance review of Team 1 sites during these same months.

During each biannual evaluation cycle, CRSs are evaluated on participant retention, data management, and laboratory management; accrual was evaluated during the enrollment phase of the trial. Additional metrics are evaluated as needed. The biannual evaluations include a summary table of a CRS's performance based on standards set out by the SPP and then explains in detail the CRS's site-specific performance and any follow-up required by the CRS if needed.

Biannual evaluations are sent via email to the CRS principal investigator and study coordinator. As outlined in the SPP, a CRS deficient in a performance measure during a 6-month period is notified of the deficiency in the biannual evaluation and may be required to submit a corrective action plan (CAP) describing a plan to address the deficiency. Supplemental Material 1 includes standards and outcomes if a CRS is not meeting a standard. For CRSs that are flagged to be at risk of falling below certain performance measures, the SSPCC provides additional assistance and training. For sites that are not responsive, there are clear escalation procedures in place: first a site is contacted via email by the trial's project manager or clinical research coordinator, next the site is contacted by a principal investigator or co-investigator and if deficiencies still persist, a site call is scheduled.

Through use of these detailed assessments and procedures, REPRIEVE has created and maintained a vibrant, highly successful trial, meeting all the major prespecified metrics.

3.6. Channels of communication

In addition to Biannual Performance Evaluations, a variety of communication channels have been developed to facilitate the timely dissemination of information to CRSs, to frequently communicate CRS performance in a variety of formats (Table 1), and to support CRS performance. These channels include monthly site score cards, monthly site newsletters, site calls, personal outreach by SSPCC leadership, and Ambassador Visits which are in-person or remote visits with the CRS team. Through these various channels, the CCC via the SSPCC provides sufficient information and assistance to communicate CRS performance, support CRS performance, and support the efforts of the SSPCC without overwhelming CRSs with additional tasks.

Site score card reports are sent via email monthly. The purpose of the site score cards is to provide an overview of overall trial and CRS performance relative to proposed benchmarks

for enrollment and retention. The site score card reports are distributed monthly by email to all CRSs and are accompanied by a cover email that describes pertinent trial performance reminders and updates while the score cards themselves include tables of overall enrollment status, figures of the number of participants enrolled, rate of loss to follow up, rate of off-treatment for nonclinical reasons, and site summaries of participants off-study or at risk for loss to follow-up. Fig. 1 provides an example of a novel figure developed by the DCC and is included in the score card describing participants at risk of loss to follow-up, defined as a participant without contact in >9 months and thus at risk for dropping out of the trial.

Site newsletters are sent via email and contain information relevant to CRS staff, for example, accrual, retention, data management, lab tips, and important trial updates. Site newsletters are distributed monthly and posted on the REPRIEVE website (see https://www.reprievetrial.org/site-resources/reprieve-site-newsletters/).

CRS team calls are conducted over a video-conferencing platform; information relevant to the trial is shared with CRSs and CRSs may pose questions directly to members of the REPRIEVE leadership team.

Finally, the SSPCC has carried out *one-on-one visits* with each CRS team, known as the *REPRIEVE Ambassador Initiative*. These visits were initially in-person but reverted to video visits in March of 2020 due to the COVID-19 pandemic. During such visits, SSPCC team members orchestrate a friendly informal discussion about the status of the trial, highlight priorities in terms of site performance and engagement, discuss ways the SSPCC can support the CRS's retention efforts, and address any questions or concerns raised by the CRS.

Through a *continuous cycle of monthly reviews and biannual evaluations*, the SSPCC identifies potential issues and obstacles to performance, provides real-time technical support and assistance to CRSs when necessary, and makes recommendations to the REPRIEVE Executive Committee for process improvements to facilitate the efficient execution of the trial.

3.7. The present analysis

Of the 210 CRSs that expressed interest in participating in the trial, 146 were protocol activated and 126 are currently following participants (Fig. 2). 126 CRSs are included in the current analysis. 20 CRSs closed after site activation, 1 CRS merged with another CRS, 15 closed because of CRS PI request and 4 closed due to site performance. Of the 20 CRSs, 15 CRSs had enrolled participants and SSPCC leadership worked with each CRS team and site PI to ensure that participants transferred to the closest REPRIEVE CRS, or to the CRS of their choosing.

Although REPRIEVE is ongoing, here we describe site performance in the trial thus far. To determine how the above-described methods have supported the trial, we analyzed site performance data from April 2019, when study enrollment was nearing completion and site performance evaluation shifted from accrual to retention, to April 2022, when the current analysis was performed. Specifically, we looked at three categories of performance: retention of participants, data management, and specimen management. Data for these

metrics were looked at overall and by country of enrollment. Data and specimen metric management were assessed by calculating the mean. Retention metrics were assessed by calculating the rate. These metrics capture CRS performance to support the achievement of key trial outcomes.

3.7.1. Retention—Retention is determined by the rate of participants electing to withdraw from the trial for reasons other than death (study discontinuation) and by the rate of participants electing to stop study treatment for reasons other than clinical necessity (e.g., CVD event requiring statin use) but remain in the trial (treatment discontinuation). Both are reported as a rate per 100 person-years (100PY). The trial goal is to have rates below 5/100PY for each metric.

3.7.2. Data management—To quantify data management performance, we evaluate data entry timeliness, calculated as new data submitted in the electronic data capture system within 3 weeks/total data submitted*100 (reported as a percent), expected data submitted (cumulative), calculated as completed visits/expected visits*100, and expected endpoint data submitted, calculated as endpoint data entered in the electronic data capture system/expected data*100. The trial standard is to have scores 90% or greater for all data management metrics.

3.7.3. Specimen management—To quantify specimen management performance, we calculate expected specimens shipped to the repository within 6 months of collection, calculated as the number of specimens shipped/total specimens*100 (reported as a percent). The trial standard is to have a score 90% or greater for all specimen management metrics.

To evaluate the impact of the above methods, we took a two-pronged approach. First, we looked at how results in the aforementioned categories of metrics changed over time, from April 2019 to April 2022. Data were examined overall and by country of enrollment. Second, in a sub-analysis, we looked at sites for whom performance along pre-specified metrics (data timeliness and study discontinuation) was not meeting anticipated performance standards during the Fall of 2021. For such sites, specific language was included in their formal biannual evaluation asking the CRS to pay close attention to their performance in the coming months. To better understand how this messaging may have impacted metrics, we looked at how these metrics changed over a period of six months following notification of poor performance, assessing the means and standard deviations of specific metrics.

4. Results

4.1. Participant retention

For active REPRIEVE CRSs, participant retention metrics remained stable over this analysis period. The average study discontinuation rate changed from 3.88/100PY in April 2019 to 2.74/100PY in April 2022, with highest (worst) discontinuation rates observed in April 2019 (Fig. 3a). This rate varied by country of enrollment; for example, in April 2022 sites in Thailand had the lowest (best) discontinuation rate (0.18/100PY) (Fig. 3b).

The average treatment discontinuation rate changed from 6.38/100PY in April 2019 to 5.05/100PY in April 2022, with the highest (worst) rate observed in April 2019 (Fig. 3a). This rate also varied by country of enrollment, with the lowest treatment discontinuation rate in Zimbabwe (0.24/100PY in April 2022) and the highest treatment discontinuation rate in the US/Canada (7.79/100PY in April 2022; Fig. 3c).

4.2. Data and specimen management

For all active REPRIEVE CRSs as of the current analysis, data and laboratory management scores remained steady over the analysis period (Fig. 4a). Data timeliness scores changed from 89.48% in April 2019 to 86.45% in April 2022 (Fig. 4b). Expected data submitted changed from 98.37% in April 2019 to 96.93% in April 2022 (Fig. 4c). Expected endpoint data submitted changed from 96.20% in April 2019 to 90.24% in April 2022 (Fig. 4d). Expected specimens shipped changed from 98.47% in April 2019 to 95.61% in April 2022 (Fig. 4e).

4.3. Sub-analyses: impact of targeted messaging in biannual evaluations

In the Fall 2021 biannual CRS evaluations, 40 of 126 CRSs had treatment discontinuation rates above the trial benchmark (indicating a deficiency) and thus targeted messaging was included in each biannual evaluation for these 40 CRSs. CRSs were notified that their treatment discontinuation rate was above the trial standard and asked to keep a close eye on these rates during the next 6-month evaluation period. The messaging also reminded CRSs of the importance of maintaining low discontinuation rates and of the option for participants to restart treatment if it was determined to be safe to do so. Of the 40 CRSs that received this targeted language in their Fall 2021 formal evaluation, 35 (88%) had rates that improved in the following evaluation period (6 months later). The mean change in treatment discontinuation rate was −1.28/100PY ± 1.70/100PY. In comparison, for the 86 CRSs that did not receive this targeted messaging, 59 (67%) had rates that either improved or stayed the same, and the mean change was +0.06/100PY ± 0.85/100PY (Fig. 5a).

Additionally, targeted messaging pertaining to data timeliness was included in the biannual evaluations for Fall 2021 for 36 CRSs that had a deficiency in this metric. These CRSs were thus notified that their data timeliness score was below the standard and asked to consider ways to ensure all REPRIEVE data is entered within 3 weeks of a study visit. Of the 36 sites that received this targeted messaging in their Fall 2021 biannual evaluation, 28 (78%) had scores that improved in the following evaluation (6 months later). The mean change was +14.1% ± 25.3%. 83 sites did not receive this targeted language in their formal evaluation as they were meeting current trial standards. Of these, 44 (53%) had metrics that either improved or stayed the same over the six-month period. The mean change was −3.7% ± 12.8% (Fig. 5b).

5. Discussion

One aspect of successful longitudinal multi-center clinical trials is dependent on meeting operational trial goals and pre-specified metrics, whilst ensuring data timeliness and quality, and participant retention and safety. Literature describing efficacious methods for tracking

and monitoring site performance is available, however, to our knowledge, site performance evaluation methods from a trial of this size and duration have not yet been published [3–6]. REPRIEVE's methods for evaluating and assessing site performance are novel and robust and have enabled successful execution of the trial thus far, with a median duration of follow-up of 51 months. Sharing best practices developed and carried out by the SSPCC may help other multi-center trials successfully evaluate and improve the performance of clinical sites, ensuring successful completion of a trial.

This analysis demonstrates that utilization of a multidimensional approach allows for thorough evaluation and ongoing improvement of site performance, facilitating site support, data and specimen management, and participant retention. Multiple forms of communication proved essential to this approach: namely, monthly site newsletters, monthly site score cards, quarterly site calls, biannual formal and personalized evaluations, annual community forums, and ad hoc site visits. This trial has also benefitted from a multidisciplinary team comprised of statisticians, clinicians, data managers, laboratory specialists, and regulatory experts. This allows for a synergistic evaluation system, utilizing the expertise of a collaborative trial team. Moreover, the adaptability of and attention to this performance evaluation system allows for modification and augmentation, as needed, to best suit the goals of an evolving trial. For example, this trial faced a major barrier starting in March 2020: the COVID-19 global pandemic, which impacted every single CRS following participants in REPRIEVE. In some geographic regions, site operations were suspended temporarily to allow for the re-allocation of resources for more pressing needs. Additionally, site performance was affected by participant hesitancy to return to health centers, shipment delays, and staff shortages. The stability of trial metrics during this difficult period demonstrates the robustness and functionality of this trial performance system. Finally, a critical aspect is the active involvement of a core leadership team continuously monitoring site performance, providing real-time feedback and support, and, where necessary, specific interventions to maintain high-quality site performance. For example, during the COVID-19 pandemic, sites were able to mobilize remote data collection and arrange for the shipment of study medication to participants (as opposed to participants having to pick up the study medication at an in-person visit).

REPRIEVE is an international trial with representation from twelve countries and over 100 CRSs. As such, this analysis allowed for a comparison of performance across diverse geographic regions. In this analysis, we found that performance metrics were generally comparable by country of enrollment. Sites in the US/Canada tended to have the poorest data and specimen management, and retention metrics. This is likely due three reasons. The first is that the bar for being included in the trial as an international site was higher. The second may be due to cultural differences: Many international sites embed research within their clinical care paradigm, which may facilitate retention as participants undergo study procedures and receive medical care concurrently. Finally, personnel costs may differ by geographic region and thus variation in the number of site staff may impact site performance. More research is certainly needed to better elucidate how site performance varies on a global scale. The global nature of REPRIEVE highlights the importance of culturally appropriate and multilingual resources and support. Although proficiency with the

English language was a requirement to enroll as a site in the trial, we also make every effort to provide resources and baseline study results available in multiple languages.

One important aspect of this analysis was to better identify which resources are most helpful. Although this is difficult to estimate precisely due to the interconnectedness of our evaluation and communication methods, we looked at sites for whom metrics were not ideal in their Fall 2021 formal evaluation. For these sites, targeted language was included in their evaluation outlining that a metric was below the trial standard and suggesting ways to improve. We found that for sites that received this language, the metrics went up among approximately 80% of these sites in the following evaluation. In contrast, for sites that did not receive this targeted language, metrics improved in 45–60% of sites.

This analysis has a number of strengths and also, limitations. Namely, the complex nature of our performance evaluation, communication, and remediation plan does not allow for specific elucidation of which resources are most and least beneficial, as these methods are not independent and there are many factors that may impact trial retention and data management. Importantly, we did not randomize sites to receive information. Further studies incorporating comparisons of methods may be useful for determining which are most beneficial and which are extraneous. Additionally, this study is ongoing and thus further evaluation will be needed to see how these metrics continue to change over time. However, at the time of publication, this study is now entering its eighth year of follow-up from first participant first visit, and metrics have been shown to be consistent over time thus far, even in the wake of a global crisis, the COVID-19 pandemic. This analysis is further strengthened by a robust performance evaluation plan utilizing metrics and reports, established during the initiation phase of the trial, allowing for continuous monitoring of trial goals.

In conclusion, this analysis describes methods for monitoring and improving site performance in an international, longitudinal, multi-site trial with thousands of participants. Site performance is vital to ensuring trial integrity, participant safety, and alliance with key trial goals, timelines, and budgets. Here we demonstrate the performance evaluation, communication and remediation methods for the REPRIEVE trial, with a presentation of important metrics over time and after interventions as a reflection of the efficacy of these methods for supporting the science of a clinical trial. We hope these principles may serve as a guidepost for future clinical trials to ensure successful trial completion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations:

CRS	Clinical Research Site
REPRIEVE	Randomized Trial to Prevent Vascular Events in HIV
MACE	Major Adverse Cardiovascular Events
PWH	People with HIV
CVD	Cardiovascular Disease
NHLBI	National Heart Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
SPP	Site Performance Plan
ACTG	AIDS Clinical Trials Group
FSTRF	Frontier Science
CCC	Clinical Coordinating Center
SSPCC	Site Selection, Performance, and Closeout Committee
CAP	Corrective Action Plan
DCC	Data Coordinating Center

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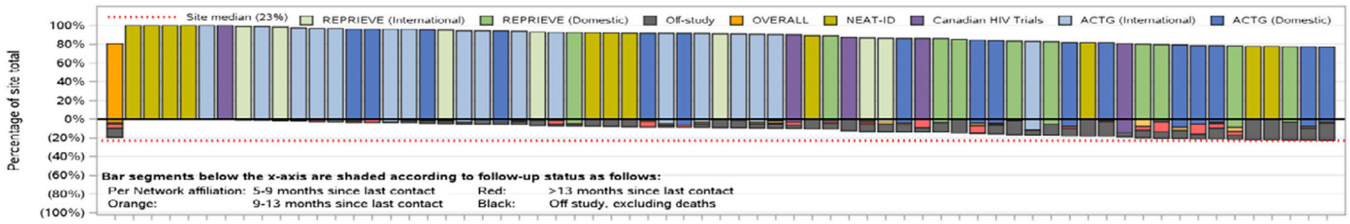

Fig. 1.

Percentage of enrolled participants off-study or at risk of loss to follow-up by site. Sites at or below the site median. Each bar shows 100% of participants at each CRS. Participants are considered in good follow-up standing (above the x-axis) if contact has been reported within the past 5 months or are known deceased; the bar segments above the x-axis indicate the CRS's network affiliation within REPRIEVE. The portion of each bar below the x-axis shows the percentage of participants off-study (excluding deaths), or with no contact reported in 5 months or greater; the bar segments below the x-axis indicate the follow-up status (time since last contact or off-study). Network affiliation description: REPRIEVE (international or domestic), no network affiliation; NEAT-ID, The European treatment network for HIV, hepatitis and global infectious diseases; Canadian HIV Trials, Canadian HIV Trials Network; ACTG (international or domestic), AIDS Clinical Trials Group.

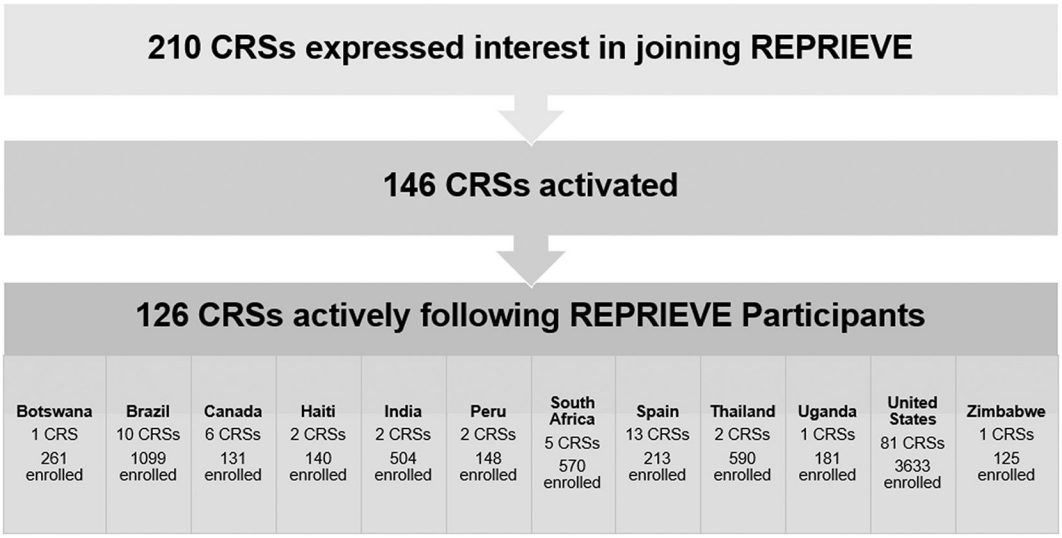

Fig. 2.

Active REPRIEVE CRSs.

Overview of REPRIEVE site activation in each country.

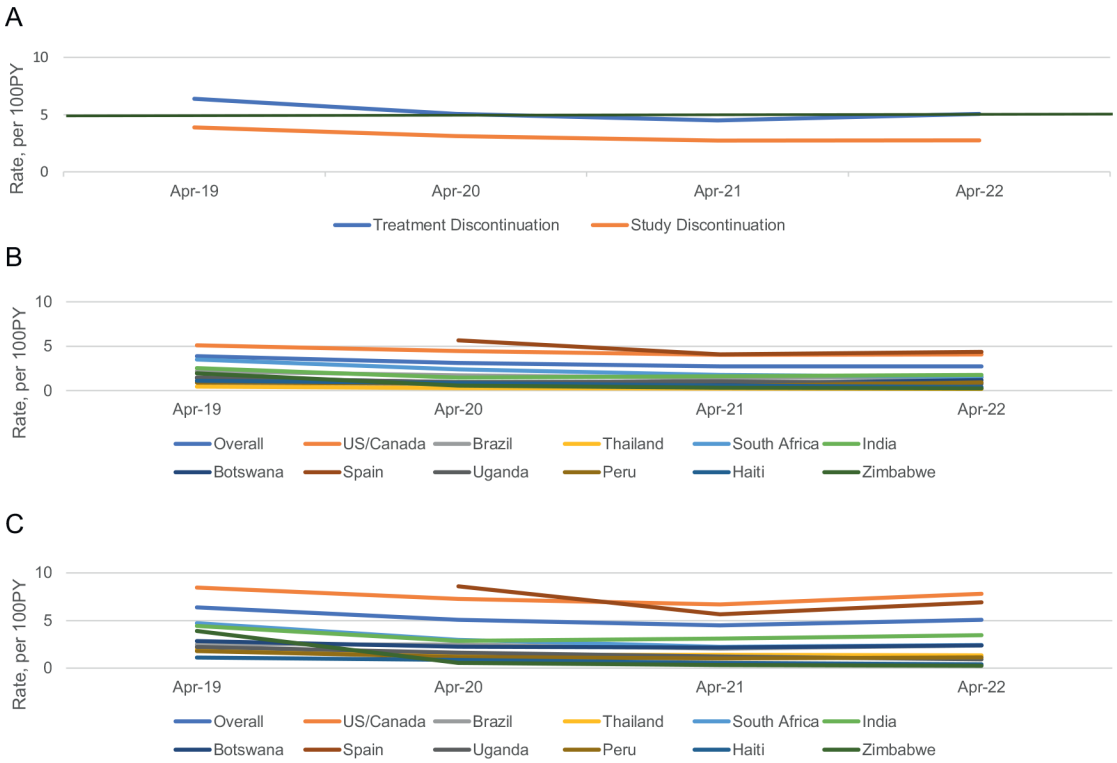

Fig. 3.

Retention Metrics April 2019–April 2022.

(A) Treatment discontinuation (blue) and study discontinuation (orange) rates for CRSs from April 2019 to April 2022. Trial benchmark (< 5/100PY) is shown by the solid green line. (B) Study discontinuation rates for each country of enrollment from April 2019 to April 2022. (C) Treatment discontinuation rates for each country of enrollment from April 2019 to April 2022. Enrollment for Spain took place from February–July 2019 thus metrics for Spain are shown from April 2020 onwards.

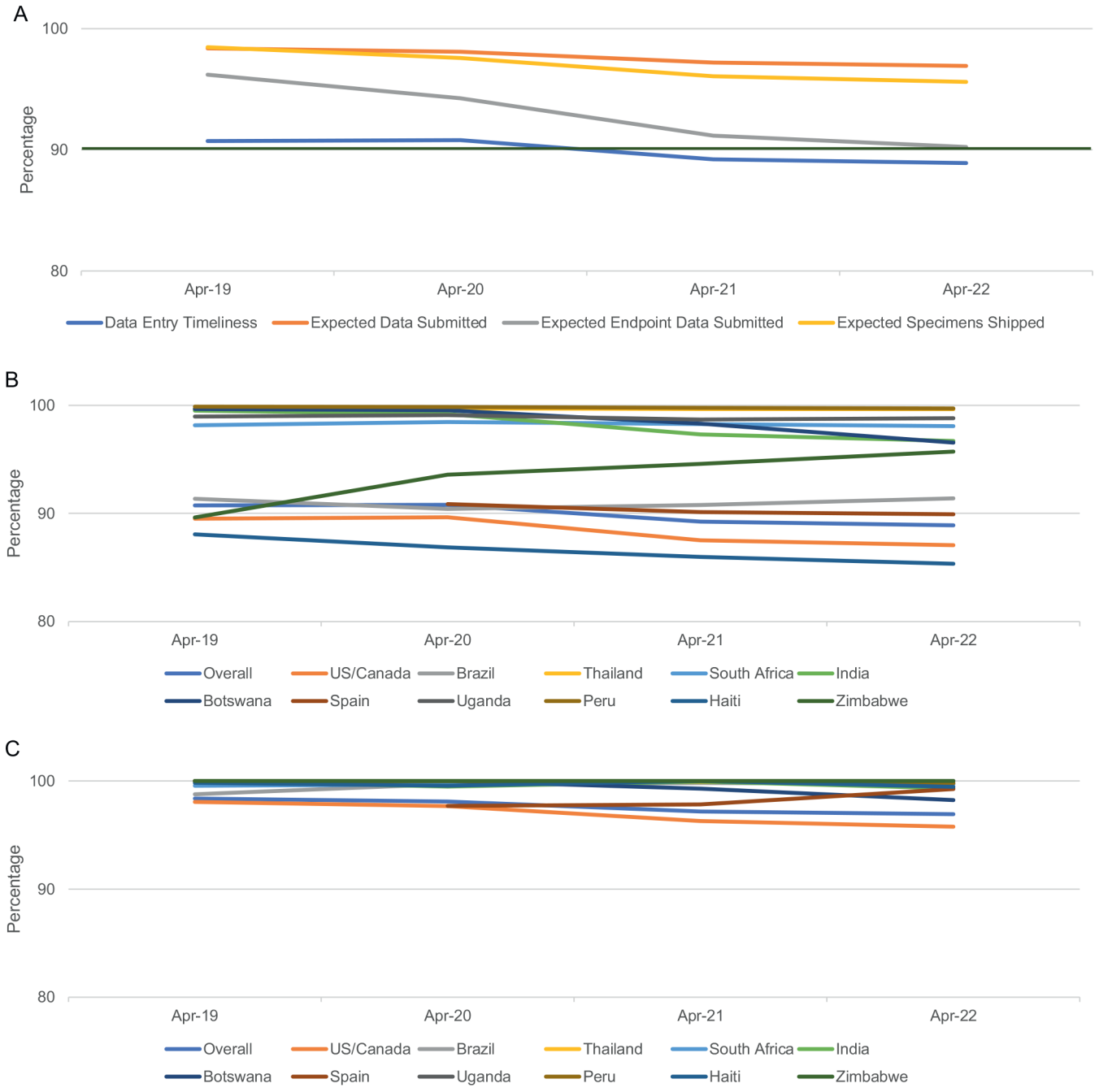

Fig. 4.

Data and Specimen Management Metrics April 2019–April 2022.

(A) Data entry timeliness (blue), expected data submitted (orange), expected endpoint data submitted (gray), and expected specimens shipped (yellow) for CRSs from April 2019 to April 2022. Trial benchmark (≥ 90%) is shown by the solid green line. (B) Data entry timeliness percentage for each country of enrollment from April 2019 to April 2022. (C) Expected data submitted percentage for each country of enrollment from April 2019 to April 2022. (D) Expected endpoint data submitted percentage for each country of enrollment from April 2019 to April 2022. (E) Expected specimens shipped percentage for each country of enrollment from April 2019 to April 2022. Enrollment for Spain took place from February–July 2019 thus metrics for Spain are shown from April 2020 onwards.

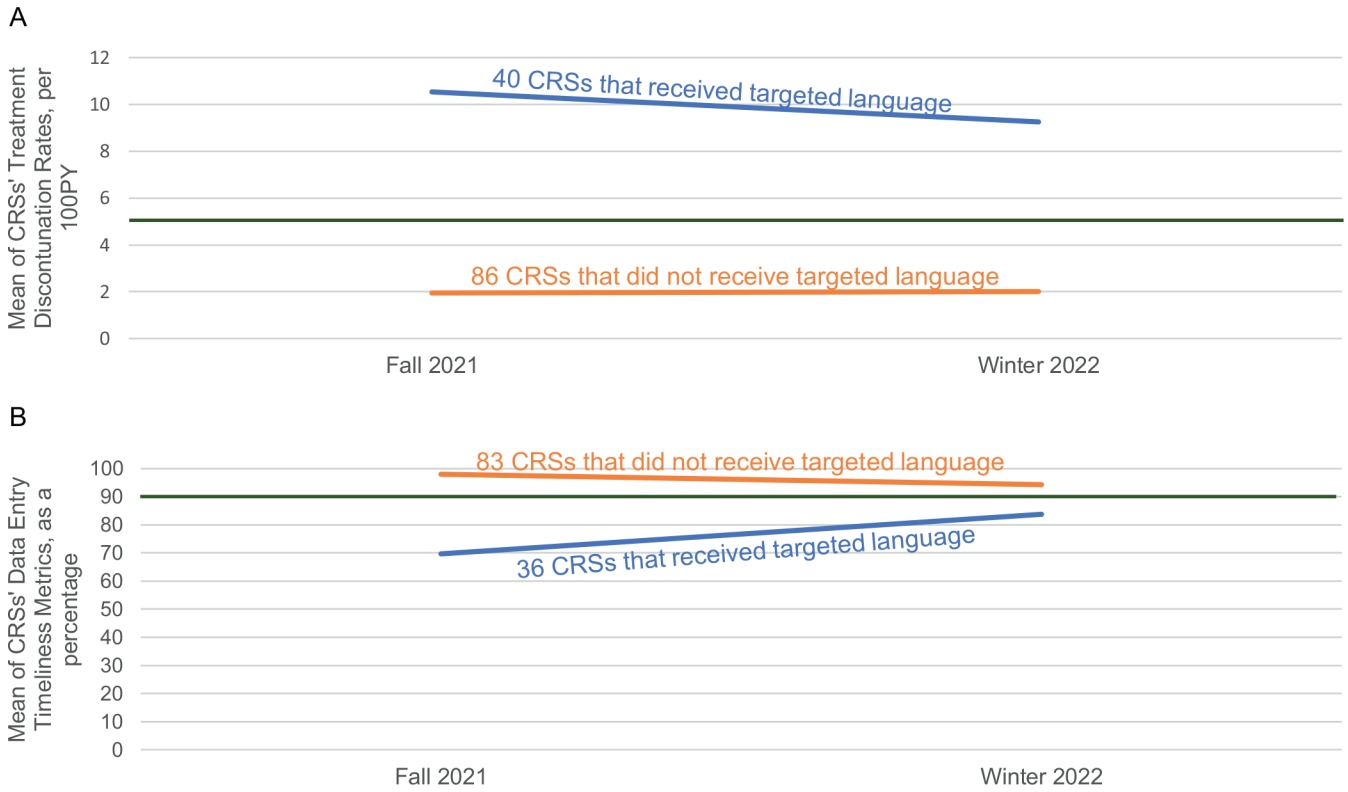

Fig. 5.

Impact of Targeted Language in Biannual Evaluations.

(A) Change in treatment discontinuation rate from Fall 2021 to Winter 2022 for sites that did or did not receive targeted language in their biannual evaluation. The trial is <5/100PY (green line) and a lower rate indicates better retention. (B) Change in data entry timeliness from Fall 2021 to Winter 2022 for sites that did or did not receive targeted evaluation in their biannual evaluation. The trial benchmark is ≥90% (green line) and a higher percentage indicates better data entry timeliness. 7 sites were not included in this comparison due to missing values for data timeliness.

Table 1

Summary of Site Communication.

See “Channels of Communication” for additional information.

January	February	March	April	May	June
• Score card • Newsletter • Site Call • Team 1 Biannual Evaluations/ • SSPCC Meeting	• Score card • Newsletter • Team 2 Biannual Evaluations • SSPCC Meeting	• Score card • Newsletter • Team 4 Biannual Evaluations • SSPCC Meeting	• Score card • Newsletter • Site Call • Team 3 Biannual Evaluations • SSPCC Meeting	• Score card • Newsletter	• Score card • Newsletter
July	**August**	**September**	**October**	**November**	**December**
• Score card • Newsletter • Site Call • Team 1 Biannual Evaluations/ • SSPCC Meeting	• Score card • Newsletter • Team 2 Biannual Evaluations • SSPCC Meeting	• Score card • Newsletter • Team 4 Biannual Evaluations • SSPCC Meeting	• Score card • Newsletter • Team 3 Biannual Evaluations • SSPCC Meeting	• Score card • Newsletter	• Score card • Newsletter

As needed:

- Ambassador Visits
- Direct emails to CRS investigator and study coordinator
- REPRIEVE Website

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