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The Status of Trial Registration Eleven Years after the ICMJE Policy

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Abstract

In the decade following the journal editors' trial registration policy, a global trial reporting system (TRS) has arisen to supplement journal publication by increasing the transparency and accountability of the clinical research enterprise (CRE), which ultimately advances evidence-based medicine. Trial registration a foundation component of the TRS. In this article, we assess impact of the trial registration on the CRE with respect to two key goals: (1) establishing a publicly accessible and structured public record of all trials and (2) ensuring access to date-stamped protocol details that change during a study. After characterizing international trial registry landscape, we summarize the published evidence of the impact of the registration laws and policies on the CRE to date. We present three analyses using ClinicalTrials.gov registration data to illustrate approaches for assessing and monitoring the TRS: (1) timing of registration (i.e., prior to trial initiation [prospective] or after trial initiation [retrospective or "late"]; (2) degree of specificity and consistency of registered primary outcome measures compared to descriptions in study protocols and published articles; and (3) a survey of the published literature to characterize how ClinicalTrials.gov data has been used in research on the CRE. These findings suggest that, while the TRS is largely moving towards goals, key stakeholders need to do more in the next decade.

Introduction

Laws and policies within the U.S. and abroad have greatly increased the transparency and accountability of the clinical research enterprise (CRE). This has been accomplished by the development of a global "trial reporting system" or TRS. The three TRS components are trial registration, aggregate results reporting, and access to individual participant data (IPD). Of these, trial registration is foundational to understanding and interpreting trial results by providing information about all relevant clinical trials (to put results into broader context) and their prespecified protocol details (to ensure adherence to the scientific plan).

In this article, we describe the current trial registration landscape and evidence of its impact to date. We then present analyses using ClinicalTrials.gov data to provide additional

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evidence regarding the degree to which current practices are fulfilling certain key goals initially envisioned for trial registration. Finally, we identify challenges and suggest potential responses for the next decade.

Key Registration Goals of the TRS

Trial registration involves the submission of descriptive information about a clinical trial to a publicly accessible web-based registry. The following goals underlie key registration requirements:

1. **Establish a publicly accessible and searchable database for disseminating a minimum set of structured information about all ongoing and completed trials**. Trial registries are designed to document publicly all human experiments, facilitate identification of trials for potential participants, and permit the incorporation of the clinical research findings into the medical evidence base.
2. **Provide access to date-stamped protocol details throughout the study lifecycle**. Access to structured, archival information allows the public to track the progress of individual studies and assess whether reported results are consistent with the prespecified protocol or statistical analysis plan.

Evolution of the Global TRS

Following announcement of the ICMJE trial registration policy in September 2004, a series of related laws and policies were implemented within the United States[1] and internationally,[2] increasing the scope and content of mandatory prospective registration. The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) established the minimum Trial Registration Data Set[3] and continues to coordinate a global network of trial registries (Table 1). To address well-documented results disclosure biases in the published literature,[4–6] some organizations subsequently enacted laws and policies requiring the systematic reporting of aggregate results to publicly accessible results databases. In the U.S., the Food and Drug Administration Amendments Act of 2007 (FDAAA) established a legal mandate requiring those responsible for initiating clinical trials to register and report summary results for certain trials of drug, biological, and device products.[7,8] In response, the National Institutes of Health (NIH) launched the ClinicalTrials.gov structured results database in September 2008.[1] In September 2016, HHS promulgated regulations to implement, clarify, and expand legal requirements under FDAAA for trial registration and results information submission.[9] Simultaneously, NIH issued a final policy requiring registration and results reporting for all clinical trials funded by NIH, whether or not the trial falls under the legal requirements of FDAAA.[10]

As of October 2016 ClinicalTrials.gov contained information on over 227,000 studies, of which nearly 23,000 have posted results entries; we estimate that only half of these have results published in the literature.[11] ClinicalTrials.gov receives approximately 580 new study registrations and 100 new results submissions per week, and about 170 million page views per month with 1.1 million unique visitors per month. The remainder of this paper analyzes data from ClinicalTrials.gov, which accounts for two-thirds of total global registrations.

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Assessing ClinicalTrials.gov and the Evolving TRS

Table 2 identifies specific evaluation criteria for each of the two foundational goals of registration. For example, the degree to which minimum trial information is publicly accessible can be assessed in many ways, including scope and coverage of registries and/or registration policies, completeness or timeliness of the registry data, accuracy of submitted information, and utility of available data to the broader community. While published evidence supports several criteria, many evidentiary gaps currently exist. To investigate some of these gaps, we collected and analyzed recent ClinicalTrials.gov data. Our efforts focused on the degree to which posted trial information (1) is registered prior to trial initiation, (2) reports outcome measures with a sufficient degree of specificity, and (3) has been used to characterize the CRE through journal publications.

The Timing of Trial Registration

Public trial registration at study initiation ensures timely access to information about all ongoing trials, while avoiding the risk of selective reporting (Key Goal 1), and documents information about the initial protocol, such as prespecified outcome measures (Key Goal 2). Comprehensive prospective registration is necessary to ensure that registered trials and, ultimately, published trial results, are not substantially biased due to cherry picking. Although no direct mechanism exists for identifying unregistered trials systematically, late registrations are a marker that stakeholders enable trials to proceed without prospective registration.[19,24]

Our goal was to identify trials that were “registered late.” On March 18, 2015, we downloaded ClinicalTrials.gov records for interventional studies (clinical trials) first received during a three-year period from 2012 to 2014. After excluding records with missing study start dates, we sorted all remaining records into two categories: (1) trials received before or within three months of the study start date and (2) trials received three or more months after the study start date (“registered late”). We also subcategorized records by funder and number of months late. We chose within 3 months of the study start date as a conservative estimate of registration occurring “on time.” The ICMJE policy requires registration prior to enrollment of the first participant (i.e., before the study start date) and FDAAA requires registration within 21 days of enrollment of the first participant. ClinicalTrials.gov collects study start date in Month-Year format. Of the 49,856 trials first received between 2012 and 2014, we excluded 105 trials that were missing a study start date.

Of the analyzed 49,751 trials, 32.8% (16,342) was “registered late,” with similar rates across years, but some variation across funder type: 23.5% (3,819/16,264) Industry, 24.9% (775/3,111) NIH, and 38.7% (11,748/30,376) academic, non-profit, or other government organizations. Among all trials “registered late,” 57.0% (9,321/16,342) were submitted to ClinicalTrials.gov more than 12 months after the study start date, with similar percentages across years and funder types.

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Specificity and Consistency of Primary Outcome Measure Reporting Across Sources

The ICMJE policy[34] requires the registration of prespecified primary and secondary outcome measures (Key Goal 2). To assess whether current registration practices provide sufficient specificity to permit assessment of the fidelity of published reports to the protocol, we assessed the level of specificity in registered primary outcome measures (POMs) using the framework we described previously.[11] We also assessed consistency across corresponding protocols, registration records, and published results using the same data set.

We identified 40 trials in each of the *New England Journal of Medicine* (*NEJM*) (extracted on Sept 16, 2015) and the *Journal of the American Medical Association* (*JAMA*) (extracted on Aug 5, 2016) reporting the results of non-phase 1 clinical trials for which full protocols were available online, and at least one ClinicalTrials.gov Identifier (NCT Number) was cited in the abstract. Descriptions of the primary outcome measures (POMs) were extracted from the final version of the full protocol; the version of the ClinicalTrials.gov record that was displayed at journal publication; and the Methods section of the published article. We note that such information could have been modified following initial submission of the record (e.g., based on ClinicalTrials.gov quality control review) or manuscript (e.g., based on feedback during the peer review process).

From our sample of 80 publications, we identified 83 trials (some articles reported results on multiple trials) and 101 registered POMs (some trials listed multiple POMs) with the following levels of specification for each POM:

- 0% domain only (e.g., “anxiety”),
- 11.9% specific measurement (e.g., “Hamilton Anxiety Rating Scale”),
- 42.6% specific metric (e.g., change from baseline),
- 45.6% method of aggregation (e.g., “mean change from baseline”), and
- 94.1% included a specific timeframe (e.g., “52 weeks”).

We identified only two published POMs with apparent inconsistencies among the three sources. (Table S1) One article pooled data from two studies registered with different POMs — one registered POM was reported for the pooled study (NCT01605136) and another (NCT00979745) was reported as a secondary outcome measure.[35] The second discrepancy was in an article that reported results of a POM that differed from the registered POM (NCT01680744) in the described measure and analysis population (i.e., outcome pertaining to the kidney donors versus recipients of kidney transplants).[36] The remaining 99 POMs seemed consistent in their description of the specific measurement across sources, although differences in levels of detail for specific definitions and/or criteria made it difficult in some cases to confirm whether measures were truly identical. For example, the meaning of “progression-free survival (PFS)” is critically dependent on the criteria used to determine “progression.” However, it is not possible to assess consistency if only one source provides those criteria. We also noted poor or inconsistent reporting of time frames, especially for time-to-event measures. (Table S2)

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Published Research Using ClinicalTrials.gov Data

Many researchers have used data from ClinicalTrials.gov to examine various aspects of the CRE. To understand the nature of such uses of the TRS more precisely and to evaluate the degree to which ClinicalTrials.gov data are meeting the needs of "meta-researchers" (i.e., researchers studying CRE), we conducted a preliminary evaluation of the published literature.

On August 7, 2015, we searched MEDLINE via PubMed to identify publications that conducted original research using data retrieved from the ClinicalTrials.gov registry and/or results database. The PubMed search string excluded MEDLINE records listing a specific ClinicalTrials.gov Identifier(s) in the Secondary Source ID field (e.g., publications reporting the findings from a particular trial) and limited the retrieval to abstracts published in English. Authors manually reviewed eligible publications for year of publication and source of ClinicalTrials.gov data (i.e., registry only, results database only, or both).

Based on this search, we retrieved 339 research articles and 1,218 systematic reviews published between 2010 and 2015 that used data from the ClinicalTrials.gov registry, results database, or both. The number of research articles increased from 24 in 2010 to 94 in 2014. We reviewed and categorized each research article into six broad areas (Table 3).

Discussion

The ICMJE registration policy instigated a cascade of events that have greatly expanded and transformed the TRS.[50] Before 2004, most investigators did not register their trials and no notion of a public summary results database existed. At that time, readers and editors had no way of knowing whether unpublished results existed for similar trials, or if the manuscripts reporting trial results accurately reflected trial protocols. Following implementation of the ICMJE policy, trial registration (whether prospective or retrospective) and acceptance of the need for structured summary results reporting and its advantages is growing, with most industry sponsors and some academic institutions developing infrastructures to help their investigators report summary results.[51] Analysis of ClinicalTrials.gov data has informed policy and research discussions, and fueled, in part, the ongoing call for sharing IPD and associated trial documents. However, gaps in the TRS and its associated policies (e.g., lack of legal reporting requirements for Phase 1 trials) and evidence of suboptimal compliance and utilization of available tools suggests room for improvement.[1] The recent issuance of the FDAAA final rule and NIH trial reporting policy will fill some of those gaps and create a framework for monitoring compliance, though considerable work remains.

For example, some funders, sponsors, IRBs, and journals continue to allow non- or late-registered trials to be conducted, and potentially published. This practice undermines Key Goal 1 by interfering with the processes designed to ensure that registries contain a list of all initiated trials; if trials can be registered late, then some trials can proceed without ever being registered at all. We found that about a third of trials across sponsor classes were registered three months or more after the start date, with a large proportion of these occurring after 12 months or more. We are aware that some trials registered late are due to changes in organizational disclosure policies (e.g., Boehringer Ingelheim registered 361

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studies in 2014 alone, some dating back to 1990),[52] but this positive movement does not explain the overall number of late registrations in all funder classes.

The use of registries to detect fidelity to the protocol using time-stamped records, has vastly improved since 2004. Requiring researchers to declare prespecified outcome measures and other study design elements as discrete structured data elements enables the tracking of each element (e.g., POMs) and facilitates comparison across trials.

Motivated editors and reviewers can compare publications to trial registry entries, a process replicated by our consistency analysis comparing the POMs reported in publications and protocols versus registration records. We note that the recently launched COMPare Project provides an ongoing platform for similar assessments.[53] While analyzed POMs were quite consistent across sources, we observed variations in the levels of specification and differences in the amount of detail provided about criteria or definitions associated with a measure. Others have noted the potential impact of differing definitional details (e.g., variations in operational meaning of “disease free survival” across breast cancer trials).[54] It is difficult to determine which discrepancies reflect benign variations in level of detail (e.g., stating “respiratory infection” as shorthand for “severe lower respiratory infection”), and which mask potential cherry picking (e.g., post-hoc selection of particular subgroups of participants). Similarly, the lack of specificity of the listed OM or the time frame leaves room for unacknowledged post hoc analytic decisions. There seems to be a special problem in the reporting of time frames for “time to event” OMs in all three sources, perhaps reflecting an underappreciation of its statistical importance.[55] (Table S2) Additionally, the lack of standards for structured protocols, which allows for internal inconsistencies and uncertainty about key study design features, reinforces the importance of requiring and enforcing registry entries that reflect the prespecified scientific plan accurately and unambiguously. It is our sense that the non-scientific personnel assigned to register trials information may have trouble identifying the relevant information from unstructured protocols, which may explain some poor registry entries. Finally, our results reflect the protocol and registration as of the time of publication; there could certainly be a greater level of discrepancy in the pre-specified versions of these documents. We anticipate that the systematic posting of full protocols and SAPs, now to be required at ClinicalTrials.gov under the FDAAA final rule and the NIH policy, will allow the research community to discuss and eventually develop consistent standards of specificity and structure needed to help ensure the valid interpretation of reported results. Efforts to standardize protocols are already underway.[56]

ClinicalTrials.gov has become a critical resource for characterizing and evaluating the CRE. Nevertheless, innumerable opportunities remain for analyzing the data more systematically to inform key decisions by investigators, funders, IRBs, and others. The next phase of the evolution of the TRS requires concerted effort from all stakeholder groups in the clinical trial ecosystem (Table 4). Full implementation of FDAAA and the NIH trial reporting policy is expected to enhance the scope and completeness of trial reporting. However, there will always be a gap between meeting the “letter” versus the “spirit” of the law. For example, investigators can meet the reporting requirements while providing minimally informative data; editors, funders and others can go through the motions to determine that a trial was

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registered, without actually using the information to assess the quality of the published reports or to inform their understanding of the results. Ultimately, significant improvements in trial reporting will require changes in the values, incentives and scientific norms at those institutions that conduct clinical trials, and those entities that use the results of clinical trials to inform medical and policy decisions. Continued attention to trial registration and summary results reporting is critical particularly as the community considers other endeavors, such as sharing of IPD.[50]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the International Registration Landscape (as of March 7, 2016)

Trial Registry	Total Number of Studies (% WHO-Identified Overlap with ClinicalTrials.gov*)	Year Launched
Australian New Zealand Clinical Trials Registry (ANZCTR)	11,703 (1.9%)	2005
Brazilian Clinical Trials Registry (ReBec)	746 (2.7%)	2010
Chinese Clinical Trials Registry (ChiCTR)	7,927 (0.3%)	2007
Clinical Research Information Service, Republic of Korea (CRiS)	1,771 (11.6%)	2010
ClinicalTrials.gov**	208,822 (100%)	2000
Clinical Trials Registry – India (CTRI)	6,562 (14.0%)	2007
Cuban Public Registry of Clinical Trials (RPCEC)	207 (0%)	2007
European Union Clinical Trials Register (EU-CTR)**	27,380 (33.2%)	2004
German Clinical Trials Register (DRKS)	4,293 (29.1%)	2008
Iranian Registry of Clinical Trials (IRCT)	9,770 (0.5%)	2008
ISRCTN registry	14,364 (6.3%)	2000
Japan Primary Registries Network (JPRN)	22,652 (4.1%)	2008
Thai Clinical Trials Registry (TCTR)	598 (1.0%)	2009
The Netherlands National Trial Register (NTR)	5,422 (1.3%)	2004
Pan African Clinical Trial Registry (PACTR)	614 (3.4%)	2009
Sri Lanka Clinical Trials Registry (SLCTR)	187 (0.5%)	2006
WHO ICTRP Search Portal – *total number of study records from all WHO ICTRP registries*	323,018 (64.4%)	2007

* Identified by WHO ICTRP using matched Secondary Identifying Numbers listed on study records

** Includes a results database

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Table 2

The Trial Reporting System (TRS): Selected Key Goals, Evaluation Criteria, and Evidence

Key Goal 1. Establish a publicly accessible and searchable database for disseminating a minimum set of structured information about all ongoing and completed trials

Description & Importance	Evaluation Criteria & Selected Evidence
• Create public record of all initiated trials, in theory • Enable search and retrieval of registered trials of interest by different users (e.g., potential participants, researchers) • Allow for tracking and assessment of results reporting bias by elucidating "denominator" • Inform the need for new trials, thereby avoiding unnecessary and unintentional duplication	**a. Scope and coverage of registered trials** • Approximately 600 new studies/week registered at ClinicalTrials.gov, which contains nearly 227,000 study records as of October 2016 • Total number of initiated, ongoing, and completed trials worldwide *unknown* ○ WHO ICTRP Search Portal listed 323,018 study records from 16 trial registries (as of March 7, 2016; Table 1), of which 15,808 registrations identified by WHO ICTRP as "duplicates" (i.e., records from two or more registries representing a single trial) ○ 208,665 of the 307,210 (68%) WHO ICTRP-identified unique study records were registered on ClinicalTrials.gov ○ Recently estimated additional duplicate registrations not detected by the WHO ICTRP Search Portal[12] ○ Unidentified duplicates create residual ambiguity when attempting to ascertain a definitive list of all trials on a given topic
	b. Completeness and timeliness of registered information • Of nearly 600 new studies/week, over half registered prior to listed study start date • Many registry entries are incomplete, out-of-date, or have not been updated recently[13] ○ As of October 2016, the recruitment status of nearly 21,000 ClinicalTrials.gov records is "Unknown" (i.e., listed as "Recruiting," "Not yet recruiting," or "Active, not recruiting," but not confirmed within at 2 years) • Some journals require registration, reject non-registered trial manuscripts,[14,15] and embed links with the registry identifier enable linkages with PubMed ○ Nearly 42,000 publications are indexed in MEDLINE with a unique ClinicalTrials.gov identifier (i.e., NCT Number listed in the Secondary Source ID [SI] field) as of October 2016 • Other publishers/editors do not require trial registration[16,17] and/or do not publish the trial identifier, interfering with ability to link between registry records and publications • Large numbers of trials have been registered retrospectively (after the study start date)[18,19] • **Analysis in this paper**: About a third of trials initially submitted to ClinicalTrials.gov during a 3-year period registered 3 months or more after listed study start date, with large proportion registered after 12 months or more after listed start date (*see "The Timing of Trial Registration"*)
	c. Utility of registered information • Potential participants can either identify relevant trials directly or use a site that downloads and makes ClinicalTrials.gov data available for select audiences (e.g., BreastCancerTrials.org). • Many funders and sponsors have promulgated trial registration requirements (e.g., NIH, CMS, VA, PCORI),[8,20–22] but how such information has been used to inform funding or other decisions is unclear

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	• **Analysis in this paper**: ClinicalTrials.gov data was used in research articles to study the CRE (*see "Published Research Using ClinicalTrials.gov Data"*)
Key Goal 2. Provide access to date-stamped protocol details throughout the study lifecycle	
Description & Importance	**Evaluation Criteria & Selected Evidence**
• Ensure listing of all prespecified primary outcome measures (POMs) and secondary outcome measures (SOMs), as well as other trial design features • Display outcome measures (OMs) with sufficient detail to allow for detection of unacknowledged changes through public audit	**a. Detection of incompleteness/inadequacies in registered information** • Many, but not all, journal-published clinical trials associated with registry records containing all 20 items of the ICMJE/WHO Trial Registration Data Set[23,24]
	b. Specification sufficiency of registered OMs • Historically, OMs were registered with low-specificity,[11] interfering with ability to detect deviations from prespecified protocol (or subsequent amendments) • **Analysis in this paper**: From a more recent sample, level of specificity for registered POMs appears to have increased (*see "Specificity and Consistency of Primary Outcome Measure Reporting Across Sources"*)
	c. Detection of infidelity/inconsistency between registration information and other sources • Readers can use ClinicalTrials.gov to identify discrepancies between published and prespecified outcome measures[25] ○ Editors/peer-reviewers do not always check nor detect such changes[26–28] • Studies comparing registration information with protocols and/or publications document broad consistency, but instances of inconsistent or discrepant entries[25,29–33] • **Analysis in this paper**: Assessing consistency among a convenience sample of POMs reported in registries, protocols and publications, POMs were largely consistent but we noted several confounding issues that allow room for post hoc selection of a specific OM for reporting (*see "Specificity and Consistency of Primary Outcome Measure Reporting Across Sources"*)

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Table 3

Sample of Published Research Using ClinicalTrials.gov Data by Research Area and Examples

Research Area and Examples by Article Title	Number (and Percentage) of Research Articles (N = 339)
1. Characterization of Clinical Research on Specific Conditions • Association between pediatric clinical trials and global burden of disease[37] • Geographic location of antiretroviral clinical trials in HIV infected pediatric patients[38] • Ongoing clinical trials in AKI [acute kidney injury][39]	151 (45%)
2. Research on Ethics, Adverse Event Reporting, Data Mining and Other Topics • Impact of FDA guidance for developing diabetes drugs on trial design: from policy to practice[40] • Systematic identification of pharmacogenomics information from clinical trials[41]	44 (13%)
3. Quality of Registered Data and Consistency with Registration and Results Reporting Policies • Completeness and changes in registered data and reporting bias of randomized controlled trials in ICMJE journals after trial registration policy[13] • Compliance with results reporting at ClinicalTrials.gov[42]	43 (13%)
4. Characterization of the Overall Clinical Research Landscape • State of the controlled clinical trial enterprise in the United States[43] • Characteristics of clinical trials registered in ClinicalTrials.gov, 2007–2010[44]	41 (12%)
5. Evaluating Publication Bias/Selective Reporting • Half of drug trials with results on ClinicalTrials.gov are not published in journals[45] • Timing and completeness of trial results posted at ClinicalTrials.gov and published in journals[46] • Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications[47]	34 (10%)
6. Assessing Specific Research-related Methods and Issues • Use of ClinicalTrials.gov to estimate condition-specific nocebo effects and other factors affecting outcomes of analgesic trials[48] • Reporting of noninferiority trials in ClinicalTrials.gov and corresponding publications[49]	26 (8%)

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Table 4

Concrete Actions by Stakeholder Group for Improving the TRS over the Next Decade

Stakeholder Group	Sample Actions for Improving the TRS

Funders	• Use ClinicalTrials.gov to identify gaps and potential overlaps in clinical research studies prior to funding new studies
	  ○ Check the "denominator" by searching registries for relevant registered trials
	• Hold grantees accountable for accurate and timely reporting of all studies
	• Ensure that trial registration—
	  ○ Is prior to Study Start Date
	  ○ Has meaningful and specific entries

IRBs	• Ensure that ClinicalTrials.gov is used to identify past and ongoing studies that might inform the need for, and the potential risks and benefits of, each new proposed research study • Ensure that each new study is properly registered so that potential and actual participants can be assured that they are participating in a study that will contribute to the medical knowledge base
Academic medical centers (AMCs)	• Provide scientific leadership and institutional resources to support trial reporting by investigators[51] • Take institutional responsibility for ensuring that trials sponsored by the AMC are reported appropriately • Create educational resources and define best practices that support quality trial documentation as part of training for clinical researchers • Create systems for providing academic incentives for high quality trial reporting
Trialists	Before starting a trial— • Search for similar trials—completed and ongoing—as part of process for determining the necessity, feasibility and proper design of the study Once trial is designed and funded— • Register trial with specificity • Use registry unique identifier (e.g., NCT Number) when communicating about the trial • Keep registry records up to date Once trial is completed— • Take time to submit accurate and complete summary results

Journal editors and peer reviewers	• Ensure that trial registration—
	  ○ Is prior to Study Start Date
	  ○ Has meaningful and specific entries
	• Verify that submitted manuscript is—
	  ○ Consistent with prespecified protocol details from registry. Concordant with summary results in ClinicalTrials.gov or EudraCT, when available; ensure that any discrepancies are explained[57]
	• Check the "denominator" by searching registries—
	  ○ For relevant registered trials

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Stakeholder Group	Sample Actions for Improving the TRS
Meta-research researchers	• Continue using components of the TRS (registration, results reporting, sharing IPD) as well as other sources to characterize and monitor the clinical research enterprise, including using the information in systematic review of the evidence base • Pursue questions listed under Evaluation Criteria and gaps in the Published Evidence (Table 1) as part of effort to improve continually both the TRS and the clinical research enterprise
ClinicalTrials.gov (and other trial registries and results databases)	To improve support for data submitters— • Continue to improve user interface to facilitate data submission • Enhance help and resource materials • Adapt to evolving clinical research approaches and stakeholder needs • Conduct training • Provide 1-on-1 assistance for results submission • Evaluate and improve methods for curation To improve support for data users— • Improve search interface to help users make optimal use of structured data • Coordinate with other WHO registries to improve ability to identify a unique list of trials (“denominator”) • Facilitate access to trial registry data sets for use by researchers and others