Standards for design and measurement would make clinical research reproducible and usable

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Edited by David B. Allison, Indiana University Bloomington, Bloomington, IN, and accepted by Editorial Board Member Susan T. Fiske September 10, 2017 (received for review June 20, 2017)

We find standards useful in everyday life and in science, although we do not always follow them. Adopting new standards can be expensive, so there may be a strong incentive to maintain the *status quo* rather than adopt new standards. The scientific community has many standards encompassing both doing clinical research and reporting it, including standards for design and measurement. Although existing research standards have improved both research and its reporting, we need to unify existing standards and to fill the gaps between steps throughout the research process. Existing gaps include implementation of standards and links between standards for study registration (to know about all studies undertaken), study protocols (to identify the preplanned study design and methods), data collection (to assess outcomes that are important and comparable across studies), dissemination of findings (to know the results of previous studies), data sharing (to make best use of existing data), and evidence synthesis (to draw appropriate conclusions from the body of evidence). The scientific community must work together to harmonize existing standards, to ensure that standards are kept up to date, to check that standards are followed, and to develop standards where they are still needed. A unified system of standards will make our work more reproducible.

clinical trials | systematic reviews | open science | data sharing | scientific standards

In February 1904, the Great Baltimore Fire destroyed over 1,500 downtown buildings. Although Philadelphia, Washington DC, and other localities sent help, many out-of-town units were unable to assist because their hoses could not connect to Baltimore fire hydrants. One year after the Baltimore fire, national standards were agreed upon; yet the standards still are not followed in all US cities (Fig. 1). By 2004, only 18 of the 48 most populous US cities had hose and pumper connections adhering to national standards (1).

There are many obstacles to standardization, but these should not deter us from tackling important problems. For example, the costs of changing hydrants, hoses, and pumpers are substantial. Also, there may be incentives not to standardize fire equipment; for example, firefighting products are produced by multiple competing companies. Today, most fire trucks carry adaptors to maximize compatibility with nonstandard systems. Adapters may seem to avoid the need to overhaul the existing system, but they are an imperfect solution. For example, lack of adequate adapters was a factor that prevented fire fighters from working together when a fire in the Oakland, California hills killed 25 people and destroyed nearly 3,000 houses and apartments in 1991 (2).

Why Standards Are Useful

Even if we do not agree on "the best" way to achieve a goal, we may support minimum standards. Standards are processes, actions, or procedures that are deemed essential by authority, custom, or general consent. For example, many medical journals adopted structured abstracts as a standard for published research reports (https://www.nlm.nih.gov/bsd/policy/structured_abstracts.html); although the organizing information is considered essential, journals use different section headings depending on their needs and preferences.

In research, standards facilitate cooperation and better overall results—namely, good science. Across disciplines, scientists tacitly and formally agree to common standards for both the conduct and reporting of our work, ranging from units of measurement to principles about research integrity (3). Standards may have important benefits without incurring substantial costs or limiting scientific creativity. For example, the American Heart Association developed standards for measuring blood pressure (4); their use may improve the consistency of data collection across times and places, thus improving the comparability of clinical trials. Failing to apply minimum standards can lead to calamitous errors. For example, in 1999, NASA lost the $125 million Mars Climate Orbiter because contractors sent their calculations in English units (pounds) when NASA was expecting metric units (Newtons) (5).

Standards for Clinical Study Design and Methods

Scientists already accept many standards for study design. For example, randomized assignment minimizes selection bias when comparing interventions for health problems. Well-conducted randomized clinical trials are the foundation of product regulation. In conducting randomized studies, many researchers also choose to follow other suggested standards by (*i*) minimizing additional biases (e.g., information bias), (*ii*) specifying methods in a protocol before data collection begins, and (*iii*) measuring and collecting data the same way for all patients in a trial. Following common design standards is essential for determining cause and effect. Even for randomized trials, however, many existing standards were developed to address specific problems; the result is a piecemeal system of standards that are incomplete and, sometimes, incompatible.

Scientists have gone a long way to developing and adhering to or implementing standards. While standards may not be viewed as exciting or novel, they are profoundly important. For example, multiple clinical trials of a single health problem may be difficult to compare if they measure the same problem in different ways (6, 7). Using core outcomes would improve summaries of clinical trial results in systematic reviews and clinical guidelines (8, 9); however, core outcomes have not been widely adopted (10–12). Scientists should work together to adopt standards that allow us to compare clinical trials (e.g., in systematic reviews).

This paper results from the Arthur M. Sackler Colloquium of the National Academy of Sciences, "Reproducibility of Research: Issues and Proposed Remedies," held March 8–10, 2017, at the National Academy of Sciences in Washington, DC. The complete program and video recordings of most presentations are available on the NAS website at www.nasonline.org/Reproducibility.

Author contributions: K.D. and E.M.-W. wrote the paper.

Conflict of interest statement: K.D. and E.M.-W. were investigators on a contract (ME 1303 5785) from the Patient Centered Outcomes Research Institute (PCORI) entitled "Integrating multiple data sources for meta-analysis to improve patient-centered outcomes research." This study (completed) stimulated much of the thinking presented in this manuscript but did not fund any aspect of the work.

This article is a PNAS Direct Submission. D.B.A. is a guest editor invited by the Editorial Board.

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Published online March 12, 2018.

Fig. 1. A nonworking standpipe (left in place for historical reasons) is signed so that fire companies will not attempt to use it in an emergency (Baltimore, MD).

The most successful standards often result from years of development and testing, and they require ongoing work to implement them (Fig. 1). For example, health researchers advocated for decades that all clinical trials should be registered so that we would know of all studies undertaken, not just those that are published (13, 14). There are now dozens of registers worldwide, and they have proved tremendously useful; however, registering all clinical trials has been an ongoing challenge (15). Moreover, it is challenging to sustain standards and systems over time. For example, NIH created a register of funded trials in the 1970s (about three decades before ClinicalTrials.gov was launched), and it ceased operations because of lack of funding (16). Lasting solutions to the challenges associated with open science and research reproducibility must come from the community of stakeholders (*Box*).

Standards for Reporting Studies

Publication in journals has long been a core standard for disseminating scientific knowledge, yet further work is needed to implement reporting standards (17). For example, investigators continue to publish only about half of the clinical research studies undertaken (17). Although reporting a study does not guarantee that the report describes what actually happened (i.e., it cannot prevent all fraud), clear and complete reporting allows readers to identify both the strengths and weaknesses of a study—they are visible, not hidden.

Many journals have implemented reporting standards (18–20). The EQUATOR network (21) and The International Peer Review Congress, held every 4 y since 1989 (22), have contributed to research on improving reporting. We now have reporting standards for protocols (23), clinical trials (18), and many other types of studies. Nevertheless, journal articles often omit important information about study methods (17, 24, 25), a major contributor to research waste (26).

Clear and accurate reporting, starting with an unambiguous description of study methods, enhances research reproducibility. *Methods reproducibility* (i.e., providing enough information to repeat the procedures used) is often necessary to achieve *results reproducibility* (i.e., obtaining the same findings by repeating the original experiment) (27, 28). For example, outcomes must be defined completely so that fellow scientists can reproduce study results and systematic reviewers can compare results across studies. An outcome is defined using five elements: outcome domain, specific measure, specific metric, method of aggregation, and time point (29). In journal articles and systematic reviews, authors often define outcomes in terms of the domain alone (e.g., depression, pain), however (8, 30, 31). Because a single outcome domain can be associated with many outcomes defined using the five elements and because each outcome may be assessed using multiple methods of analysis, investigators who do not prespecify these elements can cherry-pick the results they report (32, 33). When planned outcomes differ from outcomes reported in journal articles, published results may be misleading (34, 35), and reporting standards are not useful when studies are not published at all.

Standards for registering clinical trials (36, 37), reporting trial protocols in journal articles, and reporting trial results in trial registers (36, 37) and journal articles (18) all include standards related to outcomes. Harmonizing those standards, and reporting information in the same way across sources, would make it easier for investigators to adhere to standards and make it easier for readers to use the information in trial reports.

Standards for Open Science

Proponents of "open science" advocate verifying study findings and identifying study limitations by examining multiple data sources for clinical trials (38). The Institute of Medicine (now the National Academy of Medicine) has published two reports, more than 25 y apart, urging an open science culture (38, 39). The Transparency and Openness Project (TOP) specifically proposes standards to improve the reproducibility of science, including standards to promote "open" sharing of data (40). To reanalyze clinical trials requires access to both data and metadata (e.g., protocol, statistical analysis plan, and analytic code) used to calculate study results. Increasing access to these data sources has made our failure to follow common standards throughout the research process increasingly visible.

"Openness" is of limited value when data exist in multiple formats and cannot be readily understood (32). In medical research, scientists conducting studies within industry tend to adhere to international standards for documenting clinical trial methods and results (e.g., in a clinical study report) (41). Scientists working in industry, who have incentives, such as regulatory approval requirements, to follow standards for documenting and storing data, may also be more likely than academics to use standardized data fields for their research studies (https://www.cdisc.org/). Requirements for data management plans may vary by who is funding the research (https://dmptool.org/). Sharing all of the reports and databases from a clinical trial is only useful if readers can find and use the information they seek; in the absence of standards, it remains unclear how valuable open science will be.

Standards for sharing study information have been successful, for example, in the Human Genome project and are developing rapidly in clinical research (42). Increasingly, data can be accessed through websites (43–45) and regulatory authorities (46, 47). As far as we know, there is also no reliable way to find whether and where data for a given study are available (e.g., in a register or journal article). Multiple initiatives to increase transparency have

Some of the questions stakeholders must address to implement an open science culture:

- How many open sources of data do we want for each study?
- How much detail do we need in each data source?
- Should we have multiple systems or a single system for sharing study information (e.g., should farmers and neurologists use the same system)?
- Will industry be asked to share different data sources from academic and other scientists?
- Should funding and oversight come from a single group (e.g., a federal agency, private foundation) or from multiple groups (e.g., with different areas of expertise)?

Table 1. Challenges related to standardized design and measurement in a research study and potential solutions

Steps in a research study	Examples of standards	Challenges to adaptation and implementation	Potential solutions
Study registration	• National laws and regulations require clinical trials be registered (37, 52)	• Many studies are not registered prospectively (49, 56)	• Registration required before research can begin (e.g., through IRBs)
	• Journals require registration for publication (53, 54)	• Existing requirements might not be appropriate for all study types (57)	• Penalties enforced for noncompliance with registration requirements
	• Trial registries define minimum data elements, including standards for defining outcomes (54, 55)	• Some trials are registered more than once (58) • Completed ("legacy") trials were not covered by current requirements	• Completed studies registered retrospectively
Research protocol	• Funders and regulators have adopted requirements for study protocols (59)	• Protocol templates are not available for all study types	• A standard protocol format adopted for each study design
	• Journals require protocols follow reporting guidelines (23)	• Protocols about the same topic do not include common data elements	• Protocols included in study registers
Data collection	• Stakeholders develop core outcome sets (i.e., outcomes to collect in all studies of a health problem) (60)	• Individual researchers have different research objectives and data requirements	• Methods of measuring and recording variables standardized
	• The Clinical Data Interchange Standards Consortium (CDISC) promotes standards for developing and documenting datasets	• There are not core outcome sets for most health problems • Variables are measured and recorded in different ways using different methods	• Core outcome sets developed and utilized
Dissemination of findings	• Many journals have endorsed reporting guidelines	• About 50% of research studies are not published (62)	• Make summary results for all studies available on study registers
	• EQUATOR has catalogued many reporting standards (21)	• Some studies are reported in multiple sources, which can contain conflicting information (32, 33)	• Apply existing reporting standards for publications
	• The International Committee on Harmonization developed standards for Clinical Study Reports (CSRs) (41)		• Develop and apply new reporting standards where needed
	• Ongoing projects aim to catalogue and link all reports about clinical trials (61)		
Sharing data	• International Committee of Medical Journal Editors (ICMJE) member journals require a data sharing statement for publication (41)	• Clinical trial data can be found in multiple repositories, which are not linked	• Share individual study participant observations (datasets)
	• Many universities host data repositories*	• Datasets include different content, structure, and formats	• Index the location of datasets information centrally
	• Individual participant data are available through foundations, nonprofits, and universities (43–45)	• Datasets do not always include meta-data, which vary in content and format	• Release data submitted to regulators and others
	• Individual manufacturers have policies for sharing data (63)		
Evidence syntheses	• Organizations including the Institute of Medicine (IOM) (64) and Agency for Healthcare Research and Quality (AHRQ) (65) developed standards for systematic reviews	• Systematic reviewers may find that trialists have stored information sources in different locations that are not linked	• Information sources for individual studies should be centrally linked using a unique identifier
	• Producers of systematic reviews (e.g., Cochrane) have developed standards for systematic reviews (66, 67)	• Systematic reviewers may find that trial information in different sources is incomplete or inconsistent (32, 33)	• Information sources for individual studies should use structured databases and be complete and consistent
	• The Systematic Review Data Repository (SRDR) is a system for collecting and managing trial data included in systematic reviews exist (68)		

*See https://www.icpsr.umich.edu/icpsrweb/ for an example.

resulted in competing systems maintained by organizations with different interests and abilities. So that scientists can take advantage of data-sharing initiatives, we need to adopt common standards related to the data-based infrastructure for generating and transmitting scientific knowledge. In addition, standards for sharing clinical trial information should be linked to standards for registering clinical trials and for reporting their results.

Standards for Past and Future Studies

While new standards often apply to the future rather than the past, we also need standards for completed clinical research. For example, many top-selling drugs were approved based on completed "legacy" trials; as long as we continue to use those drugs, studies about them remain relevant to current practice (38). Moreover, systematic reviews depend on completed research. If data and metadata from past studies are not shared soon, we will lose them over time. Publications provide important information, but they are often an incomplete picture (48, 49), and our inability to access information about completed studies is a major source of research waste (50).

When considering standards for completed research, the scientific community must determine whether the same standards should apply to future studies, ongoing studies, and completed research. We cannot preserve every document from every completed trial; information has been lost that cannot be recovered, and data sharing may be associated with considerable expense (e.g., for deidentifying or digitizing data). In addition, differences in policies and laws present challenges that will have to be identified and discussed. As a community, we must decide which studies are important and how we will archive and maintain data for future use.

One model for sharing completed studies is the Legacy Tobacco Documents Library (LTDL), which includes data, metadata, and supporting documents (e.g., memos) that aid interpretation. Hundreds of scientific papers have been written using information from LTDL (https://www.industrydocumentslibrary.ucsf.edu/tobacco); they have transformed thinking about marketing tobacco to children, how data are hidden, and the financial implications of research and transparency. As with LTDL, standards for data sharing may be most likely to succeed if resources are provided to investigators to achieve compliance and if stable resources are provided to maintain information systems.

Vision for the Future

To improve future research, we should identify existing and potential standards for each step in the scientific process and identify links across those steps that could move us toward a more comprehensive and less piecemeal system to promote reproducible research (Table 1 focuses on steps most related to planning, conduct, and reporting of design and measurement).

Governments, funders, journals, scientific societies, universities, and individual investigators (51) will have to work together for a reproducible research initiative to succeed. If we are to achieve widespread and lasting standards for design and measurement, they should require minimal effort and cost. Greater automation, for example, could make it simple to register studies, develop and locate study protocols, develop forms for data collection, disseminate findings, and share and retrieve data. Standards for interoperability are needed to decrease the variability in data and systems used to store data. Easy-to-use and standardized systems are critical to achieving a usable system for data producers and secondary analysts alike.

Conclusion

Until recently, the messiness of science has been hidden from public view. In the absence of standards, open science threatens to overwhelm us with myriad documents and datasets that we cannot use or cannot use efficiently. As policies and social norms change, greater transparency resulting from open science continues to reveal challenges in the methods and dissemination of research that are complex, widespread, yet ultimately solvable. To take full advantage of open science, we need a unified system of standards that links each step in the data production and sharing chain. We need standards that connect study registration and protocols, data collection and management systems, dissemination, data sharing, and performing systematic reviews. Furthermore, we need standards that apply to both completed research and new research. We need to build on existing work, and begin new collaborations, to develop standards that will lead to reproducibility before we can fully achieve it.

1. Seck MD, Evans DD (2004) *Major U.S. Cities Using National Standard Fire Hydrants, One Century After the Great Baltimore Fire, NISTIR 7158* (Maryland National Institute of Standards and Technology, Gaithersburg).
2. East Bay Hills Fire Operations Review Group (1992) The East Bay Hills Fire: A multiagency review of the October 1991 fire in the Oakland/Berkeley hills. Available at http://ggweather.com/firestorm/1991OESreport.pdf. Accessed October 27, 2017.
3. Alberts B (2010) Promoting scientific standards. *Science* 327:12.
4. Pickering TG, et al. (2005) Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation* 111:697–716.
5. NASA (1999) Mars Climate Orbiter mishap investigation board phase I report. Available at ftp://ftp.hq.nasa.gov/pub/pao/reports/1999/MCO_report.pdf. Accessed October 27, 2017.
6. Saldanha IJ, et al. (2016) Social network analysis identified central outcomes for core outcome sets using systematic reviews of HIV/AIDS. *J Clin Epidemiol* 70:164–175.
7. Saldanha IJ, et al. (2017) Clinical trials and systematic reviews addressing similar interventions for the same condition do not consider similar outcomes to be important: a case study in HIV/AIDS. *J Clin Epidemiol* 84:85–94.
8. Page MJ, Forbes A, Chau M, Green SE, McKenzie JE (2016) Investigation of bias in meta-analyses due to selective inclusion of trial effect estimates: Empirical study. *BMJ Open* 6:e011863.
9. Williamson P, Clarke M (2012) The COMET (Core Outcome Measures in Effectiveness Trials) initiative: Its role in improving Cochrane reviews. *Cochrane Database Syst Rev*, ED000041.
10. Gargon E, Williamson PR, Altman DG, Blazeby JM, Clarke M (2015) The COMET initiative database: progress and activities update (2014). *Trials* 16:515.
11. Kirkham JJ, Clarke M, Williamson PR (2017) A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: Findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ* 357:j2262.
12. Kirkham JJ, Gargon E, Clarke M, Williamson PR (2013) Can a core outcome set improve the quality of systematic reviews?—A survey of the Co-ordinating Editors of Cochrane Review Groups. *Trials* 14:21.
13. Dickersin K, Rennie D (2003) Registering clinical trials. *JAMA* 290:516–523.
14. Dickersin K, Rennie D (2012) The evolution of trial registries and their use to assess the clinical trial enterprise. *JAMA* 307:1861–1864.
15. Piller C (2015) Law ignored, patients at risk. *Stat*. Available at https://www.statnews.com/2015/12/13/clinical-trials-investigation/. Accessed October 24, 2017.
16. Dickersin K, Min YI (1993) NIH clinical trials and publication bias. *Online J Curr Clin Trials*, 50.
17. Turner L, et al. (2012) Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev* 11:MR000030.
18. Schulz KF, Altman DG, Moher D; CONSORT Group (2010) CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *PLoS Med* 7: e1000251.
19. Day R (1989) The origins of the scientific paper: The IMRAD format. *J Am Med Writers Assoc* 4:16–18.
20. Ad Hoc Working Group for Critical Appraisal of the Medical Literature (1987) A proposal for more informative abstracts of clinical articles. *Ann Intern Med* 106: 598–604.
21. Simera I (2008) EQUATOR Network collates resources for good research. *BMJ* 337: a2471.
22. Rennie D, Flanagin A, Godlee F, Bloom T (2015) The Eighth International Congress on Peer Review and Biomedical Publication: A call for research. *JAMA* 313:2031–2032.
23. Chan AW, et al. (2013) SPIRIT 2013 statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 158:200–207.
24. Dechartres A, et al. (2017) Evolution of poor reporting and inadequate methods over time in 20 920 randomised controlled trials included in Cochrane reviews: Research on research study. *BMJ* 357:j2490.
25. Grant SP, Mayo-Wilson E, Melendez-Torres GJ, Montgomery P (2013) Reporting quality of social and psychological intervention trials: A systematic review of reporting guidelines and trial publications. *PLoS One* 8:e65442.

26. Glasziou P, et al. (2014) Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 383:267–276.
27. Goodman SN, Fanelli D, Ioannidis JP (2016) What does research reproducibility mean? *Sci Transl Med* 8:341ps12.
28. Open Science Collaboration (2015) PSYCHOLOGY. Estimating the reproducibility of psychological science. *Science* 349:aac4716.
29. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC (2011) The ClinicalTrials.gov results database–Update and key issues. *N Engl J Med* 364:852–860.
30. Saldanha IJ, Dickersin K, Wang X, Li T (2014) Outcomes in Cochrane systematic reviews addressing four common eye conditions: An evaluation of completeness and comparability. *PLoS One* 9:e109400.
31. Tendal B, Nüesch E, Higgins JP, Jüni P, Gøtzsche PC (2011) Multiplicity of data in trial reports and the reliability of meta-analyses: Empirical study. *BMJ* 343:d4829.
32. Mayo-Wilson E, et al. (2017) Cherry-picking by trialists and meta-analysts can drive conclusions about intervention efficacy. *J Clin Epidemiol*, 10.1016/j.jclinepi.2017.07.014.
33. Mayo-Wilson E, et al.; MUDS investigators (2017) Multiple outcomes and analyses in clinical trials create challenges for interpretation and research synthesis. *J Clin Epidemiol* 86:39–50.
34. Dwan K, Gamble C, Williamson PR, Kirkham JJ; Reporting Bias Group (2013) Systematic review of the empirical evidence of study publication bias and outcome reporting bias—An updated review. *PLoS One* 8:e66844.
35. Vedula SS, Bero L, Scherer RW, Dickersin K (2009) Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med* 361:1963–1971.
36. Zarin DA, Tse T, Williams RJ, Carr S (2016) Trial reporting in ClinicalTrials.gov—The Final Rule. *N Engl J Med* 375:1998–2004.
37. 81. *Federal Register* 183 (2016), pp 64982–65157.
38. Institute of Medicine (2015) *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* (The National Academies Press, Washington, DC).
39. National Research Council (1985) *Sharing Research Data* (National Academy Press, Washington, DC).
40. Nosek BA, et al. (2015) SCIENTIFIC STANDARDS. Promoting an open research culture. *Science* 348:1422–1425.
41. ICH Expert Working Group (1995) Structure and content of clinical study reports: International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf. Accessed October 24, 2017.
42. Cook-Deegan R (1994) *The Gene Wars: Science, Politics, and the Human Genome* (W. W. Norton & Company, New York).
43. Strom BL, Buyse ME, Hughes J, Knoppers BM (2016) Data sharing—Is the juice worth the squeeze? *N Engl J Med* 375:1608–1609.
44. Krumholz HM, Waldstreicher J (2016) The Yale Open Data Access (YODA) Project—A mechanism for data sharing. *N Engl J Med* 375:403–405.
45. Bierer BE, Li R, Barnes M, Sim I (2016) A global, neutral platform for sharing trial data. *N Engl J Med* 374:2411–2413.
46. Bonini S, Eichler HG, Wathion N, Rasi G (2014) Transparency and the European Medicines Agency—Sharing of clinical trial data. *N Engl J Med* 371:2452–2455.
47. Turner EH (2007) Posting FDA new drug application reviews. *JAMA* 298:863–864.
48. Turner EH (2013) How to access and process FDA drug approval packages for use in research. *BMJ* 347:f5992.
49. Zarin DA, Tse T, Williams RJ, Rajakannan T (2017) Update on trial registration 11 years after the ICMJE policy was established. *N Engl J Med* 376:383–391.
50. Chan AW, et al. (2014) Increasing value and reducing waste: Addressing inaccessible research. *Lancet* 383:257–266.
51. McNutt M, et al. (2016) RESEARCH INTEGRITY. Liberating field science samples and data. *Science* 351:1024–1026.
52. 42 USC §8012007 (2007).
53. DeAngelis CD, et al.; International Committee of Medical Journal Editors (2004) Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *JAMA* 292:1363–1364.
54. DeAngelis CD, et al.; International Committee of Medical Journal Editors (2005) Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *JAMA* 293:2927–2929.
55. World Health Organization (2008) WHO Trial Registration Data Set, Version 1.2.1. Available at http://www.who.int/ictrp/network/trds/en/. Accessed August 20, 2017.
56. Boccia S, et al. (2016) Registration practices for observational studies on ClinicalTrials.gov indicated low adherence. *J Clin Epidemiol* 70:176–182.
57. de Jonge P, et al. (2011) Prevention of false positive findings in observational studies: Registration will not work but replication might. *J Epidemiol Community Health* 65:95–96.
58. van Valkenhoef G, Loane RF, Zarin DA (2016) Previously unidentified duplicate registrations of clinical trials: An exploratory analysis of registry data worldwide. *Syst Rev* 5:116.
59. National Institutes of Health (NIH) (2017) NIH and FDA Release Protocol Template for Phase 2 and 3 IND/IDE Clinical Trials, NOT-OD-17-064. Available at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-064.html. Accessed October 27, 2017.
60. Williamson PR, et al. (2012) Developing core outcome sets for clinical trials: Issues to consider. *Trials* 13:132.
61. Goldacre B, Gray J (2016) OpenTrials: Towards a collaborative open database of all available information on all clinical trials. *Trials* 17:164.
62. Ross JS, et al. (2012) Publication of NIH funded trials registered in ClinicalTrials.gov: Cross sectional analysis. *BMJ* 344:d7292.
63. Goldacre B, et al. (2017) Pharmaceutical companies' policies on access to trial data, results, and methods: Audit study. *BMJ* 358:j3334.
64. Institute of Medicine (2011) *Finding What Works in Health Care: Standards for Systematic Reviews* (The National Academies Press, Washington, DC).
65. Agency for Healthcare Research and Quality (2014) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (Agency for Healthcare Research and Quality, Rockville, MD), 10(14)-EHC063-EF.
66. Higgins JP, Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions* (The Cochrane Collaboration, London), Version 5.1.0.
67. Higgins J, Lasserson T, Chandler J, Tovey D, Churchill R (2016) Methodological Expectations of Cochrane Intervention Reviews (MECIR): Standards for the conduct and reporting of new Cochrane intervention reviews, reporting of protocols and the planning, conduct and reporting of updates. Available at http://communitycochraneorg/mecir-manual. Accessed October 27, 2017.
68. Li T, et al. (2015) Innovations in data collection, management, and archiving for systematic reviews. *Ann Intern Med* 162:287–294.