BMJ Open

Clinical Trial Registration, Reporting, Publication, and FDAAA Compliance: A cross-sectional analysis and ranking of new drugs approved by the FDA in 2012

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009758
Article Type:	Research
Date Submitted by the Author:	19-Aug-2015
Complete List of Authors:	Miller, Jennifer; New York Langone Medical Center, Population Health; Harvard University, Edmond J. Safra Center for Ethics Korn, David; Harvard University, Harvard Medical School Ross, Joseph; Yale University, Yale School of Medicine
Primary Subject Heading:	Ethics
Secondary Subject Heading:	Evidence based practice, Health policy, Health services research, Public health, Medical publishing and peer review
Keywords:	MEDICAL ETHICS, Clinical trials < THERAPEUTICS, PUBLIC HEALTH, GENERAL MEDICINE (see Internal Medicine), Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Clinical Trial Registration, Reporting, Publication, and FDAAA Compliance: A cross-sectional analysis and ranking of new drugs approved by the FDA in 2012

Jennifer E. Miller, PhD[1], David Korn, MD[2] and Joseph S. Ross, MD, MHS[3]

Author Affiliations:
[1] Edmond J. Safra Center for Ethics, Harvard University; Kenan Institute for Ethics, Duke University; Division of Medical Ethics, Department of Population Health, NYU Langone Medical Center [2] Edmond J. Safra Center for Ethics, Harvard University; Massachusetts General Hospital; Harvard Medical School,[3] Section of General Internal Medicine and the Robert Wood Johnson Clinical Scholars Program, Department of Internal Medicine, Yale School of Medicine; Department of Health Policy and Management, Yale School of Public Health; and Center for Outcomes Research and Evaluation, Yale–New Haven Hospital, all New Haven, Connecticut

Corresponding Author:
Jennifer E. Miller, PhD
Assistant Professor
Division of Medical Ethics
Department of Population Health
NYU Langone Medical Center

Word count: 3,260 (text), 2 tables, 2 appendices

Objective: To evaluate clinical trial registration, reporting, and publication rates for new drugs by: (1) legal requirements and (2) the ethical standard that all human subjects research should be publicly accessible to contribute to generalizable knowledge.

Design and Setting: Cross sectional analysis of all clinical trials submitted to the Food and Drug Administration (FDA) for drugs approved in 2012, sponsored by large bio-pharmaceutical companies.

Data Sources: Publicly available information from Drugs@FDA, ClinicalTrials.gov, Medline-indexed journals, and drug company communications.

Main outcome measures: Clinical trial registration and results reporting in ClinicalTrials.gov, publication in the medical literature, and compliance with the 2007 FDA Amendments Acts (FDAAA), analyzed on the drug level.

Results: The FDA approved 15 drugs sponsored by 10 large companies in 2012. We identified 318 relevant trials involving 99,599 research subjects. Per drug, a median of 57% (interquartile range [IQR], 32%-83%) of trials were registered, 20% (IQR, 12%-28%) reported results in ClinicalTrials.gov, 56% (IQR, 41%-83%) were published, and 65% (IQR, 41%-83%) were either published or reported results. Almost half of all reviewed drugs had at least one undisclosed Phase II or III trial. Per drug, a median of 17% (IQR, 8%-20%) of trials supporting FDA approvals were subject to FDAAA mandated public disclosure; of these, a median of 67% (IQR, 0%-100%) were FDAAA-compliant. Sixty-eight percent of research subjects (67,629 of 99,599) participated in FDAAA-subject trials, with 51% (33,405 of 67,629) enrolled in noncompliant trials. Transparency varied widely among companies.

Conclusions: Trial disclosures for new drugs remain below legal and ethics standards, with wide variation in practices among drugs and their sponsors. Best practices are emerging. Two companies disclosed all trials and complied with legal disclosure requirements for their 2012 approved drugs. Ranking new drugs on transparency criteria may improve compliance with legal and ethics standards and the quality of medical knowledge.

Article summary: Strengths and limitations of this study

- This study uniquely analyzes the transparency of clinical trial information for new drugs, whereas other studies analyze transparency on the trial level.
- This study uses FDA databases as a key data source, because they characterize all clinical trials supporting new drug approvals. Prior studies evaluate the transparency of already registered trials in ClinicalTrials.gov, providing limited insights into the many unregistered studies.
- This study takes a uniquely comprehensive approach, analyzing five critical elements of transparency for trials of new drugs: (1) registration, (2) results reporting, (3) publication in a medical journal, (4) compliance with legal disclosure requirements, and (5) adherence with the ethics standards enshrined in the Common Rule, Helsinki Declaration and elsewhere which state that all trials should be "designed to develop or contribute to generalizable knowledge," that is, should be publicly accessible.
- A main limitation for this study is the need to extend and repeat the analysis beyond the 15 drugs approved by the FDA in 2012 that were manufactured by large companies, to include drugs approved in other years and sponsored by other institutions.

INTRODUCTION

For decades, many clinical trials have been publicly inaccessible, raising ethics, medical practice, and population health concerns. While recent transparency efforts have improved practices, a significant portion of both commercially and publicly funded trials and trial results still remain inaccessible, because they are unregistered and their results are unreported in trial registries, [1 2] or they are never published in the medical literature. [3 4]

Studies have shown that roughly 30% to 50% of clinical trials remain unpublished, often years after their completion, [5 6] and most fail to meet baseline legal disclosure requirements, such as those established in the 2007 US Food and Drug Administration Amendments Act (FDAAA).[7] Moreover, studies that are published by sponsors, journals and researchers, tend to show favorable or statistically significant results.[8 9 10 11] This selective trial dissemination can distort the medical evidence and challenge physicians, prescription guideline writers, payers, and formulary decision-makers' abilities to recommend and provide the right drugs for the right patients. It also represents a violation of the rights of human research subjects, as experimenting on humans is largely justified by its potential to contribute to generalizable knowledge (as stated in the 1981 United States Common Rule). Furthermore, transparency may be essential to ensuring the integrity and trustworthiness of the clinical research enterprise.

Despite numerous major reform strategies, the transparency problem persists, raising questions of what more can be done. Efforts include the 1997 US Food and Drug Administration Modernization Act requiring the registration of drug trials for serious or life-threatening conditions, FDAAA requiring that select trials be registered and publicly report results, and the 2008 World Medical Association guidelines identifying trial registration and results reporting as an ethical obligation in the Declaration of Helsinki. The International Committee of Medical Journal Editors, Institute of Medicine, individual drug companies and their trade associations, the European Medicines Agency, World Health Organization (WHO) and Bill and Melinda Gates Foundation have also made efforts to improve transparency in clinical research. Recently, both the Department of Health and Human Services and National Institutes of Health (NIH) called for public comment on two new proposals to further expand access to clinical trial information. The DHHS proposal would substantially expand the scope of registration and results reporting requirements under FDAAA.[12 13] The NIH proposal would require registration and results reporting for all NIH funded clinical trials, including phase I trials. [14]

To help understand the efficacy of these transparency efforts for new drugs and how to improve them, this paper examines whether clinical trials for drugs approved by the FDA in 2012, that were sponsored by large companies, were registered, reported, published in the medical literature, and complied with legal transparency requirements established in FDAAA. This study and approach is novel for at least five reasons. First, we evaluated the transparency around individual new drugs. Previous studies generally evaluate transparency on the trial level. We thought evaluating on the drug level could help make the transparency problem more

understandable and proximate for stakeholders who consume, prescribe, reimburse, stockpile or otherwise regulate medicines and vaccines. Second, we used FDA approval packages as a key data source, because they characterize all clinical trials supporting new drug approvals. Prior studies evaluate the transparency of already registered trials in ClinicalTrials.gov, which provide limited insights into the many unregistered studies. Third, we focused on large companies because, as a group, they sponsor a significant portion of the trials conducted annually and the majority of new drug applications (NDAs) submitted to the FDA. Also, they were expected to have the infrastructure to comply with regulatory and ethics standards. Thus, we likely captured a best-case scenario. Fourth, we evaluated transparency on both legal and ethics standards, providing a uniquely comprehensive overview. Lastly, we introduce an innovative strategy to improve the state of transparency for drugs: an annual transparency scorecard that audits and ranks all new medicines and vaccines.

METHODS

Data sources

We used data collected from Drugs@FDA, a publicly accessible database containing records of FDA drug regulatory decisions, including drug approvals and medical and scientific reviews of approved drugs; ClinicalTrials.gov, a clinical trial registry and database maintained by the National Library of Medicine (NLM) at the NIH; Medline indexed journals (accessed through PubMed); information from the NLM to identify certificates of delay (provided by Tse T to Anderson M: personal communication); information from large companies that had new drugs approved by the FDA in 2012; and pharmaceutical company press releases. The databases were accessed several times between October 2013 and April 2014.

Study samples

Drugs

New drugs approved by the FDA in the calendar and fiscal year of 2012 were identified from FDA reports,[15 16] and included innovative and novel drugs and new molecular entities, henceforth referred to simply as "drugs". We restricted the total number of drugs to those that were sponsored by large biotechnology and pharmaceutical companies, defined as the twenty institutions with the highest market capitalizations in 2012.[17]

Clinical trials

All trials conducted to gain FDA approval in 2012 for each drug

Each drug's 2012 FDA approval package was located in the Drugs@FDA database. We reviewed all pages of a drug's summary review, Medical Review(s), Chemistry Review(s),

Pharmacology Review(s), Statistical Review(s), Clinical Pharmacology Biopharmaceutics Review(s), Risk Assessment and Risk Mitigation Review(s), and other reviews to create a list of every clinical trial reviewed by the FDA to approve each drug. Where possible, the basic characteristics of each trial were catalogued, including the organizational identification number, phase, study population, number of research subjects, primary endpoint(s), study start and completion date(s), location, and description of the treatment (e.g. dosage and comparators), subjects received in the various arms, and whether the trial was controlled and/or interventional.. We excluded any trials that were terminated without enrollment of subjects, still ongoing, or not at least one year past their primary completion date by our study cut-off date of February 1, 2014.

FDAAA applicable trials for each drug

We narrowed the "all trials" sample to only those subject to mandatory registration and reporting requirements under FDAAA, that is, generally, "controlled clinical investigation(s), other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act." [18] These trials should have "either initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007," and meet one of the following conditions:

a. The trial has one or more sites in the United States,
b. The trial is conducted under an FDA investigational new drug application, or
c. The trial involves a drug or biologic that is manufactured in the United States or its territories and is exported for research" [19]

Because of conflicting understandings on the reach of FDAAA, we created two sample pools of FDAAA-subject trials, one for controlled and one for interventional trials. Trials with unknown phases or that were listed as phase I/II in at least two primary data sources were excluded from the FDAAA analysis (n=1).

Main Outcome Measures

Determining transparency according to the ethics standard that all trial results should be publicly accessible

We ascertained in ClinicalTrials.gov whether each identified trial from the FDA approval packages of each drug (the "all trials" study sample) was registered and reported results. Search terms to locate and match trials included the trial's organizational identification number (org ID), product name, number of trial participants, and other trial characteristics captured from the approval packages. Once identified, we abstracted the National Clinical Trial number (NCT number), number of research subjects enrolled in the various treatment arms, description of the treatment (e.g. dosage and comparators), whether the trial was controlled and/or interventional, primary outcome measurements, trial start date, registration date, primary completion date (date

the last participant was examined and data for the primary outcome measure collected), and any links to clinical study reports. Any clinical trial(s) with results received by ClinicalTrials.gov on or before February 1, 2014, was deemed to have results publicly available. This study cutoff date was chosen to provide at least 13 months for trial results disclosure post FDA approval of a drug.

Second, using search terms that included the branded drug name or active ingredient and trial indication, we determined from PubMed whether individual trials for each drug were published in a MEDLINE-indexed journal, on or before our cut-off date. We then matched at least two of the following characteristics -- the NCT number or organizational trial identification number, number of enrolled research subjects, descriptions of the treatment (e.g. dosage and comparators), and/or primary outcome measurements-- in the publication with what was in ClinicalTrials.gov or the Drugs@FDA databases. We also reviewed papers listed on ClinicalTrials.gov for registered trials and used the same matching criteria. Papers summarizing and reviewing multiple phase I trial results in a single publication, although rare, were counted.

Determining transparency according to FDAAA legal requirements

We reviewed whether FDAAA applicable trials (for both the "controlled" and "interventional" samples) had timely registration and reporting as defined by FDAAA. Registration (which in our case are trials for approved drugs), in general, should occur within twenty-one days after enrolling the first subject. Results should be reported, generally, no later than 12 months after the trial's primary completion date, in ClinicalTrials.gov, although results submissions can be delayed by submitting certificates to the NIH (See Appendix I). If a trial met FDAAA requirements for both registration and disclosure of results, it was counted as compliant with legal requirements.

Validation

The data gathering was repeated by at least two research assistants (blinded to each other's work), with discrepancies resolved through discussion and consensus (see acknowledgments for a list of research assistants). Our final datasets for each drug were sent to each New Drug Application company sponsor to verify the accuracy and completeness of our extracted information. Data and input received from companies (response rate was 100%) were verified by public data sources.

Statistical Analysis

We used descriptive statistics to calculate the median number of clinical trials per drug that were registered and reported results in ClinicalTrials.gov, were published in a MEDLINE indexed journal, and were publicly accessible. Public accessibility of a trial was defined as being either reported in Clinicaltrials.gov or published in a MEDLINE indexed journal. We also used descriptive statistics to calculate the median number of clinical trials per drug subject to FDAAA

that were in compliance with the statute. All data were collected and analyzed in Microsoft Excel v2013 (Redmond, Washington).

RESULTS

In 2012, the FDA approved 39 novel new medicines, known as new molecular entities (NMEs), and 35 novel drugs. Combining these lists, the FDA approved a total of forty-eight new drug entities, fifteen of which were sponsored by ten large pharmaceutical or biotechnology companies with market capitalizations valued over $19 billion. A total of 342 trials were conducted to gain regulatory approval of the 15 drugs, 24 of which were excluded from our analysis, leaving 318 trials involving 99,599 subjects relevant to our study, a median of 17 trials per drug (see Table 1).

Transparency evaluated by the ethics standard that all trial results should be publicly accessible

The median proportion, per drug, of publicly registered trials was 57% (IQR, 32% to 83%), of trials reporting results in ClinicalTrials.gov, 20% (IQR, 12% to 28%), and of published trials, 56% (IQR, 41% to 83%) (see Table 1). A median of 65% (IQR, 41% to 83%) of clinical trial results were publicly available, that is, the results were either reported in ClinicalTrials.gov or published in the medical literature, but with considerable variation (see Table 1). Importantly, among trials that reported results in ClinicalTrials.gov, a median of 100% (IQR, 86-100%) were also published.

Among clinical trials with results unavailable in either the medical literature or ClinicalTrials.gov, a median of 91% (IQR, 60% to 100%) were Phase I, 0% were phase II (IQR, 0% to 15%), 0% were Phase III trials (IQR, 0% to 2%) and 0% were of unknown phase). Among the 15 drugs, 20% had at least one phase III trial with results publicly unavailable, 27% had at least one undisclosed phase II trial, and 47% one of either. In total, 5,566 research subjects (of the 99,599 total participants) participated in publicly undisclosed trials for these 15 drugs.

Public availability of clinical trial information varied widely by company, and sometimes within companies for those with multiple drugs approved in 2012 (Table 1). For example, three of the ten companies (GSK, J&J and Pfizer) publicly disclosed all clinical trial results for at least one of their reviewed drugs, whereas the lowest scoring company, Gilead, disclosed 21% (seven of thirty-four) of the trial results for its HIV medicine Stribild.

Transparency evaluated by FDAAA legal requirements

The legal requirements enshrined in FDAAA (Table 2) offer at least two potential interpretations for what constitutes an applicable clinical trial: controlled and interventional trials. Applying the "controlled" definition, a median of 17% (IQR, 8% to 20%) of trials per drug were subject to legal disclosure requirements, hereafter referred to as "applicable trials" .A median of 100%

(IQR, 93% to 100%) of these trials met registration requirements, whereas 67% (IQR, 0% to 100%) met reporting requirements. Overall, per drug, a median of 67% (IQR, 0% to 100%) of applicable trials fully complied with the law, (See Table 2), with considerable variation. Sixty-eight percent of research subjects (67,629 of 99,599) participated in FDAAA-subject trials, with fifty-one percent of them (33,405 of 67,629) enrolled in noncompliant trials. Six of the ten reviewed companies showed 100% compliance with the law for at least one drug. However, an almost equal number, five of ten, had at least one drug that was 0% compliant.

Applying the "interventional" definition, a median of 19% (IQR, 15% to 29%) of trials, per drug, were subject to legal disclosure requirements under FDAAA. A median of 100% (IQR, 93% to 100%) of these trials met registration requirements, whereas 71% (IQR, 0% to 100%) met reporting requirements. Overall, a median, per drug, of 71% (IQR, 0% to 100%) of applicable trials complied with FDAAA (See Table 2). Sixty-nine percent of research subjects (68,703 of 99,599) participated in FDAAA-subject trials, with fifty-one percent of them (33,786 of 68,703) enrolled in noncompliant trials. Five of the ten reviewed companies had at least one drug that showed 100% compliance with FDAAA. The same number of companies (5 of ten) had at least one drug that was 0% compliant.

DISCUSSION

Medical practice remains largely an empirical discipline, highly dependent for its advancement on the complete and accurate sharing of information. Nowhere is this truer than in the reporting of clinical trials, in particular those that support the efficacy and safety of new medicines. The purpose of this study was to review all new drugs approved by the FDA in 2012 that were sponsored by large companies, identifying all clinical trials that supported their approval and determining whether the trials were publicly registered and had trial results reported in ClinicalTrials.gov, were published in the medical literature within at least 13 months of FDA approval, and complied with federal disclosure laws. While nearly two-thirds of clinical trials, per drug, were publicly disclosed, there was wide variation among drugs and companies. At first approximation, it may seem difficult to understand failures to comply with federal law, now eight years old, whose origins track back to 1997, and even more difficult to understand failures to meet the over-riding ethics obligation that human research be designed to contribute to generalizable knowledge.

Transparency by legal standards

There are at least three reasons why compliance with current disclosure laws might be suboptimal. First, legal requirements are perceived to be unclear or ambiguous, as a spectrum of interpretations of FDAAA has emerged. Some companies believe controlled trials are subject to mandatory disclosure, others only interventional trials. Some believe that results are due one year after a trial's primary completion date regardless of whether the drug has been approved,

while others believe results are not due until thirty days post FDA approval of a trial's investigated indication. There is also confusion about the role of certificates of delay.

Second, mergers, acquisitions, collaborations and licensing agreements may complicate compliance. Two companies in our sample acquired or licensed drugs initially developed by smaller companies, and another used a partner company for some trials, raising questions about whose responsibility it was to ensure trials complied with FDAAA. Under current law, the company that files the investigational new drug (IND) application is generally the responsible party.

Finally, compliance may be affected by a perceived lack of enforcement. FDAAA empowers the FDA to impose a $10,000 a day penalty for noncompliance. To date, this penalty has never been imposed.

Transparency by ethics principles

In contrast to legal requirements that applied to roughly only one-fifth of all clinical trials supporting a new drug approval, ethics standards enshrined in the Common Rule, Helsinki Declaration and elsewhere, apply to all clinical trials. Ethically, all research involving human subjects should be "designed to develop or contribute to generalizable knowledge,"[20] that is, should be publicly accessible. Surprisingly, adherence to this ethics standard was similar to that to legal standards: the results of approximately two-thirds of the studied trials, per drug, were publicly accessible, either through results reporting in ClinicalTrials.gov or publication. Adherence may be less than complete because companies may not act without an authoritative body promulgating an organizing policy. Perhaps the new WHO guidelines calling for all trial results to be publicly disclosed, including phase I trials, may serve this purpose.[21] Our proposed pharmaceutical transparency scorecard may also help.

Motivating Transparency

Given the wide variation in compliance with both legal and ethics standards across drugs and companies, implementing a clinical trials transparency monitoring system for all new drugs could improve and help standardize the industry's practices and thereby contribute importantly to an enrichment of medical knowledge. Such a system might also provide the basis for regular auditing, ranking and indexing of new drugs and trial sponsors. [22 23 24] Transparency as well as the types of data analytics described in this paper have been effective governance and learning opportunities in other industries. [25] They have the potential to identify best practices, create knowledge exchange platforms and learning opportunities, and incent better behaviors, and it would benefit consumers of clinical trial information by helping to assure them of the integrity and completeness of their databases. Not least, full transparency of clinical trials would strengthen the protection of human research subjects by avoiding their unknowing recruitment into already failed experiments.

Limitations

Several limitations deserve further consideration. We limited our study to one year of FDA approvals: 15 drugs manufactured by 10 large companies. Further study is needed of trials for drugs approved in other years, of additional sponsors (such as smaller companies and academic centers), and of the quality of reported information. At times, mergers, acquisitions, subsidiaries, partnerships and licensing practices complicated determining the sponsors and responsible parties for trial transparency. This study is part of a larger pilot to explore implementing an annual transparency scorecard or index for medicines, vaccines and sponsors. Next steps may include adding a weighting mechanism to account for the variation in the number of trials conducted per drug to gain FDA regulatory approval.

CONCLUSION

Nearly two-thirds of clinical trials supporting new drugs approved by the FDA in 2012 were publicly disclosed, perhaps encouraging but below both legal and ethics standards. While several large companies' drugs were superseding legal requirements, others had low rates of transparency. Implementing a transparency scorecard and ranking system for all newly approved drugs could motivate and increase transparency, thereby supporting existing transparency initiatives, advancing clinical innovation, promoting a trustworthy innovation sector, and strengthening protection of human research subjects globally.

Funding Disclosures: The conceptualization and pilot of this study and index (tentatively called the OpenPharma Index or Pharma Integrity Scorecard) were supported by Harvard University's Edmond J. Safra Center for Ethics; Duke University's Kenan Institute for Ethics, Trinity College of Arts and Sciences and Fuqua School of Business; Fordham University's Global Healthcare Innovation Management Center; Susan G. Komen Foundation; Raskob Foundation; and Bioethics International. A conference exploring the rating concept (co-chaired by Jennifer Miller and Nir Eyal) was held at Harvard Medical School, funded by the Division of Medical Ethics (currently the Harvard Medical School Center for Bioethics); the Petrie-Flom Center for Health Law, Biotechnology, and Bioethics at Harvard Law School; the Harvard Global Health Institute; and the Harvard University Program in Ethics and Health. Dr. Ross is supported by the National Institute on Aging (K08 AG032886) and by the American Federation for Aging Research through the Paul B. Beeson Career Development Award Program and receives research support through Yale University from Medtronic, Inc. and Johnson & Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance

of medical devices. Drs. Miller and Korn receive no financial support from pharmaceutical companies.

Acknowledgements: The authors thank Robert Califf (Duke University), Aaron Kesselheim (Brigham and Women's Hospital and Harvard Medical School), Kevin Schulman (Duke University) and Arti Rai (Duke University) for comments on this paper; Brittany Rush, Jason Dong, Marsha Sukash, Julie Dorais, Jessica Ericson, Rajan Patel, Eidan Jacob, Brooke Whitfield, Priyanka Kanal, Raichel Perper and Nicole Miller for data-gathering assistance; and Malcolm Salter (Harvard Business School), Larry Lessig (Harvard Law School), Arthur Caplan (New York University), Ed Balleisen (Duke University), the directors of Bioethics International, and the fellows of Edmond J. Safra Center for Ethics at Harvard University for their input and feedback on the index and ranking concept. They also thank Janet Woodcock (FDA) and Tony Tse (NIH) for answering FDAAA related questions and Monique Anderson (Duke University) for providing access to certificate of delay data.

Contributors: JEM, JSR, and DK were responsible for the conception and design of this work. JEM drafted the manuscript, conducted the statistical analysis, and is guarantor. All authors participated in the analysis and interpretation of the data and critically revised the manuscript for important intellectual content.

Data-sharing: No additional data available.

Table 1. Transparency Index: Ranking of new drugs according to the ethics standard that *all* trial results should be publicly available to contribute to generalizable knowledge

Drug*	Sponsor	Indication	No. of trials analyzed from FDA* approval package	Percentage of trials registered	Percentage of trials reported	Percentage of trials published	Percentage of trial results that are publicly available (reported or published)
Stribild	Gilead	HIV	34	24%	9%	21%	**21%**
Aubagio	Sanofi	Multiple sclerosis	32	34%	19%	16%	**22%**
Elelyso	Pfizer & Protalix	Gaucher disease	5	100%	20%	40%	**40%**
Zaltrap	Sanofi	Colorectal cancer	30	40%	30%	37%	**40%**
Stivarga	Bayer	Colorectal cancer	12	75%	17%	42%	**42%**
Eliquis	BMS	Anticoagulant	39	26%	10%	44%	**44%**
Zioptan	Merck & Santen	Eye pressure, glaucoma	16	25%	13%	44%	**44%**
Xeljanz	Pfizer	Rheumatoid arthritis	34	82%	53%	56%	**65%**
Bosulif	Pfizer	Leukemia	17	100%	24%	71%	**71%**
Perjeta	Genentech/Roche	Breast cancer	12	50%	8%	75%	**75%**
Signifor	Novartis	Cushing's disease	17	29%	12%	82%	**82%**
Erivedge	Genentech/Roche	Basal cell carcinoma	12	83%	25%	83%	**83%**
Inlyta	Pfizer	Renal cell carcinoma	28	61%	46%	100%	**100%**
Sirturo	Janssen (J&J)	Tuberculosis	14	57%	21%	93%	**100%**
MenHibrix	GSK	Meningitis vaccine, children	16	100%	100%	100%	**100%**
Median			17	57%	20%	56%	**65%**
Interquartile range [IQR]			13-31	32-83%	12-28%	41-83%	**41-83%**

* For a list of the active ingredients for these drugs, see Appendix 2.

Table 2. Legal Compliance Index: Ranking of new drugs according to their compliance with disclosure requirements under the Food and Drug Administration Amendments Acts (FDAAA)

				FDAAA Definition 1: "controlled" trials			FDAAA Definition 2: "interventional" trials			
Drug*	Company	Indication	No. Trials Subject to FDAAA	Timely Registration	Timely Reporting	FDAAA Compliance	No. Trials Subject to FDAAA	Timely Registration	Timely Reporting	FDAAA Compliance
Elelyso	Pfizer/ Protalix	Gaucher disease	1	100%	0%	**0%**	3	100%	0%	**0%**
Stivarga	Bayer	Colorectal cancer	1	100%	0%	**0%**	2	100%	0%	**0%**
Perjeta	Genentech/ Roche	Breast cancer	2	50%	0%	**0%**	2	50%	0%	**0%**
Signifor	Novartis	Cushing's disease	1	100%	0%	**0%**	2	100%	0%	**0%**
Erivedge	Genentech/ Roche	Basal cell carcinoma	2	100%	0%	**0%**	3	100%	0%	**0%**
Zioptan	Merck/ Santen	Eye-pressure, glaucoma	7	17%	17%	**17%**	7	29%	14%	**14%**
Eliquis	Eliquis	BMS	6	83%	33%	**33%**	6	83%	33%	**33%**
Aubagio	Sanofi	Multiple sclerosis	7	86%	71%	**71%**	7	86%	71%	**71%**
Zaltrap	Sanofi	Colorectal cancer	6	100%	67%	**67%**	9	100%	78%	**78%**
Inlyta	Pfizer	Renal cell carcinoma	2	100%	100%	**100%**	7	100%	86%	**86%**
Stribild	Gilead	HIV	3	100%	100%	**100%**	3	100%	100%	**100%**
Xeljanz	Pfizer	Rheumatoid arthritis	11	100%	100%	**100%**	11	100%	100%	**100%**
Bosulif	Pfizer	Leukemia	1	100%	100%	**100%**	2	100%	100%	**100%**
MenHibrix	GSK	Meningitis vaccine, children	3	100%	100%	**100%**	3	100%	100%	**100%**
Sirturo	Janssen (J&J)	Tuberculosis	1	100%	100%	**100%**	2	100%	100%	**100%**
Median			2	100%	67%	**67%**	3	100%	71%	**71%**
Interquartile range [IQR]			1-6	93-100%	0-100%	**0-100%**	2-7	93-100%	0-100%	**0-100%**

* For a list of the active ingredients for these drugs, see Appendix 2.

APPENDIX 1

Submission of trial results can be delayed by submitting one of two types of certificates. First, responsible parties may submit a certification of "initial approval", indicating a trial reached its primary completion date before the drug is initially approved, licensed, or cleared by FDA for any use. In this case, the results are due no later than 30 days post FDA approval, license or clearance. Second, a certification of "new use" can be filed indicating the "trial studies a new use of an FDA-approved drug… and the manufacturer of the drug, biologic, or device is the sponsor of the trial and has filed or will file within 1 year an application to FDA for approval or clearance of that use." In this case, the results are due either two years after the submission of the certification or 30 days after the below occurs, whichever occurs first:

a. The new use of the drug or device is approved, licensed, or cleared by FDA,
b. FDA issues a letter for the new use of the drug or device, such as a complete response letter,
c. The application or premarket notification for the new use is withdrawn without resubmission for no less than 210 days.

APPENDIX 2

Below is a list of the Active Ingredients for each of our analyzed drugs.

Aubagio: TERIFLUNOMIDE
Bosulif: BOSUTINIB MONOHYDRATE
Elelyso: TALIGLUCERASE ALFA
Eliquis: APIXABAN
Erivedge: VISMODEGIB
Inlyta: AXITINIB
MenHibrix: MENINGOCOCCAL GROUPS C AND Y AND HAEMOPHILUS B TETANUS TOXOID CONJUGATE VACCINE
Perjeta: PERTUZUMAB
Signifor: PASIREOTIDE DIASPARTATE
Sirturo: BEDAQUILINE FUMARATE
Stivarga: REGORAFENIB
Stribild: COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR DISOPROXIL FUMARATE
Xeljanz: TOFACITINIB CITRATE
Zaltrap: ZIV-AFLIBERCEPT
Zioptan: TAFLUPROST

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. (****We did not include the word “review” in the title, but can easily add if preferred).	NA
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9;13-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9;13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-9;13-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11-12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Clinical Trial Registration, Reporting, Publication, and FDAAA Compliance: A cross-sectional analysis and ranking of new drugs approved by the FDA in 2012

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009758.R1
Article Type:	Research
Date Submitted by the Author:	14-Oct-2015
Complete List of Authors:	Miller, Jennifer; New York University (NYU) School of Medicine, Department of Population Health, Division of Medical Ethics Korn, David; Harvard University, Harvard Medical School Ross, Joseph; Yale University, Yale School of Medicine
Primary Subject Heading:	Ethics
Secondary Subject Heading:	Evidence based practice, Health policy, Health services research, Public health, Medical publishing and peer review
Keywords:	MEDICAL ETHICS, Clinical trials < THERAPEUTICS, PUBLIC HEALTH, GENERAL MEDICINE (see Internal Medicine), Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Clinical Trial Registration, Reporting, Publication, and FDAAA Compliance: A cross-sectional analysis and ranking of new drugs approved by the FDA in 2012

Jennifer E. Miller, PhD[1], David Korn, MD[2] and Joseph S. Ross, MD, MHS[3]

Author Affiliations:
[1] NYU Langone Medical Center, NYU School of Medicine; Bioethics International [2] Edmond J. Safra Center for Ethics, Harvard University; Massachusetts General Hospital; Harvard Medical School,[3] Section of General Internal Medicine and the Robert Wood Johnson Clinical Scholars Program, Department of Internal Medicine, Yale School of Medicine; Department of Health Policy and Management, Yale School of Public Health; and Center for Outcomes Research and Evaluation, Yale–New Haven Hospital, all New Haven, Connecticut

Corresponding Author:
Jennifer E. Miller, PhD
Assistant Professor
Division of Medical Ethics
Department of Population Health
NYU School of Medicine

Word count: 3,355 (text), 2 tables, 2 appendices

ABSTRACT

Objective: To evaluate clinical trial registration, reporting, and publication rates for new drugs by: (1) legal requirements and (2) the ethical standard that all human subjects research should be publicly accessible to contribute to generalizable knowledge.

Design: Cross sectional analysis of all clinical trials submitted to the Food and Drug Administration (FDA) for drugs approved in 2012, sponsored by large bio-pharmaceutical companies.

Data Sources: Information from Drugs@FDA, ClinicalTrials.gov, Medline-indexed journals, and drug company communications.

Main outcome measures: Clinical trial registration and results reporting in ClinicalTrials.gov, publication in the medical literature, and compliance with the 2007 FDA Amendments Acts (FDAAA), analyzed on the drug level.

Results: The FDA approved 15 drugs sponsored by 10 large companies in 2012. We identified 318 relevant trials involving 99,599 research subjects. Per drug, a median of 57% (interquartile range [IQR], 32%-83%) of trials were registered, 20% (IQR, 12%-28%) reported results in ClinicalTrials.gov, 56% (IQR, 41%-83%) were published, and 65% (IQR, 41%-83%) were either published or reported results. Almost half of all reviewed drugs had at least one undisclosed Phase II or III trial. Per drug, a median of 17% (IQR, 8%-20%) of trials supporting FDA approvals were subject to FDAAA mandated public disclosure; of these, a median of 67% (IQR, 0%-100%) were FDAAA-compliant. Sixty-eight percent of research subjects (67,629 of 99,599) participated in FDAAA-subject trials, with 51% (33,405 of 67,629) enrolled in noncompliant trials. Transparency varied widely among companies.

Conclusions: Trial disclosures for new drugs remain below legal and ethics standards, with wide variation in practices among drugs and their sponsors. Best practices are emerging. Two of our ten reviewed companies disclosed all trials and complied with legal disclosure requirements for their 2012 approved drugs. Ranking new drugs on transparency criteria may improve compliance with legal and ethics standards and the quality of medical knowledge.

Article summary: Strengths and limitations of this study

- This study uniquely analyzes the transparency of clinical trial information for new drugs, whereas other studies analyze transparency on the trial level. It also debuts an innovative strategy for reforming areas of low transparency.
- This study uses FDA databases as a key data source, because they characterize all clinical trials supporting new drug approvals. Prior studies evaluate the transparency of already registered trials in ClinicalTrials.gov, providing limited insights into the many unregistered studies.
- This study takes a uniquely comprehensive approach, analyzing five critical elements of transparency for trials of new drugs: (1) registration, (2) results reporting, (3) publication in a medical journal, (4) compliance with legal disclosure requirements, and (5) adherence with the ethics standards enshrined in the Common Rule, Helsinki Declaration and elsewhere which state that all trials should be "designed to develop or contribute to generalizable knowledge," that is, should be publicly accessible.
- A main limitation for this study is the need to extend and repeat the analysis beyond the 15 drugs approved by the FDA in 2012 that were manufactured by large companies, to include drugs approved in other years and sponsored by other institutions. We are in the process of expanding the rankings to include drugs approved in other years as well as additional trial sponsors.

INTRODUCTION

For decades, many clinical trials have been publicly inaccessible, raising ethics, medical practice, and population health concerns. While recent transparency efforts have improved practices, a significant portion of both commercially and publicly funded trials and trial results still remain inaccessible, because they are unregistered and their results are unreported in trial registries, [1 2] or they are never published in the medical literature. [3 4]

Studies have shown that roughly 30% to 50% of clinical trials remain unpublished, often years after their completion, [5 6] and most fail to meet baseline legal disclosure requirements, such as those established in the 2007 US Food and Drug Administration Amendments Act (FDAAA).[7] Moreover, studies that are published by sponsors, journals and researchers, tend to show favorable or statistically significant results.[8 9 10 11] This selective trial dissemination can distort the medical evidence and challenge physicians, prescription guideline writers, payers, and formulary decision-makers' abilities to recommend and provide the right drugs for the right patients. It also represents a violation of the rights of human research subjects, as experimenting on humans is largely justified by its potential to contribute to generalizable knowledge (as stated in the 1981 United States Common Rule). Furthermore, transparency may be essential to ensuring the integrity and trustworthiness of the clinical research enterprise.

Despite numerous major reform strategies, the transparency problem persists, raising questions of what more can be done. Efforts include the 1997 US Food and Drug Administration Modernization Act requiring the registration of drug trials for serious or life-threatening conditions, FDAAA requiring that select trials be registered and publicly report results, and the 2008 World Medical Association guidelines identifying trial registration and results reporting as an ethical obligation in the Declaration of Helsinki. The International Committee of Medical Journal Editors, Institute of Medicine, individual drug companies and their trade associations, the European Medicines Agency, World Health Organization (WHO) and Bill and Melinda Gates Foundation have also made efforts to improve transparency in clinical research. Recently, both the Department of Health and Human Services and National Institutes of Health (NIH) called for public comment on two new proposals to further expand access to clinical trial information. The DHHS proposal would substantially expand the scope of registration and results reporting requirements under FDAAA.[12 13] The NIH proposal would require registration and results reporting for all NIH funded clinical trials, including phase I trials. [14]

To help understand the efficacy of these transparency efforts for new drugs and how to improve them, this paper examines whether clinical trials for drugs approved by the FDA in 2012, which were sponsored by large companies, were registered, reported, published in the medical literature, and complied with legal transparency requirements established in FDAAA.

This study and approach are novel for at least five reasons. First, we evaluated the transparency around individual new drugs. Previous studies generally evaluate transparency on the trial level.

We thought evaluating on the drug level could help make the transparency problem more understandable and proximate for stakeholders who consume, prescribe, reimburse, stockpile or otherwise regulate medicines and vaccines. Moreover, drug level transparency evaluations are critical to improving clinical practice. When a new drug enters the market, the trials we evaluated in our rating system contain the safety and efficacy profile for that drug, and all, or nearly all, available evidence to inform clinical practice.

Second, we used FDA approval packages as a key data source, because they characterize all clinical trials supporting new drug approvals. Prior studies evaluate the transparency of already registered trials in ClinicalTrials.gov, which provide limited insights into the many unregistered studies. Third, we focused on large companies because, as a group, they sponsor a significant portion of the trials conducted annually and the majority of new drug applications (NDAs) submitted to the FDA. Also, they were expected to have the infrastructure to comply with regulatory and ethics standards. Thus, we likely captured a best-case scenario. Fourth, we evaluated transparency on both legal and ethics standards, providing a uniquely comprehensive overview. Lastly, we introduce an innovative strategy to improve the state of transparency for drugs: an annual transparency scorecard that audits and ranks all new medicines and vaccines.

METHODS

Data sources

We used data collected from Drugs@FDA, a publicly accessible database containing records of FDA drug regulatory decisions, including drug approvals and medical and scientific reviews of approved drugs; ClinicalTrials.gov, a clinical trial registry and database maintained by the National Library of Medicine (NLM) at the NIH; Medline indexed journals (accessed through PubMed); information from the NLM to identify certificates of delay (provided by Tse T to Anderson M: personal communication); information from large companies that had new drugs approved by the FDA in 2012; and pharmaceutical company press releases. The databases were accessed several times between October 2013 and April 2014.

Study samples

Drugs

New drugs approved by the FDA in the calendar and fiscal year of 2012 were identified from FDA reports, [15 16] and included innovative and novel drugs and new molecular entities, henceforth referred to simply as "drugs". We restricted the total number of drugs to those that were sponsored by large biotechnology and pharmaceutical companies, defined as the twenty institutions with the highest market capitalizations in 2012.[17]

Clinical trials

All trials conducted to gain FDA approval in 2012 for each drug

Each drug's 2012 FDA approval package was located in the Drugs@FDA database. We reviewed all pages of a drug's summary review, Medical Review(s), Chemistry Review(s), Pharmacology Review(s), Statistical Review(s), Clinical Pharmacology Biopharmaceutics Review(s), Risk Assessment and Risk Mitigation Review(s), and other reviews to create a list of every clinical trial reviewed by the FDA to approve each drug. Where possible, the basic characteristics of each trial were catalogued, including the organizational identification number, phase, study population, number of research subjects, primary endpoint(s), study start and completion date(s), location, and description of the treatment (e.g. dosage and comparators), subjects received in the various arms, and whether the trial was controlled and/or interventional.. We excluded any trials that were terminated without enrollment of subjects, still ongoing, or not at least one year past their primary completion date by our study cut-off date of February 1, 2014.

FDAAA applicable trials for each drug

We narrowed the "all trials" sample to only those subject to mandatory registration and reporting requirements under FDAAA, that is, generally, "controlled clinical investigation(s), other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act." [18] These trials should have "either initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007," and meet one of the following conditions:

a. The trial has one or more sites in the United States,
b. The trial is conducted under an FDA investigational new drug application, or
c. The trial involves a drug or biologic that is manufactured in the United States or its territories and is exported for research" [19]

Because of conflicting understandings on the reach of FDAAA, we created two sample pools of FDAAA-subject trials, one for controlled and one for interventional trials. Trials with unknown phases or that were listed as phase I/II in at least two primary data sources were excluded from the FDAAA analysis (n=1).

Main Outcome Measures

Determining transparency according to the ethics standard that all trial results should be publicly accessible

We ascertained in ClinicalTrials.gov whether each identified trial from the FDA approval packages of each drug (the "all trials" study sample) was registered and reported results. Search terms to locate and match trials included the trial's organizational identification number (org ID), product name, number of trial participants, and other trial characteristics captured from the

approval packages. Once identified, we abstracted the National Clinical Trial number (NCT number), number of research subjects enrolled in the various treatment arms, description of the treatment (e.g. dosage and comparators), whether the trial was controlled and/or interventional, primary outcome measurements, trial start date, registration date, primary completion date (date the last participant was examined and data for the primary outcome measure collected), and any links to clinical study reports. Any clinical trial(s) with results received by ClinicalTrials.gov on or before February 1, 2014, was deemed to have results publicly available. This study cutoff date was chosen to provide at least 13 months for trial results disclosure post FDA approval of a drug.

Second, using search terms that included the branded drug name or active ingredient and trial indication, we determined from PubMed whether individual trials for each drug were published in a MEDLINE-indexed journal, on or before our cut-off date. We then matched at least two of the following characteristics -- the NCT number or organizational trial identification number, number of enrolled research subjects, descriptions of the treatment (e.g. dosage and comparators), and/or primary outcome measurements-- in the publication with what was in ClinicalTrials.gov or the Drugs@FDA databases. We also reviewed papers listed on ClinicalTrials.gov for registered trials and used the same matching criteria. Papers summarizing and reviewing multiple phase I trial results in a single publication, although rare, were counted.

Determining transparency according to FDAAA legal requirements

We reviewed whether FDAAA applicable trials (for both the "controlled" and "interventional" samples) had timely registration and reporting as defined by FDAAA. Registration (which in our case are trials for approved drugs), in general, should occur within twenty-one days after enrolling the first subject. Results should be reported, generally, no later than 12 months after the trial's primary completion date, in ClinicalTrials.gov, although results submissions can be delayed by submitting certificates to the NIH (See Appendix I). If a trial met FDAAA requirements for both registration and disclosure of results, it was counted as compliant with legal requirements.

Validation

Data were extracted by at least two research assistants (working independently and blinded to each other's work), with discrepancies resolved through discussion and consensus (see acknowledgments for a list of research assistants). Our final datasets for each drug were sent to each New Drug Application company sponsor to verify the accuracy and completeness of our extracted information. Data and input received from companies (response rate was 100%) were verified by public data sources.

Statistical Analysis

We used descriptive statistics to calculate the median number of clinical trials per drug that were registered and reported results in ClinicalTrials.gov, were published in a MEDLINE indexed

journal, and were publicly accessible. Public accessibility of a trial was defined as being either reported in Clinicaltrials.gov or published in a MEDLINE indexed journal. We also used descriptive statistics to calculate the median number of clinical trials per drug subject to FDAAA that were in compliance with the statute. All data were collected and analyzed in Microsoft Excel v2013 (Redmond, Washington).

RESULTS

In 2012, the FDA approved 39 novel new medicines, known as new molecular entities (NMEs), and 35 novel drugs. Combining these lists, the FDA approved a total of forty-eight new drug entities, fifteen of which were sponsored by ten large pharmaceutical or biotechnology companies with market capitalizations valued over $19 billion. A total of 342 trials were conducted to gain regulatory approval of the 15 drugs, 24 of which were excluded from our analysis, leaving 318 trials involving 99,599 subjects relevant to our study, a median of 17 trials per drug (see Table 1).

Transparency evaluated by the ethics standard that all trial results should be publicly accessible

The median proportion, per drug, of publicly registered trials was 57% (IQR, 32% to 83%), of trials reporting results in ClinicalTrials.gov, 20% (IQR, 12% to 28%), and of published trials, 56% (IQR, 41% to 83%) (see Table 1). A median of 65% (IQR, 41% to 83%) of clinical trial results were publicly available, that is, the results were either reported in ClinicalTrials.gov or published in the medical literature, but with considerable variation (see Table 1). Importantly, among trials that reported results in ClinicalTrials.gov, a median of 100% (IQR, 86-100%) were also published.

Among the 35% of trials, per drug, with results unavailable in either the medical literature or ClinicalTrials.gov, a median of 91% (IQR, 60% to 100%) were Phase I, 0% were phase II (IQR, 0% to 15%), 0% were Phase III trials (IQR, 0% to 2%) and 0% were of unknown phase). Among the 15 drugs, 20% had at least one publicly unavailable phase III trial, 27% had at least one undisclosed phase II trial, and 47% one of either. In total, 5,566 research subjects (of the 99,599 total participants) participated in publicly undisclosed trials for these 15 drugs.

Public availability of clinical trial information varied widely by company, and sometimes within companies for those with multiple drugs approved in 2012 (Table 1). For example, three of the ten companies (GSK, J&J and Pfizer) publicly disclosed all clinical trial results for at least one of their reviewed drugs, whereas the lowest scoring company, Gilead, disclosed 21% (seven of thirty-four) of the trial results for its HIV medicine Stribild.

Transparency evaluated by FDAAA legal requirements

The legal requirements enshrined in FDAAA (Table 2) offer at least two potential interpretations for what constitutes an applicable clinical trial: controlled and interventional trials. Applying the "controlled" definition, a median of 17% (IQR, 8% to 20%) of trials per drug were subject to legal disclosure requirements, hereafter referred to as "applicable trials" .A median of 100% (IQR, 93% to 100%) of these trials met registration requirements, whereas 67% (IQR, 0% to 100%) met reporting requirements. Overall, per drug, a median of 67% (IQR, 0% to 100%) of applicable trials fully complied with the law, (See Table 2), with considerable variation. Sixty-eight percent of research subjects (67,629 of 99,599) participated in FDAAA-subject trials, with fifty-one percent of them (33,405 of 67,629) enrolled in noncompliant trials. Six of the ten reviewed companies showed 100% compliance with the law for at least one drug. However, an almost equal number, five of ten, had at least one drug that was 0% compliant.

Applying the "interventional" definition, a median of 19% (IQR, 15% to 29%) of trials, per drug, were subject to legal disclosure requirements under FDAAA. A median of 100% (IQR, 93% to 100%) of these trials met registration requirements, whereas 71% (IQR, 0% to 100%) met reporting requirements. Overall, a median, per drug, of 71% (IQR, 0% to 100%) of applicable trials complied with FDAAA (See Table 2). Sixty-nine percent of research subjects (68,703 of 99,599) participated in FDAAA-subject trials, with fifty-one percent of them (33,786 of 68,703) enrolled in noncompliant trials. Five of the ten reviewed companies had at least one drug that showed 100% compliance with FDAAA. The same number of companies (5 of ten) had at least one drug that was 0% compliant.

DISCUSSION

Medical practice remains largely an empirical discipline, highly dependent for its advancement on the complete and accurate sharing of information. Nowhere is this truer than in the reporting of clinical trials, in particular those that support the efficacy and safety of new medicines. The purpose of this study was to review all new drugs approved by the FDA in 2012 that were sponsored by large companies, identifying all clinical trials that supported their approval and determining whether the trials were publicly registered and had trial results reported in ClinicalTrials.gov, were published in the medical literature within at least 13 months of FDA approval, and complied with federal disclosure laws. While nearly two-thirds of clinical trials, per drug, were publicly disclosed, there was wide variation among drugs and companies. At first approximation, it may seem difficult to understand failures to comply with federal law, now eight years old, whose origins track back to 1997, and even more difficult to understand failures to meet the over-riding ethics obligation that human research be designed to contribute to generalizable knowledge.

Transparency by legal standards

There are at least three reasons why compliance with current disclosure laws might be suboptimal. First, legal requirements are perceived to be unclear or ambiguous, as a spectrum of interpretations of FDAAA has emerged. Some companies believe only controlled trials are subject to mandatory disclosure, others interventional trials. Some believe that results are due one year after a trial's primary completion date regardless of whether the drug has been approved, while others believe results are not due until thirty days post FDA approval of a trial's investigated indication. There is also disagreement about the role of certificates of delay. These varying interpretations for FDAAA came to light during our discussions with the ranked companies. Recall that we sent all data to the companies whose products we scored (with a 100% response rate).

Second, mergers, acquisitions, collaborations and licensing agreements may complicate compliance. Two companies in our sample acquired or licensed drugs initially developed by smaller companies, and another used a partner company for some trials, raising questions about whose responsibility it was to ensure trials complied with FDAAA.

Finally, compliance may be affected by a perceived lack of enforcement. FDAAA empowers the FDA to impose a $10,000 a day penalty for noncompliance. To date, this penalty has never been imposed.

Transparency by ethics principles

In contrast to legal requirements, that applied to roughly only one-fifth of all clinical trials supporting a new drug approval, ethics standards enshrined in the Common Rule, Helsinki Declaration and elsewhere, apply to *all* clinical trials. Ethically, all research involving human subjects should be "designed to develop or contribute to generalizable knowledge,"[20] that is, should be publicly accessible. Surprisingly, adherence to this ethics standard was similar to that to legal standards: the results of approximately two-thirds of the studied trials, per drug, were publicly accessible, either through results reporting in ClinicalTrials.gov or publication. Adherence may be less than complete because companies may not act without an authoritative body promulgating an organizing policy. Perhaps the new WHO guidelines calling for all trial results to be publicly disclosed, including phase I trials, may serve this purpose.[21] Our proposed pharmaceutical transparency scorecard may also help.

Motivating Transparency

Given the wide variation in compliance with both legal and ethical standards across drugs and companies, we propose continuing our clinical trials transparency monitoring, evaluations and scoring of new drugs approved by the FDA, along with their sponsors. These ongoing rankings---developed initially with support from Harvard University, Duke University, Susan G. Komen Foundation, and the Raskob Foundation (For a full list of sponsors, see the Acknowledgements

Section)--- will be conducted annually under the auspicious of Bioethics International, with grant support from the Laura and John Arnold Foundation. [22 23 24]

This system will help identify best practices, incent better behaviors, and standardize the industry's practices and thereby contribute importantly to an enrichment of medical knowledge. Moreover, the scorecard and rankings have the potential to benefit consumers of clinical trial information by helping to assure them of the integrity and completeness of their data. Not least, full transparency of clinical trials would also strengthen the protection of human research subjects by avoiding their unknowing recruitment into already failed experiments.

Limitations

Several limitations deserve further consideration. We limited our study to one year of FDA approvals: 15 drugs sponsored by 10 large companies. Further measurements are needed of trials for drugs approved in other years, of additional sponsors (such as smaller companies and academic centers), and of the quality of reported information. We are in the process of expanding the rankings to include drugs approved in other years as well as additional trial sponsors. At times, mergers, acquisitions, subsidiaries, partnerships and licensing practices complicated determining the sponsors and responsible parties for trial transparency. Lastly, there is some disagreement on whether the scores and index we presented should include a weighting mechanism to account for the variation in the number of trials conducted per drug to gain FDA regulatory approval.

CONCLUSION

Nearly two-thirds of clinical trials supporting new drugs approved by the FDA in 2012 were publicly disclosed, perhaps encouraging but below both legal and ethics standards. While several large companies' drugs were superseding legal requirements, others had low rates of transparency. Implementing a transparency scorecard and ranking system for all newly approved drugs could motivate and increase transparency, thereby supporting existing transparency initiatives, advancing clinical innovation, promoting a trustworthy innovation sector, and strengthening protection of human research subjects globally.

Funding Disclosures: The conceptualization and pilot of this study and index (tentatively called the OpenPharma Index or Pharma Integrity Scorecard) were supported by Harvard University's Edmond J. Safra Center for Ethics; Duke University's Kenan Institute for Ethics, Trinity College of Arts and Sciences and Fuqua School of Business; Fordham University's Global Healthcare Innovation Management Center; Susan G. Komen Foundation; Raskob Foundation; and Bioethics International. A conference exploring the rating concept (co-chaired by Jennifer Miller

and Nir Eyal) was held at Harvard Medical School, funded by the Division of Medical Ethics (currently the Harvard Medical School Center for Bioethics); the Petrie-Flom Center for Health Law, Biotechnology, and Bioethics at Harvard Law School; the Harvard Global Health Institute; and the Harvard University Program in Ethics and Health. Dr. Ross is supported by the National Institute on Aging (K08 AG032886) and by the American Federation for Aging Research through the Paul B. Beeson Career Development Award Program and receives research support through Yale University from Medtronic, Inc. and Johnson & Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices. Drs. Miller and Korn receive no financial support from pharmaceutical companies. Bioethics International and the Laura and John Arnold Foundation will support further development and implementation of the ranking system described in this paper. This paper remains an independent work product and the views expressed do not necessarily represent those of the funder(s).

Acknowledgements: The authors thank Robert Califf (Duke University), Aaron Kesselheim (Brigham and Women's Hospital and Harvard Medical School), Kevin Schulman (Duke University) and Arti Rai (Duke University) for comments on this paper; Brittany Rush, Jason Dong, Marsha Sukash, Julie Dorais, Jessica Ericson, Rajan Patel, Eidan Jacob, Brooke Whitfield, Priyanka Kanal, Raichel Perper and Nicole Miller for data-gathering assistance; and Malcolm Salter (Harvard Business School), Larry Lessig (Harvard Law School), Arthur Caplan (New York University), Ed Balleisen (Duke University), the directors of Bioethics International, and the fellows of Edmond J. Safra Center for Ethics at Harvard University for their input and feedback on the index and ranking concept. They also thank Janet Woodcock (FDA) and Tony Tse (NIH) for answering FDAAA related questions and Monique Anderson (Duke University) for providing access to certificate of delay data.

Contributors: JEM, JSR, and DK were responsible for the conception and design of this work. JEM drafted the manuscript, conducted the statistical analysis, and is guarantor. All authors participated in the analysis and interpretation of the data and critically revised the manuscript for important intellectual content.

Data-sharing: No additional data available.

Competing interest:

Dr. Ross is supported by the National Institute on Aging (K08 AG032886) and by the American Federation for Aging Research through the Paul B. Beeson Career Development Award Program and receives research support through Yale University from Medtronic, Inc. and Johnson & Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices. Drs. Miller and Korn receive no financial support from pharmaceutical companies.

Table 1. Transparency Index: Ranking of new drugs according to the ethics standard that *all* trial results should be publicly available to contribute to generalizable knowledge

Drug*	Sponsor	Indication	No. of trials analyzed from FDA* approval package	Percentage of trials registered	Percentage of trials reported	Percentage of trials published	Percentage of trial results that are publicly available (reported or published)
Stribild	Gilead	HIV	34	24%	9%	21%	**21%**
Aubagio	Sanofi	Multiple sclerosis	32	34%	19%	16%	**22%**
Elelyso	Pfizer & Protalix	Gaucher disease	5	100%	20%	40%	**40%**
Zaltrap	Sanofi	Colorectal cancer	30	40%	30%	37%	**40%**
Stivarga	Bayer	Colorectal cancer	12	75%	17%	42%	**42%**
Eliquis	BMS	Anticoagulant	39	26%	10%	44%	**44%**
Zioptan	Merck & Santen	Eye pressure, glaucoma	16	25%	13%	44%	**44%**
Xeljanz	Pfizer	Rheumatoid arthritis	34	82%	53%	56%	**65%**
Bosulif	Pfizer	Leukemia	17	100%	24%	71%	**71%**
Perjeta	Genentech/Roche	Breast cancer	12	50%	8%	75%	**75%**
Signifor	Novartis	Cushing's disease	17	29%	12%	82%	**82%**
Erivedge	Genentech/Roche	Basal cell carcinoma	12	83%	25%	83%	**83%**
Inlyta	Pfizer	Renal cell carcinoma	28	61%	46%	100%	**100%**
Sirturo	Janssen (J&J)	Tuberculosis	14	57%	21%	93%	**100%**
MenHibrix	GSK	Meningitis vaccine, children	16	100%	100%	100%	**100%**
Median			17	57%	20%	56%	**65%**
Interquartile range [IQR]			13-31	32-83%	12-28%	41-83%	**41-83%**

* For a list of the active ingredients for these drugs, see Appendix 2.

Table 2. Legal Compliance Index: Ranking of new drugs according to their compliance with disclosure requirements under the Food and Drug Administration Amendments Acts (FDAAA)

				FDAAA Definition 1: "controlled" trials			FDAAA Definition 2: "interventional" trials			
Drug*	Company	Indication	No. Trials Subject to FDAAA	Timely Registration	Timely Reporting	FDAAA Compliance	No. Trials Subject to FDAAA	Timely Registration	Timely Reporting	FDAAA Compliance
Elelyso	Pfizer/ Protalix	Gaucher disease	1	100%	0%	**0%**	3	100%	0%	**0%**
Stivarga	Bayer	Colorectal cancer	1	100%	0%	**0%**	2	100%	0%	**0%**
Perjeta	Genentech/ Roche	Breast cancer	2	50%	0%	**0%**	2	50%	0%	**0%**
Signifor	Novartis	Cushing's disease	1	100%	0%	**0%**	2	100%	0%	**0%**
Erivedge	Genentech/ Roche	Basal cell carcinoma	2	100%	0%	**0%**	3	100%	0%	**0%**
Zioptan	Merck/ Santen	Eye-pressure, glaucoma	7	17%	17%	**17%**	7	29%	14%	**14%**
Eliquis	Eliquis	BMS	6	83%	33%	**33%**	6	83%	33%	**33%**
Aubagio	Sanofi	Multiple sclerosis	7	86%	71%	**71%**	7	86%	71%	**71%**
Zaltrap	Sanofi	Colorectal cancer	6	100%	67%	**67%**	9	100%	78%	**78%**
Inlyta	Pfizer	Renal cell carcinoma	2	100%	100%	**100%**	7	100%	86%	**86%**
Stribild	Gilead	HIV	3	100%	100%	**100%**	3	100%	100%	**100%**
Xeljanz	Pfizer	Rheumatoid arthritis	11	100%	100%	**100%**	11	100%	100%	**100%**
Bosulif	Pfizer	Leukemia	1	100%	100%	**100%**	2	100%	100%	**100%**
MenHibrix	GSK	Meningitis vaccine, children	3	100%	100%	**100%**	3	100%	100%	**100%**
Sirturo	Janssen (J&J)	Tuberculosis	1	100%	100%	**100%**	2	100%	100%	**100%**
Median			2	100%	67%	**67%**	3	100%	71%	**71%**
Interquartile range [IQR]			1-6	93-100%	0-100%	**0-100%**	2-7	93-100%	0-100%	**0-100%**

* For a list of the active ingredients for these drugs, see Appendix 2.

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APPENDIX 1

Submission of trial results can be delayed by submitting one of two types of certificates. First, responsible parties may submit a certification of "initial approval", indicating a trial reached its primary completion date before the drug is initially approved, licensed, or cleared by FDA for any use. In this case, the results are due no later than 30 days post FDA approval, license or clearance. Second, a certification of "new use" can be filed indicating the "trial studies a new use of an FDA-approved drug… and the manufacturer of the drug, biologic, or device is the sponsor of the trial and has filed or will file within 1 year an application to FDA for approval or clearance of that use." In this case, the results are due either two years after the submission of the certification or 30 days after the below occurs, whichever occurs first:

a. The new use of the drug or device is approved, licensed, or cleared by FDA,
b. FDA issues a letter for the new use of the drug or device, such as a complete response letter,
c. The application or premarket notification for the new use is withdrawn without resubmission for no less than 210 days.

APPENDIX 2

Below is a list of the Active Ingredients for each of our analyzed drugs.

Aubagio: TERIFLUNOMIDE
Bosulif: BOSUTINIB MONOHYDRATE
Elelyso: TALIGLUCERASE ALFA
Eliquis: APIXABAN
Erivedge: VISMODEGIB
Inlyta: AXITINIB
MenHibrix: MENINGOCOCCAL GROUPS C AND Y AND HAEMOPHILUS B TETANUS TOXOID CONJUGATE VACCINE
Perjeta: PERTUZUMAB
Signifor: PASIREOTIDE DIASPARTATE
Sirturo: BEDAQUILINE FUMARATE
Stivarga: REGORAFENIB
Stribild: COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR DISOPROXIL FUMARATE
Xeljanz: TOFACITINIB CITRATE
Zaltrap: ZIV-AFLIBERCEPT
Zioptan: TAFLUPROST

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. (****We did not include the word “review” in the title, but can easily add if preferred).	NA
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9;13-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9;13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9;13-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11-12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	*NA*
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	5-8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11-12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.