PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical Trial Registration, Reporting, Publication, and FDAAA Compliance: A cross-sectional analysis and ranking of new drugs approved by the FDA in 2012
AUTHORS	Miller, JennifeR; Korn, David; Ross, Joseph

VERSION 1 - REVIEW

REVIEWER	Gordon Guyatt McMaster University
REVIEW RETURNED	15-Jun-2015

GENERAL COMMENTS	With the aim of evaluating the transparency of new drugs and vaccines, the authors of this study used two standards, 1) the ethical standard that all trial results should be publicly accessible and 2) the legal standard according to the US Food and Drug Administration Amendments Act (FDAAA) requirements, to descriptively report the current situation. The authors identified the FDA-approved 15 new drugs and vaccine that were sponsored by ten large companies in 2012, ascertained 318 trials of these 15 drugs and vaccine from their FDA approval packages. For the first transparency standard, the authors assessed all the 318 trials' accessibility for each drug and vaccine by searching in ClinicalTrials.gov and MEDLINE (Table 1). For the second transparency standard, the authors reviewed the status of the 15 drugs and vaccine's timely registration and reporting (in ClinicalTrial.gov) as defined by FDAAA. The major problem with this study is that the authors appear to be making a big issue about something that is not a big issue at all. As we understand it, almost all the trials that are not publicly accessible are Phase I trials, and only approximately 5.6% of the data (i.e. 5.6% of the subjects – those participating in Phase I trials) is unavailable. This strikes us as an essentially non-problematic situation – key findings are, in general, being full disclosed. It is a big problem when a substantial proportion of the evidence regarding a particular drug remains undisclosed, but in the sample the authors have used this seems to happen very infrequently, if at all. With regard to the legal requirements, the problem seems to be late reporting. In that they have never penalized companies for late reporting, the FDA appears not to think this is a big problem either. If the authors think that the violation of the timely reporting standard is one that the general public should be concerned about, they need to

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	make a compelling case why this is so. We do not see such a case in the submitted manuscript. The bottom line is that unless the authors can persuade us they have uncovered a serious problem, this paper is not suitable for the BMJ. If the authors fail to demonstrate an important problem, and subsequently publish elsewhere, the entire presentation should acknowledge that they have not uncovered a serious problem. There are a few additional comments and questions that authors may consider addressing to improve the manuscript. 1. Given that there isn't a serious problem, the new transparency rating the authors suggest is probably not a good use of time and energy. If it were, however, it would be useful to know who should be putting together this rating: it would be a lot of time and work, would need quality standards, and would have to be done by someone authoritative to be taken seriously. 2. The FDA is a federal agency of the United States Department of Health and Human Services and is responsible for the new drugs approval in the USA. Although the two standards described in the manuscript have potential applicability in other countries and regions by using their own literature databases, trial registration agencies and legal requirements, might be of use, particularly in a non-American journal, to discuss the generalizability of the study results. 3. Aside of MEDLINE, EMBASE is a biomedical and pharmacological database of published literature. The authors might wish to explain and discuss their not including EMBASE in the search as one of the limitations. 4. Table 1 and Table 2 need explanation of abbreviations of IQR, Q1, Q3, FDA and FDAAA. 5. The format of several references need revision, for example, references 8, 11, 14 and 15. The statement in Line 55, Page 8 needs reference.

REVIEWER	Mª José Martínez Zapata Iberoamerican Cochrane Centre. IIB Sant Pau.
REVIEW RETURNED	21-Jun-2015

GENERAL COMMENTS	This is a manuscript of a cross sectional study that evaluates and ranks new medicines and vaccines with respect to the transparency of clinical trials and trial results. In general, it is good written, but there are some points that should improve. The most important is the discussion. The results of the study are not compared with other similar studies and there is no clear explanation of what the study adds to current knowledge. Information of the Tables 1 and 2: it is better to present the last column in a descendent way. The name of the drug is better to present the active drug than the trade name.

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REVIEWER	Swaroop Vedula Johns Hopkins University
REVIEW RETURNED	25-Jun-2015

GENERAL COMMENTS	This is a well conceived and thoroughly conducted study with interesting findings. But the significance or relevance of this work is not clear to me; it has not been adequately discussed in the manuscript. 1. Which of the data sources were considered "primary" when excluding trials that were listed as phase I/II? 2. Verify for typos, for example, correcting "Clinicaltrials.gov" to "ClinicalTrials.gov". 3. What was the distribution of FDA approvals by the twenty eligible companies? 4. Why were only 15 new drug entities sponsored by ten large companies considered instead of trials by the twenty eligible companies? 5. Provide abbreviations for acronyms used in the Tables. 6. The writing is hard to read in many places. For example, the first sentence in the second paragraph of the Results is confusing to read. 7. Table 1 - the column labeled "Percentage of trials reported" - reported at what venue? It will help to explain this label so the reader need not refer back to the text. 8. Table 1 - last column - why is a trial that was registered not considered to be "publicly available"? This definition is different from what is described in the text. 9. Table 1 - First column, last and penultimate rows - "drug level" in parentheses - what does this indicate? It's confusing. 10. Tables 1 and 2 - The titles are unclear - why are they called "Transparency Index" and "Legal Compliance Index"? Are these indices defined in the Methods? 11. The phase III trials with results publicly unavailable - were the findings statistically significant for the primary outcome(s)? 12. The descriptive value of the findings apart, what is the point the authors are making based on the findings? The argument about a transparency rating and ranking system, which the authors briefly describe in the conclusion section, is not convincing to me. Who establishes the ranking system, who administers it, who monitors its accuracy, and why should it make a difference to how clinical trials are reported? Furthermore, the ranking approach as suggested in the context of this work is focused entirely on trials conducted by the industry. Such a narrow focus will only provide room for arguments against implementing a ranking system because it does not consider trials conducted by not-for-profit entities and individuals. 13. Why should the industry buy into the ranking system? 14. What does the public have to gain from a transparency rating and ranking system? Can it be part of a consent form so patients consenting for participation in a trial are informed of the investigators' track record of publicly reporting their findings?

REVIEWER	Andreas Lundh Department of Internal Medicine, Roskilde Hospital, Denmark
REVIEW RETURNED	03-Jul-2015

GENERAL COMMENTS	Version 1

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	General comments The authors identified 15 drugs approved by the FDA in 2012 and produces by the 10 largest drug companies. For these 15 drugs the authors included 318 company-sponsored trials from FDA documents. They found that per drug a median of 57% were registered and 65% either reported results on clinical trials.gov or were published in a MEDLINE-indexed journal. Around a fifth of these trials were applicable to the FDA Amendments Act and of these around two-thirds compliant in relation to timely registration and reporting. Major compulsory revision The paper's focus on reporting of results seems to be based on trial level and not outcome level. As far as I can see from the paper, any trial posting any result on either clinicaltrials.gov or in a MEDLINE-index journal is compliant. However, relevant outcomes may still remain unpublished/unreported and it seems that while the authors extracted data on primary endpoint(s) in the registration of trials they did not check to see whether they were actually reported/published. Also there seems to have been no assessment of secondary outcomes. This will in my mind paint a too optimistic picture in relation to compliance and needs to be addressed as a limitation in the paper. Minor compulsory revision Title: I suggest changing the title. While ranking of drugs in relation to transparency is part of the paper, it is not the main focus of the paper. Furthermore, solely ranking just by the proportion of registered and reported trials is problematic as it does not take into account the size of the trial or the relevance of reported/unreported outcomes, length of follow-up etc. For example, not registering and reporting on some Phase I trial is less problematic than not reporting on a large Phase III trial or not reporting on important outcomes from that trial. p3 para 2 In general the background section is very long and could be shortened somehow. Particularly, the last three sentences about the DHHS and NIH proposal is in my mind more fitting for the discussion section. Furthermore, because there is not provided enough detail in this section, for example it is not stated what the DHHS proposal includes. p4 para 2 line 4 It is not clear why 20 and not 10 companies are mentioned here. In addition, the provided hyperlink for the reference (ref 15) is for the 2013 list, not the 2012 list. In the linked citation there is a top 15 pharmaceutical firm list and a top 25 biotechnology companies list. Nine of the ten included companies are from the pharmaceutical firm list, and one (Gilead) is from the biotechnology companies list. According to the list Gilead had a 2012 market cap of $19.751 billions. However, six companies from the biotechnology list (Novo Nordisk, Amgen, Celgene, Biogen, Merck KgaA and Teva Pharmaceutical Industries) and three companies from the pharmaceutical list (AstraZeneca, Eli Lilly and Takeda) had a higher 2012 market cap. Two of these companies with a higher market cap had drugs approved in 2012 Omontys (Takeda) and Synribo (Teva). So it is unclear why Stribild from Gilead is on the list instead of Synribo from Teva with a $39.282 billion 2012 market cap. The

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	methods should be more clear in order for others to be able to reproduce the authors' findings. p5 para 3 line 2 The terms 'controlled' and 'interventional' trials are used in the manuscript without a definition. I am unsure whether the authors' have used the terms from the FDA glossary (https://clinicaltrials.gov/ct2/about-studies/glossary). The authors should define what is meant by controlled and interventional. p6 para 4 line 1 According to the paper 48 new drug entities (NMEs) were approved in 2012. It is not clear from the methods how the list of 48 new drug entities were identified. According to the FDA Novel New Drug Summary (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM337830.pdf) only 39 NMEs were approved in 2012. All of the 15 drugs from the paper are on that list, except one (the GSK vaccine MenHibrix). How these 15 drugs were identified should be more clear from the methods, preferably with direct citation to the relevant reports (reference 14 does not allow this identification). p6 para 4 line 3-4 The authors should describe the reason for excluding the 24 trials. p6 para 5 The authors should report some baseline data from their sample of trials. E.g. the proportion of phase I, II and III trials and median trial size. Also, data on median registration and reporting/publication time would be of interest. p9 para 3 The authors should also describe their choice of databases and registries as a limitation. Some trials might be registered in other trial registries and some trials might have been missed due to limitation in search strategy and not searching other databases such as EMBASE and CENTRAL. Furthermore, company trial registries could have been searched (e.g. www.gsk-clinicalstudyregister.com) p8-9 Discussion The authors should preferably describe the large difference in number of trials between the 'ethics' and 'legal' sample. Was this due to Phase I trials? In addition, it would add relevant information if the authors could describe how many of the non-compliant trials in the 'legal' sample where non-compliant due to a time factor only (i.e. registered after 21 days or reported after 13 months). p9 para 2 It is not clear whom the authors suggest should carry out the monitoring and ranking of transparency. Furthermore, the authors state that “transparency has proved effective in other industries” and cites a single 2005 study related to food-borne-diseases hospitalization in Los Angeles (ref. 23, nb. nn the references it is cites as a 2015 paper, but it is from 2005). That was a before-and-after study that received substantial criticism in a following letter to the editor. To make their case I suggest the authors cite better evidence from more than one industry. Discretionary revision Abstract-Design and setting Line 2 I would suggest changing “large” to “the ten largest”. Abstract-Results line 6 Undisclosed is in my mind to vague. I suggest

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	using similar terminology as previously (i.e. not reported or published). Abstract-Conclusion line 1-3 The part of the sentence “below legal and ethics standards” might not read well for a non-native speaker of English, as below seems to suggest that a certain criteria was not met. What about complied with legal and ethics standards as is used in the rest of the paper? p4 para 1 line 5 It is not clear what “certificates of delay” are. p6 para 2 line 1 Does “the data gathering was repeated by at least two research assistants)” mean that data was extracted by a minimum of three research assistants? If so I would write the total number of data extractors as this is what is conventionally reported. p6 para 2 line 3 This is the first time the abbreviation NDA is used so the full phrase should be used. p7 para 3 line 3 The authors should consider focusing on GSK and J&J as they both published all trial results, while the results for Pfizer was mixed ranging from 40% to 100%. p9 para 1 line 3 The authors should provide a citation for WHO's call for trial reporting. Table 1 & 2 In the main manuscript J&J is used, in Table 1 Janssen and in Table 2 J&J (Janssen). The authors should use the same name throughout the manuscript. For example, Janssen Pharmaceuticals (a J&J company). Language: Acceptable. Stat review: Does not need to be reviewed by a statistician.

REVIEWER	Anonymous
REVIEW RETURNED	

GENERAL COMMENTS	The terms of this reviewer's employment preclude sharing additional details. Comments/Questions regarding “Shining Light on Medical Evidence: Ranking new drugs for transparency of clinical trials and trial results” 1. This is an interesting paper addressing an important topic, but it is a bit small and reported in a needlessly complex fashion. We have three overarching points, following by more specific comments on particular sections of the manuscript. 2. As the paper acknowledges, FDAAA generally requires registration and reporting for “controlled clinical investigation(s),

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	other than a phase 1 clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act." (Page 4, lines 51-55) An "applicable" clinical trial is, by statutory definition, one that is "controlled" rather than merely "interventional" (and possibly not "controlled"). The authors suggest, without citation, that there is "conflicting understanding on the reach of FDAAA," under which only "interventional" trials would need to be registered. (Page 5, line 13) In any event, the results are not that different for the "controlled" and the "interventional" definitions (see Table 2). For these reasons we would suggest eliminating the entire "interventional" analysis. In the alternative, one could say that some believe the registration requirement applies to "interventional" trials (providing a citation for who says this), but that you analyzed the data that way and there was little difference. This would simplify the paper greatly. 3. The authors rely heavily on the median as a descriptive measure. This presents a series of problems. First, the most obvious measure, often not presented, is simply the % of trials that are reported (not per drug, for example). Second, because some of these medians are based on very small numbers, they are very unstable. Third, in some cases, the median obscures the actual distribution of the data. For example, under Definition 2, for timely reporting, there are actually about 1/3 that are 100%, about 1/3 that are 0% and about 1/3 that are in between. A median in a setting like this does not convey the overall distribution of the data. 4. From various findings, one can infer that a large number of early studies drives many of the results and that these are generally small and more likely to be unpublished. This point needs to be made clearly. Reporting rates by the various phases would also be helpful. 5. Page 2, line 39: The abstract does not really establish that there was wide variation between companies. 6. Page 3, line 18: needs a reference. Who is arguing this? 7. Page 3: It would be helpful to distinguish this research from other published research assessing the transparency of clinical trials as reflected in the literature and clinicaltrials.gov. How does this paper differ from previously published research in this area? 8. Page 4, line 12: It is unclear how the pharmaceutical company press releases contribute to the data in the paper. 9. Page 4, line 22: Why is the analysis restricted to large companies? The authors point out this is a conservative bias, but still, small companies are not released from applicable ethical or legal requirements, and readers would be interested in differences between small and large companies.

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	10. Page 5, line 41: The February 1, 2014, cutoff was chosen to provide at least 13 months post approval. The reasons for this should be explained (presumably because the statute says one year and there is some “rounding” error). Are the authors concerned that there might be bias in that the drugs approved early in the year have more time to be published? Isn’t the appropriate cutoff 13 months after drug approval? 11. Have the authors considered the difference between “submission” dates for results and “posting” dates? NIH does curation on the submitted data, and it can take months to post. The submission date can be determined from archives accessible from the ct.gov record. 12. Page 5, lines 43-54: The authors indicate that they determined ct.gov trials from approval packages and summaries. Is this one of the things the companies verified? In our experience, it is difficult to make a match. Might this be an explanation for the low matching rate? 13. Page 6, lines 8-11: The paper states: “Results should be reported, generally, no later than 12 months after the trial’s primary completion date, in ClinicalTrials.gov, although result submissions can be delayed by submitting certificates to the NIH.” (p. 6, lines 9-10) The paper might note here that no such certificate is needed 12 months following completion of a trial involving a drug that FDA has not approved. 14. Page 6, lines 20-23: What specifically did the companies verify? 15. Page 6, lines 29-30: Was any assessment made of the completeness of reporting in Medline compared to clinicaltrials.gov? In this connection, what does “published in a MEDLINE index journal” (p. 6, lines 29-30) mean? Would mentioning or discussing a trial without extensively reporting on its results qualify? 16. Page 6, line 44: Please explain why these studies were excluded. 17. Page 7, lines 10-13. Since the median of “unavailable” clinical trials with results in phases 2 and 3 was 0, it might be helpful to provide the numbers upon which the following sentence is based: “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.” More generally, this is another place where a simple % might be a better metric. 18. Page 7, lines 13-14F: The paper reports that 5,566 of 99,599 research subjects (which amounts to 5.6 percent of all subjects) were in “undisclosed trials” for the 15 drugs studied. What percentage of trials were publicly undisclosed? This makes the point that the undisclosed trials are generally small.

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	19. Page 7, lines 16-22: I question the usefulness of the company rating from this dataset, when many companies had only a single drug. For them it is really a drug rating, not a company rating. 20. Page 7, lines 37-40: This is one of the places where an overall reporting rate (here, for a company) would be more informative than the data presented. 21. Page 8: It might be helpful to address the extent to which FDAAA requirements were inapplicable because trials did not involve one or more sites in the United States, were not conducted under an FDA investigational new drug application, and did not involve drugs manufactured in the U.S. 22. Page 8, lines 41-42: "Yet current law is clear: the company that files an investigational new drug (IND) application is the responsible party." By law, if the company so designates, the principal investigator is the responsible party so long as he has access to and control over the clinical trial data. 23. Page 9, lines 12-18: The paper furnishes no explanation or detail illuminating its recommendation for annual transparency ratings and rankings. Would it be modeled on Table 1? 24. Page 9, line 37: Given the use of the median metric, I am not sure one can say simply that 2/3 were publicly disclosed. 25. General comment: If the article provided CT.gov identifiers (the numbers NLM provided) for each of the trials discussed, it would help readers and reviewers identify those trials.

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer 1:

1) The major problem with this study is that the authors appear to be making a big issue about something that is not a big issue at all. As we understand it, almost all the trials that are not publicly accessible are Phase I trials, and only approximately 5.6% of the data (i.e. 5.6% of the subjects – those participating in Phase I trials) is unavailable. This strikes us as an essentially non-problematic situation – key findings are, in general, being full disclosed. It is a big problem when a substantial proportion of the evidence regarding a particular drug remains undisclosed, but in the sample the authors have used this seems to happen very infrequently, if at all.With regard to the legal requirements, the problem seems to be late reporting. In that they have never penalized companies for late reporting, the FDA appears not to think this is a big problem either. If the authors think that the violation of the timely reporting standard is one that the general public should be concerned about, they need to make a compelling case why this is so. We do not see such a case in the submitted manuscript. The bottom line is that unless the authors can persuade us they have uncovered a serious problem, this paper is not suitable for the BMJ. If the authors fail

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to demonstrate an important problem, and subsequently publish elsewhere, the entire presentation should acknowledge that they have not uncovered a serious problem.

This paper looks at two sets of standards. The first is implementation of the ethical standard that all clinical trial results should be publicly available to contribute to generalizable knowledge and protect and respect the rights of human research subjects, as reflected in the US Common Rule, Helsinki Declaration and WHO guidelines. These foundational guidance documents do not generally exempt phase I trials from disclosure. Notwithstanding, our data shows that half of all reviewed drugs have at least one undisclosed Phase II or III trial. Low transparency is not limited to phase I trials.

We disagree, however, with the reviewer's opinion that because the FDA is not concerned with violations of legal reporting requirements that the general public should not be concerned. It is not clear that the FDA is unconcerned. It is simply clear that Congress passed a law that is largely unenforced up to this point. Second, if the timeliness of trial disclosures was unimportant, why did we embed timeliness requirements into the law?

2) The FDA is a federal agency of the United States Department of Health and Human Services and is responsible for the new drugs approval in the USA. Although the two standards described in the manuscript have potential applicability in other countries and regions by using their own literature databases, trial registration agencies and legal requirements, might be of use, particularly in a non-American journal, to discuss the generalizability of the study results.

Many of the trials evaluated in this study will support the regulatory approval processes of these drugs in other countries. Moreover, the trials were conducted globally and enrolled participants in many different countries. Additionally, there likely were not any trials registered or reported in databases of other regions or countries that were not already registered in clinicaltrials.gov, as we asked companies for evidence of registration and reporting in any trial database.

3) Aside of MEDLINE, EMBASE is a biomedical and pharmacological database of published literature. The authors might wish to explain and discuss their not including EMBASE in the search as one of the limitations.

As indicated in our methods, we asked companies to provide us with any relevant publications that were not captured in our review. These publications were added, if we could match them according to our methodology. As such, it was not necessary to review EMBASE.

4) Table 1 and Table 2 need explanation of abbreviations of IQR, Q1, Q3, FDA and FDAAA.

We have added these to the tables.

5) The format of several references need revision, for example, references 8, 11, 14 and 15. The statement in Line 55, Page 8 needs reference.

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We have fixed the references.

Responses to Reviewer 2:

Recommendation:

6) The results of the study are not compared with other similar studies and there is no clear explanation of what the study adds to current knowledge.

Thank you for this comment. We have added a section to the introduction on how our study fits into and adds to current knowledge. Please see pages 4-5 in the revised paper. The relevant text is also pasted below:

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.

7) Information of the Tables 1 and 2: it is better to present the last column in a descendent way. The name of the drug is better to present the active drug than the trade name.

The authors thank the reviewer for this comment. We have decided to maintain the ordering in the tables. WE have added the active ingredients to accompany the brand names of the drugs in an Appendix. See Appendix 2 of the revised paper and below:

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

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Signifor: PASIREOTIDE DIASPARTATE

Sirturo: BEDAQUILINE FUMARATE

Stivarga: REGORAFENIB

Stribild: COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR DISOPROXIL FUMARATE

Xeljanz: TOFACITINIB CITRATE

Zaltrap: ZIV-AFLIBERCEPT

Zioptan: TAFLUPROST

Responses to Reviewer 3:

8) Which of the data sources were considered "primary" when excluding trials that were listed as phase I/II?

Our methods state that data was included if it was consistent in two of our three data sources (we gathered data from clinicaltrials.gov, FDA approval packages, and the medical literature). We weighted the sources equally.

9) Verify for typos, for example, correcting "Clinicaltrials.gov" to "ClinicalTrials.gov".

We have corrected this typo.

10) Why were only 15 new drug entities sponsored by ten large companies considered instead of trials by the twenty eligible companies?

Not all 20 large companies had products approved in 2012.

11) Provide abbreviations for acronyms used in the Tables.

We have amended the tables.

12) The writing is hard to read in many places. For example, the first sentence in the second paragraph of the Results is confusing to read.

We have amended and simplified the language throughout the paper, including the second paragraph.

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13) Table 1 - last column - why is a trial that was registered not considered to be "publicly available"? This definition is different from what is described in the text.

We have amended the last column of table 1 to state “percentage of trial results that are publicly available”.

14) Table 1 - First column, last and penultimate rows - "drug level" in parentheses - what does this indicate? It's confusing.

We deleted this.

15) Tables 1 and 2 - The titles are unclear - why are they called "Transparency Index" and "Legal Compliance Index"? Are these indices defined in the Methods?

These two tables are clearly defined in our methods, results and discussions sections.

16) The descriptive value of the findings apart, what is the point the authors are making based on the findings? The argument about a transparency rating and ranking system, which the authors briefly describe in the conclusion section, is not convincing to me. Who establishes the ranking system, who administers it, who monitors its accuracy, and why should it make a difference to how clinical trials are reported? Furthermore, the ranking approach as suggested in the context of this work is focused entirely on trials conducted by the industry. Such a narrow focus will only provide room for arguments against implementing a ranking system because it does not consider trials conducted by not-for-profit entities and individuals.

This paper states that we looked at 15 of the 48 new entities approved by the FDA in 2012 and used the drugs sponsored by large companies as a convenience sample. We are evaluating transparency on the drug level, not the institutional level in this paper.

17) Why should the industry buy into the ranking system?

Thank you for the good question. The industry does not need to “buy into the ranking system.” We asked them to validate our data, something that has never been done before in the area of transparency studies. As indicated in the paper, we had a 100% response rate from all evaluated companies and the conversation and data exchange process was a learning opportunity for all involved.

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Responses to Review 4

18) The paper's focus on reporting of results seems to be based on trial level and not outcome level. As far as I can see from the paper, any trial posting any result on either clinicaltrials.gov or in a MEDLINE-index journal is compliant. However, relevant outcomes may still remain unpublished/unreported and it seems that while the authors extracted data on primary endpoint(s) in the registration of trials they did not check to see whether they were actually reported/published. Also there seems to have been no assessment of secondary outcomes. This will in my mind paint a too optimistic picture in relation to compliance and needs to be addressed as a limitation in the paper.

The limitations section of the paper states this issue.

19) Title: I suggest changing the title. While ranking of drugs in relation to transparency is part of the paper, it is not the main focus of the paper.

We have amended the title of the paper to more fully capture the study aims and findings.

20) Furthermore, solely ranking just by the proportion of registered and reported trials is problematic as it does not take into account the size of the trial or the relevance of reported/unreported outcomes, length of follow-up etc. For example, not registering and reporting on some Phase I trial is less problematic than not reporting on a large Phase III trial or not reporting on important outcomes from that trial.

Transparency laws (FDAAA), generally apply to all non-phase I trials. So the sample size of Table I is all trials and the sample size of Table II is generally non-phase I trials (so phase II and III trials). Notwithstanding, we reflect this in the limitations section of the paper.

21) p4 para 2 line 4 It is not clear why 20 and not 10 companies are mentioned here. In addition, the provided hyperlink for the reference (ref 15) is for the 2013 list, not the 2012 list. In the linked citation there is a top 15 pharmaceutical firm list and a top 25 biotechnology companies list. Nine of the ten included companies are from the pharmaceutical firm list, and one (Gilead) is from the biotechnology companies list. According to the list Gilead had a 2012 market cap of $19.751 billions. However, six companies from the biotechnology list (Novo Nordisk, Amgen, Celgene, Biogen, Merck KgaA and Teva Pharmaceutical Industries) and three companies from the pharmaceutical list (AstraZeneca, Eli Lilly and Takeda) had a higher 2012 market cap. Two of these companies with a higher market cap had drugs approved in 2012 Omontys (Takeda) and Synribo (Teva). So it is unclear why Stribild from Gilead is on the list instead of Synribo from Teva with a $39.282 billion 2012 market cap. The methods should be more clear in order for others to be able to reproduce the authors' findings.

The link we provided contains both the 2013 and 2012 marketcaps. The data source requires a subscription. Perhaps the reviewer could not open the full file. The FDA files Synribo as sponsored by

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IVAX International. Omontys was originally attributed to Affymax. We note in the limitations of this paper that mergers, acquisitions, subsidiaries, partnerships and licensing practices can complicate the process of evaluating who is responsible for the transparency of clinical trials.

22) p6 para 4 line 1 According to the paper 48 new drug entities (NMEs) were approved in 2012. It is not clear from the methods how the list of 48 new drug entities were identified. According to the FDA Novel New Drug Summary (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM337830.pdf) only 39 NMEs were approved in 2012. All of the 15 drugs from the paper are on that list, except one (the GSK vaccine MenHibrix). How these 15 drugs were identified should be more clear from the methods, preferably with direct citation to the relevant reports (reference 14 does not allow this identification).

We have added citations to the relevant sub-reports (one for NMEs and one for novel drug approvals) and explained this in the results section. Please see citations 15-16 in the revised paper.

23) p6 para 4 line 3-4 The authors should describe the reason for excluding the 24 trials.

As stated in the methods section, we excluded trials that were terminated without enrollment of subjects, were still ongoing, or not at least one year past their primary completion date by our study cut-off date of February 14, 2014.

24) p6 para 5 The authors should report some baseline data from their sample of trials. E.g. the proportion of phase I, II and III trials and median trial size. Also, data on median registration and reporting/publication time would be of interest.

We believe the measure of a median is appropriate given the variance in sample sizes and skewed distribution of the trial numbers for each drug.

25) p9 para 3 The authors should also describe their choice of databases and registries as a limitation. Some trials might be registered in other trial registries and some trials might have been missed due to limitation in search strategy and not searching other databases such as EMBASE and CENTRAL. Furthermore, company trial registries could have been searched (e.g. www.gsk-clinicalstudyregister.com)

The methods section of our paper states that we sent our findings to companies asking them to send registrations, results reporting and publications that were not captured in our study. We had a 100% response rate from companies. We found no trials registered or reported in other registries (corporate or otherwise) that were not already captured in clinicaltrials.gov.

26) p8-9 Discussion The authors should preferably describe the large difference in number of trials between the 'ethics' and 'legal' sample. Was this due to Phase I trials? In addition, it would add relevant information if the authors could describe how many of the non-compliant trials in the 'legal' sample where non-compliant due to a time

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factor only (i.e. registered after 21 days or reported after 13 months).

Appendix I explains how the sample size was narrowed.

27) Abstract-Results line 6 Undisclosed is in my mind to vague. I suggest using similar terminology as previously (i.e. not reported or published).

We amended the language.

28) -Conclusion line 1-3 The part of the sentence "below legal and ethics standards" might not read well for a non-native speaker of English, as below seems to suggest that a certain criteria was not met. What about complied with legal and ethics standards as is used in the rest of the paper?

We amended the language.

29) p4 para 1 line 5 It is not clear what "certificates of delay" are.

Please see Appendix I of the paper where we explain the two types of certificates of delay.

30) p6 para 2 line 3 This is the first time the abbreviation NDA is used so the full phrase should be used.

We have amended the language, accordingly.

31) p7 para 3 line 3 The authors should consider focusing on GSK and J&J as they both published all trial results, while the results for Pfizer was mixed ranging from 40% to 100%.

We amended the abstract language to emphasize J&J and GSK.

32) p9 para 1 line 3 The authors should provide a citation for WHO's call for trial reporting.

We added this citation.

33) Table 1 & 2 In the main manuscript J&J is used, in Table 1 Janssen and in Table 2

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J&J (Janssen). The authors should use the same name throughout the manuscript. For example, Janssen Pharmaceuticals (a J&J company).

We have changed the language to be consistent.

Responses to Reviewer 5:

34) As the paper acknowledges, FDAAA generally requires registration and reporting for "controlled clinical investigation(s), other than a phase 1 clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act." (Page 4, lines 51-55) An "applicable" clinical trial is, by statutory definition, one that is "controlled" rather than merely "interventional" (and possibly not "controlled"). The authors suggest, without citation, that there is "conflicting understanding on the reach of FDAAA," under which only "interventional" trials would need to be registered. (Page 5, line 13) In any event, the results are not that different for the "controlled" and the "interventional" definitions (see Table 2). For these reasons we would suggest eliminating the entire "interventional" analysis. In the alternative, one could say that some believe the registration requirement applies to "interventional" trials (providing a citation for who says this), but that you analyzed the data that way and there was little difference. This would simplify the paper greatly.

There is substantial debate about which trials are subject to mandatory disclosures under FDAAA. To avoid adding more unnecessary subjectivity to our study, we measured compliance using both sets of understandings: controlled trials and interventional trials.

Of note, the main published study that analyzed trial compliance with FDAAA was conducted by Rob Califf and published in NEJM. It considered interventional trials as subject to FDAAA, not controlled trials.

35) The authors rely heavily on the median as a descriptive measure. This presents a series of problems. First, the most obvious measure, often not presented, is simply the % of trials that are reported (not per drug, for example). Second, because some of these medians are based on very small numbers, they are very unstable. Third, in some cases, the median obscures the actual distribution of the data. For example, under Definition 2, for timely reporting, there are actually about 1/3 that are 100%, about 1/3 that are 0% and about 1/3 that are in between. A median in a setting like this does not convey the overall distribution of the data.

We believe our measure of a median is more appropriate than other measures given variances in sample sizes and the skewed distribution of the number of trials for each drug. Also, we provide interquartile ranges to help give a sense of the distribution of the data.

36) From various findings, one can infer that a large number of early studies drives many of the results and that these are generally small and more likely to be

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unpublished. This point needs to be made clearly. Reporting rates by the various phases would also be helpful.

Page 7, paragraph 1 of our paper includes a breakdown by phase of undisclosed trials, as does the abstract of our paper.

37) Page 2, line 39: The abstract does not really establish that there was wide variation between companies.

We added the following statement to the abstract: Two companies disclosed all trials and complied with legal disclosure requirements for their 2012 approved drugs. See page 2, last paragraph, in the revised submitted paper.

38) Page 3, line 18: needs a reference. Who is arguing this?

We deleted this statement from the paper.

39) Page 3: It would be helpful to distinguish this research from other published research assessing the transparency of clinical trials as reflected in the literature and clinicaltrials.gov. How does this paper differ from previously published research in this area?

As stated above, we have amended the introduction to better explain how our study fits into the existing literature.

40) Page 4, line 12: It is unclear how the pharmaceutical company press releases contribute to the data in the paper.

The press releases help identify merges, acquisitions, and partnerships that might have occurred between the time an IND and NDA are filed for each drug. They also provide the dates of any such activity. Legally, the IND filer is generally the responsible party for disclosing results for FDAAA-applicable trials. This information can be in press releases.

41) Page 4, line 22: Why is the analysis restricted to large companies? The authors point out this is a conservative bias, but still, small companies are not released from applicable ethical or legal requirements, and readers would be interested in differences between small and large companies.

Our paper states this is a convenience sample.

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42) Have the authors considered the difference between "submission" dates for results and "posting" dates? NIH does curation on the submitted data, and it can take months to post. The submission date can be determined from archives accessible from the ct.gov record.

Yes, our methods section states that we use the "first received" date in clinicaltrials.gov, which is generally the submission date.

43) Page 5, lines 43-54: The authors indicate that they determined ct.gov trials from approval packages and summaries. Is this one of the things the companies verified? In our experience, it is difficult to make a match. Might this be an explanation for the low matching rate?

All data sets were sent and verified by the responding companies, as stated in the paper.

44) Page 6, lines 8-11: The paper states: "Results should be reported, generally, no later than 12 months after the trial's primary completion date, in ClinicalTrials.gov, although result submissions can be delayed by submitting certificates to the NIH." (p. 6, lines 9-10) The paper might note here that no such certificate is needed 12 months following completion of a trial involving a drug that FDA has not approved.

Our paper only looks at approved drugs.

45) Page 6, lines 29-30: Was any assessment made of the completeness of reporting in Medline compared to clinicaltrials.gov? In this connection, what does "published in a MEDLINE index journal" (p. 6, lines 29-30) mean? Would mentioning or discussing a trial without extensively reporting on its results qualify?

Our methods section states how we matched the relevant paper to the trial: at least two of our recorded trial characteristics needed to match. Trial characteristics included primary outcomes, number of enrolled research subjects, and descriptions of treatment (dosage and comparator).

46) Page 6, line 44: Please explain why these studies were excluded.

See our answer to question 33.

47) Page 7, lines 13-14F: The paper reports that 5,566 of 99,599 research subjects (which amounts to 5.6 percent of all subjects) were in "undisclosed trials" for the 15 drugs studied. What percentage of trials were publicly undisclosed? This makes the point that the undisclosed trials are generally small.

This paper provides disclosure rates for trials on the drug level.

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48) Page 7, lines 16-22: I question the usefulness of the company rating from this dataset, when many companies had only a single drug. For them it is really a drug rating, not a company rating.

The title of the study is "ranking new drugs for transparency of clinical trials and trial results." We propose a ranking of drugs in this paper.

49) Page 8: It might be helpful to address the extent to which FDAAA requirements were inapplicable because trials did not involve one or more sites in the United States, were not conducted under an FDA investigational new drug application, and did not involve drugs manufactured in the U.S.

This is not the correct language or understanding of the legal statute. Please see page 5 of our paper.

50) Page 8, lines 41-42: "Yet current law is clear: the company that files an investigational new drug (IND) application is the responsible party." By law, if the company so designates, the principal investigator is the responsible party so long as he has access to and control over the clinical trial data.

This is not the prevalent interpretation in the literature. Please see the appropriate study by Rob Califf and colleagues in NEJM: http://www.nejm.org/doi/full/10.1056/NEJMsa1409364

51) Page 9, lines 12-18: The paper furnishes no explanation or detail illuminating its recommendation for annual transparency ratings and rankings. Would it be modeled on Table 1?

We updated the paper to more clearly indicate that this study is associated with a larger pilot of the ranking system.

52) Page 9, line 37: Given the use of the median metric, I am not sure one can say simply that 2/3 were publicly disclosed.

We have amended this summary statement.

53) General comment: If the article provided CT.gov identifiers (the numbers NLM provided) for each of the trials discussed, it would help readers and reviewers identify those trials.

A statement on our data-sharing practices has been added to the paper.

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