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Reviewer Response: **"Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012: cross-sectional evaluation"**

Editor reports:

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- The main message of the paper could be made clearer. One editor did not understand what point you were making in the second bullet of the "what this paper adds section." Another editor commented: "I wasn't sure what the reporting requirements were and so couldn't judge the degree of "wrongness" or where any problem lies. Are the companies failing to carry out the required research? Is the FDA failing to monitor compliance? Is public reporting and dissemination less transparent than the authors and public may wish?… So I'm not sure what the nature of the problem is that they are reporting or where the remedies lie." This comment highlights the need to emphasize the main message of your paper.

Response:

We would like to thank the editors for considering our manuscript and for giving us the opportunity to revise and clarify the main message of our paper. We appreciate the helpful comments provided by the editors and reviewers.

We believe that there are two main messages in our manuscript: 1) Public information regarding postmarketing requirements currently lacks transparency and 2) Although approximately three-fourths of postmarket studies are registered and nearly three-fourths reported results or were published, our findings suggest that at least one-quarter of these required studies are not being publicly disseminated. We have updated the "what this study adds" section to further clarify that the registration and reporting of required prospective cohort studies, registries, and clinical trials is important because these studies are often the greatest clinical importance to physicians and patients.

We have also modified our manuscript in order to provide information regarding postmarket *clinical trials*, which are highly likely to be subject to mandatory registration and results reporting under FDAAA, US legislation that mandates clinical trial registration and outcome reporting on ClinicalTruals.gov. Therefore, opportunities exist for the FDA to mitigate selective registration and results reporting of postmarket studies on ClinicalTrials.gov.

To emphasize the implications of first message in the "what this study adds" section, we have clarified that there is often not enough information for physicians, patients, and researchers to understand the purpose of the requirement or study designs. In order to further clarify the second message, we have now modified our Introduction, Abstract, Methods, and Discussion sections to emphasize the nature of the problem as well as potential remedies.

All of our changes/additions are *italicized and underlined.*

Page 4, "What this study adds" Section:

Many postmarketing requirements issued by the US Food and Drug Administration (FDA) at the time of approval are only briefly described and often do not contain enough public information for physicians, patients, and researchers to understand the purpose of the requirements or characterize the study designs.

Among required prospective cohort studies, registries, and clinical trials, which are often the greatest clinical importance to physicians and patients, approximately three-fourths were registered on ClinicalTrials.gov, whereas among all registered studies for which results reporting would be expected, approximately three-fourths had done so, suggesting that at least one-quarter of these required studies are not being publicly disseminated.

Among required prospective cohort studies, registries, and clinical trials that either reported results or were published, the median time from FDA approval to reporting or publication was approximately 4 years, with two-thirds not reporting results publicly by the time of their original FDA report submission deadline.

Opportunities exist for FDA to increase the transparency of postmarketing requirements as well as mitigate selective registration and ensure timely results reporting on ClinicalTrials.gov.

Page 2, Abstract:

Results *Between 2009 and 2012, the FDA approved 97 new drugs and biologics for 106 indications with at least one postmarketing requirement at the time of first approval, for a total of 437 postmarketing requirements. Postmarket study descriptions were often short (median word count of 44 [interquartile range (IQR), 29-71]) and there was not enough information to determine the progress of nearly one-third (131 of 437 [30.0%]). Half (220 [50.3%]) of the 437 postmarketing requirements were for new animal or 'other' studies, including pharmacokinetic ~~and in vitro/in vivo~~ studies, ~~whereas~~ nearly one-third (134 [30.7%]) were for prospective cohort studies, registries, and clinical trials, and one-fifth (83 [19.0%)] were for secondary analyses or follow-up clinical, animal, or "other" studies. Among the 110 clinical trials, there was not enough information to establish use of randomization, comparator type, allocation, outcome, and number of patients to be enrolled for 38 (34.5%), 44 (40.0%), 62 (56.4%), 66 (60.0%), and 98 (89.1%), respectively. Just over three-fourths (102 of 134, 76.1%) of the required prospective cohort studies, registries, and clinical trials were registered on ClinicalTrials.gov. Among the 50 registered and completed studies, 36 (72.0%) had reported results on ClinicalTrials.gov. ~~Among the 65 completed studies, regardless of ClinicalTrials.gov registration, 36 (55.4%) were published in the peer-reviewed literature~~. Among the 65 completed studies, 47 (72.3%) had either reported results or were published ~~Among the 47 studies that either reported results or were published, and the~~ a median ~~time from FDA approval to reported results or publication was~~ of 47 (IQR, 32-67) months after FDA approval. Two-thirds (32 of 47 [68.1%)] of these studies did not report results publicly by the time of their original FDA report submission deadline. Similar registration and reporting rates were observed when focused exclusively on clinical trials.*

Conclusions

Postmarketing requirements for new drugs and biologics were often briefly described and did not contain enough information to characterize the required study designs. Approximately three-fourths of postmarketing requirements for prospective cohort studies, registries, and clinical trials were registered on ClinicalTrials.gov, and nearly three-fourths of completed studies reported results or were published, suggesting that at least one-quarter of these required studies are not being publicly disseminated. Opportunities exist for FDA to increase the transparency of postmarketing requirements as well as mitigate selective registration and ensure timely results reporting on ClinicalTrials.gov.

Page 5, Introduction:

Furthermore, it is not sufficient for postmarket studies to be completed; successful translation of clinical trial evidence into practice requires timely dissemination of their results. In 2007, the US FDA Amendments Act (FDAAA) was enacted, which mandated registration and results reporting on a publicly accessible clinical trial registry established by the National Institutes of Health, ClinicalTrials.gov, for all ongoing and forthcoming "applicable clinical trials" of FDA-regulated products.[1 2] According to a recent internal evaluation by FDA, over one-third of "fulfilled" postmarket studies are not published in either the scientific literature or on the ClinicalTrials.gov website.[3]

Page 9, Methods:

*For all new prospective cohort studies, registries, and clinical trials and all requirements that call for the completion and submission of the results from 'ongoing' prospective cohort studies and trials (hereafter 'prospective cohort studies, registries, and clinical trials'), we determined study registration and results reporting on ClinicalTrials.gov. These study designs are likely of greatest clinical importance to physicians and patients. However, we also evaluated registration and results reporting rates separately for clinical trials, since only ongoing and forthcoming "applicable clinical trials", which excludes noninterventional studies, of FDA-regulated products are subject to mandated clinical trial registration and results reporting on ClinicalTrials.gov according to the Final Rule for Section 801 of FDAAA in 2016 (**see supplementary appendix box 2**).[1 2] One requirement for FDAAA coverage requires manufacturing data. In particular, FDAAA says that a trial must have a drug manufacturer in the US for export, or be conducted in the US, to be covered.[1 2 4 5] This information is difficult to determine using public sources. Therefore, our sample of postmarket clinical trials are "highly likely" to be "applicable clinical trials."*

Appendix Box 2. FDAAA applicable trials

"Applicable clinical trials" are those subject to mandatory registration and reporting requirements under the Food and Drug Administration Amendments Act (FDAAA). Generally, this includes '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'.[1] Furthermore, these trials should have 'either initiated after 27 September 2007, or initiated on or before that date and were still ongoing as of 26 December 2007',[1] and meet one of the following conditions:

A. *The trial has one or more sites in the USA,*
B. *The trial is conducted under an FDA investigational new drug application (IND), or*
C. *The trial involves a drug or biological that is manufactured in the USA or its territories and is exported for research.[1 2 6]*

As outlined on ClinicalTrials.gov, according to the Final Rule for Section 801 of FDAAA, "noninterventional (observational) clinical research (such as cohort or case-control studies)" are generally excluded from the registration and results submission requirements.[2]

Page 15, Discussion:

Among 97 new drugs and biologics approved by FDA between 2009 and 2012, we identified 437 associated postmarketing requirements issued by FDA at the time of approval, many of which were only

briefly described and often did not contain enough public information to understand the purpose of the requirement or characterize the required study designs. Furthermore, we were unable to locate up-to-date information on the progress of approximately one-third. Among prospective cohort studies, registries, and clinical trials, which are likely of greatest clinical importance to physicians and patients, we found evidence of successful dissemination of research findings: three-fourths were registered on ClinicalTrials.gov and nearly three-fourths had either reported results or were published. However, two-thirds of the postmarket studies reported results publicly after their original FDA report submission deadline, potentially limiting their application to clinical practice. Furthermore, considering that similar dissemination rates were observed when focusing exclusively on clinical trials, which are highly likely to be subject mandatory registration and results reporting under FDAAA, US legislation that mandates clinical trial registration and outcome reporting on ClinicalTruals.gov, opportunities exist to increase transparency and mitigate selective registration and results reporting.

Page 16, Discussion:

Our study also found ~~evidence of successful registration and dissemination of the results of postmarketing requirements for prospective cohort studies, registries, and clinical trials~~. ~~However,~~ that approximately three-fourths of postmarket clinical trials were registered on ClinicalTrials.gov, which is less than previously reported registration rates for clinical trials supporting New Drug Applications.[5 6] Our finding that approximately three-fourths of the postmarket clinical trials had either reported results or were published is consistent with a recent study by FDA, which showed that nearly two-thirds of postmarket drug interventional clinical trials and other trials designated as "fulfilled" were published in either the scientific literature or on the ClinicalTrials.gov website.[3]

Page 18, Implications and Recommendations:

Although we found relatively high rates of registration, results reporting, and publication of required clinical trials, registration and results reporting is required by law for ongoing and forthcoming noninterventional "applicable clinical trials" of FDA-regulated products.[1] Our findings may suggest that clearer and more consistent regulatory standards and FDA oversight may be necessary to ensure universal registration and result reporting on ClinicalTrials.gov for applicable postmarket studies.[5 6] In particular, FDA may need to provide additional clarity to sponsors about which trials need to be registered and when results need to be reported. Furthermore, new regulations may be necessary to ensure that the results from postmarket studies that are the greatest interest to the clinical community, including prospective cohort studies and registries, are publicly disseminated.[3] Alternatively, sponsors can also voluntarily take on part of the responsibility and commit to greater registration and results dissemination.

Page 20, Limitations of this study:

Third, we did not determine whether the results from required 'ongoing' prospective cohort studies, registries, or clinical trials were reported or published. While some 'ongoing' studies may have reported or published results, ongoing studies are less likely to have results reported and publications. Lastly, it is possible that our sample of clinical trials contains some studies that are not "applicable clinical trials" according to FDAAA. In particular, FDAAA says that a trial must have a drug manufacturer in the US for export, or be conducted in the US, to be covered.[1 2 4 5] Considering that this information is difficult to determine using public sources, our sample of postmarket clinical trials are "highly likely" to be "applicable clinical trials."

Page 20, Conclusions:

Postmarketing requirements for new drugs and biologics were often briefly described, difficult to categorize, and frequently did not contain enough information to characterize the required study designs. Nearly three-fourths of postmarket prospective cohort studies, registries, and clinical trials, which are often the greatest interest to clinicians and patients, were registered on ClinicalTrials.gov or had either reported results or were published, suggesting that at least one-quarter of these required studies are not being publicly disseminated. Furthermore, two-thirds of the postmarket studies reported public results after their original FDA report submission deadline. Similar registration and reporting rates were observed when focused exclusively on clinical trials, which are highly likely to be subject to mandatory registration and results reporting on ClinicalTrials.gov under FDAAA. These findings highlight the need for more detailed postmarket study descriptions, increased FDA transparency, and clearer and more consistent registration and results reporting standards.

- Our statistical consultant was not convinced that the p-values were necessary in this descriptive paper. We leave it to your judgement whether to leave them or take them out but please justify your decision.

Response:

Thank you for this comment. We agree that the *P* values may not be necessary, especially in Table 4. However, in our protocol, we pre-specified that Fisher's exact and Kruskal-Wallis tests would be used to examine differences among postmarket study characteristics, including by therapeutic area, orphan status, and postmarketing requirement category. Therefore, we would prefer not to completely omit these results. However, given the statistical consultant's comment, we have removed the *P* values from the table provided in the main manuscript and instead included a footnote that says "Descriptive *P* values are available in the supplementary materials".

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Response: Thank you for these helpful comments, which we believe have significantly strengthened our manuscript. Please find our point by point replies to the comments made by the reviews below.

Comments from Reviewers

Reviewer: 1, Florence Bourgeois, MD, MPH

Recommendation:

Comments:
This is a well-written and original study that aims to characterize post-marketing studies required by the FDA under several authorization pathways currently in place. As the drug approval process has shifted to an increasing reliance on post-approval drug requirements and monitoring, these data provide a critical assessment of the current status of this piece of the drug evaluation process. The study is highly relevant to the current FDA approval process, and adds to existing studies that have focused on post-approval studies for devices, for drugs approved under specific pathways, or for products used in certain types of conditions.

Response: We thank Review #1 for their support and thorough report.

1. One of the study's findings is that post-marketing studies are poorly described in public reports and their status not consistently updated. Almost a third of mandated post-marketing studies did not have a discoverable status, despite searches in multiple sources.

While this is an important finding in and of itself, it does also present some limitations to the study. For one, the values around the proportion of studies fulfilled vs delayed vs pending may not be accurate with such a high number of missing values.

Response:

Thank you for sharing this concern. We agree that the proportion of studies within each status category may not be completely accurate with respect to what the FDA knows, but it remains the best estimate available made using public information. In addition, we believe that is also one of the main findings of the manuscript. In the opening paragraph of the Discussion, we state that "Furthermore, we were unable to locate up-to-date information on the progress of approximately one-third." In order to clarify this finding, we modified one of the sentences in the "what this study adds" section. Furthermore, our results reporting and publication analyses did not rely exclusively on the statuses reported publicly by the FDA. As outlined in our manuscript, for these analyses, we looked for ClinicalTrials.gov registration for all postmarket cohort studies, registries, and clinical trials, regardless of their FDA status. We then evaluated results reporting for all studies classified as *Completed* or *Terminated* on ClinicalTrials.gov. When determining the publication rate, we included in our sample all postmarket cohort studies, registries, and clinical trials with an "unclear" FDA status.

Page 4, "What this study adds":

Many postmarketing requirements issued by FDA at the time of approval are only briefly described and often do not contain enough public information for physicians, patients, and researchers to understand the purpose of the requirements or characterize the study designs.

2. In addition, the status classification was important in defining cohorts of studies for further analysis. For example, trials with a status of fulfilled, released or "unclear" were all deemed "eligible for results reporting" and the publication rate calculated using this denominator. However, it's not clear that trials with an unknown completion status should be included in the publication search, and, in fact, it is likely that these trials have a higher rate of not being completed than those which are reported as completed in the database (and therefore would not be eligible for publication). In addition, (though unrelated to the issue of missing data), trials that are released may also not be appropriate for this group since these are trials for which the FDA removed the post-marketing requirement. The same applies to trials listed as "terminated" on ClinicalTrials.gov (the main factor behind trial termination is failure to meet accrual goals, in which case a publication may not be feasible). In the discussion, the authors mention that the rate of publication of 55% in this study is lower than prior reports, which reported rates closer to 90%. It is possible that the definition of which trials were considered "eligible for publication" contributed to this low rate.

Response:

We appreciate this concern. We discussed this issue among our study team in detail before outlining and pre-specifying our cohort definitions. As noted in our manuscript, *Fulfilled* and *Released* requirements are only displayed on the online FDA database for one year after the date of fulfillment or release. Furthermore, we were unable to locate archived databases for all years of follow-up. In order to establish a reasonable inclusion and exclusion criteria, we decided that studies without a clear FDA status could have corresponding publications. The difficulty determining a suitable cohort is further reflected by the fact that Reviewer #1 and Reviewer #2

have different opinions regarding which studies could have been published. For instance, in comment #1 below, Review #2 states that we could have searched for publications from "trials which are not recorded as completed or terminated on ClinicalTrials.gov".

In order to further justify our inclusion/exclusion criteria, we evaluated the 65 studies in our sample for which publication would be expected. We found that there were only 11 where the status was "unclear" based on FDA or drug sponsor data. Among these 11 studies, 7 were classified as *Completed* and 2 were classified as *Terminated* on ClinicalTrials.gov. Considering that our sample only included 2 studies without an up-to-date FDA or ClinicalTrials.gov status, the inclusion/exclusion criteria that we used is unlikely to explain our lower estimated rate of publication and results reporting.

Similarly, in response to this comment, when we limited analyses to *Released* and "unclear" studies, the results reporting and publication rates were approximately the same (10/16 (62.5%) and 8/16 (50%), respectively). Among the 7 studies classified as *Terminated* according to ClinicalTrials.gov, 5 either reported results or had a corresponding publication. We have outlined these findings under the "Prospective Cohort Studies, Registries, and Clinical Trials: Result Reporting and Publication" section.

Page 13-14, Prospective Cohort Studies, Registries, and Clinical Trials: Result Reporting and Publication:

The results reporting and publication rates were consistent when studies with an unclear status according to FDA or ClinicalTrials.gov were excluded. Furthermore, the dissemination rates were only slightly lower when limited to studies with Released or unclear statuses according to FDA or ClinicalTrials.gov (10 of 16 [62.5%] and 8 of 16 [50.0%], respectively). Finally, among the 7 studies classified as Terminated according to ClinicalTrials.gov, 5 (71.4%) had either reported results or were published.

3. The authors also encountered very sparse data around the descriptions of the post-marketing studies—another important finding around FDA communication for post-approval obligations. As a result, the methods describe some difficulties in classifying studies into the different study types and about half the trials were incorporated into the "other" group. If there was indeed a large number of studies included in this group because of unclear trial descriptions, then this would present limitations to some of the subsequent analyses that focus on specific groups of trials based on study type (e.g. cohort studies, registries, and clinical trials comprised just 30% of all trials, but were the focus of analyses on trial registration and publication).

Response:

Thank you for sharing this comment. During our data abstraction, we did encounter sparse postmarketing requirement descriptions. However, we do not believe that this influenced our registration, results reporting, and publication analyses. We would like to note that the "other" group does not imply that a study design is actually "unclear". As noted in Table 2, "New animal or "other" studies required" includes "new animal trials, pharmacokinetic and/or pharmacodynamics trials; in vitro or in vivo studies; drug transport, drug-drug, or drug-therapeutic, prenatal and postnatal development, assessments of anti-drug antibody response, mass balance, dosing, lactation, and QT/QTc studies." Thus, although it was difficult to determine the exact study design of certain PK/PD studies, our classification approach was reasonable with respect to identifying those studies that were appropriate to include in the registration, results reporting, and publication analyses. When the postmarket study descriptions outlined efficacy or long term safety outcomes, we included them in the "cohort study, registry, and clinical trial" category. Other PK/PD studies,

without clear outcomes, were classified as "New animal or "other" studies required", since these are not required to be registered and have reported results on ClinicalTrials.gov. Furthermore, when we mention that studies were briefly described and often did not contain enough public information to understand the purpose of the requirement or characterize the study, we were referencing specific study design characteristics, such as outcome(s) and duration, not the actual study design.

Lastly, according to a previous evaluation of postmarketing requirements conducted by the Office of Inspector General,[7] 28% of all postmarketing requirements between 2008-2014 were for clinical trials. In our independent evaluation, using publicly available data sources, we found that 30.7% of the studies were for prospective cohort studies, registries, and clinical trials (25.2% were for clinical trials only). Considering that we observed a similar proportion of clinical trials, we are reassured that we are not misclassifying a significant number of clinical trials due to sparse descriptions. Moreover, since the Office of Inspector General report did classify the non-clinical trial study designs, we attempted to provide additional study design granularity.

In order to address the concerns raised by Reviewer #1, we have updated our Methods section to include a description of the "new animal or "other" studies required" category. We have also modified our Limitations section to explain the similarity between our analysis and the Office of Inspector General report.

Page 7, Methods:

*For example, a one sentence postmarketing requirement for a pharmacokinetic study, without study duration or outcomes, would be classified as a "new animal or 'other' study required", since there may be inconsistent registration and results reporting of pharmacokinetic (PK) and phase 1 trial data on ClinicalTrials.gov.[1] This category would include all new animal trials; pharmacokinetic and/or pharmacodynamics trials; in vitro or in vivo studies; drug transport, drug-drug, or drug-therapeutic, prenatal and postnatal development, assessments of anti-drug antibody response, mass balance, dosing, lactation, and QT/QTc studies (**Box 2**).*

Page 18-19, Limitations of this study:

This study has limitations. First, we relied on publicly available data sources. The brief postmarketing requirement descriptions provided in the FDA approval letters made categorizing postmarket drug studies and determining ClinicalTrials.gov registrations and peer-reviewed publications difficult. However, it is unlikely that we misclassified clinical trials as other study designs; approximately one-quarter of the postmarket studies in our sample were classified as new clinical trials, consistent with an estimate of 28% reported in a previous evaluation by the Office of Inspector General.[7]

4. One potential approach to address these issues would be to de-emphasize the focus on rates of registration and publication and instead highlight the issues around poor transparency and limited communication from the FDA around study requirements, their rationale, and their progress. These issues on their own are significant to many stakeholders, including industry and researchers working to coordinate and prioritize studies for specific drugs and diseases.]

Response:

Thank you for this suggestion. As we outline above, there is evidence suggesting that the proportion of postmarket clinical trials in our sample is accurate. Furthermore, we believe that both the

transparency and dissemination components of our study, which were pre-specified in our study protocol, are important to highlight.

A few specific comments as well as a number of minor ones that may improve the manuscript:

5. Abstract – half of the PMRs are described as animal or "other" studies and one-third as clinical trials; what were the remainder?

Response:

Thank you for this question. In our abstract, we only reported on two of the study categories. We report the other areas (e.g., "Complete or submit results from prospective cohort studies, registries, and trials") in Table 2. In order to improve clarity, we had added another sentence outlining that the remaining studies were either secondary analyses or follow-up clinical, animal, or "other" studies.

Page 2, Abstract:

Half (220 [50.3%]) of the 437 postmarketing requirements were for new animal or 'other' studies, including pharmacokinetic ~~and in vitro/in vivo~~ studies, ~~whereas~~ nearly one-third (134 [30.7%]) were for prospective cohort studies, registries, and clinical trials, and one-fifth (83 [19.0%]) were for secondary analyses or follow-up clinical, animal, or "other" studies.

6. Abstract – could the authors simplify the presentation of the registered and completed studies, which currently may be hard to follow given the shifting N's (50 vs. 65 vs. 47). One suggestion to clarify would be to present, as an example, of X trials that were registered, Y were completed, and Z were reported or published

Response:

We appreciate the suggestion to clarify the reporting, but we do not believe that it would be accurate to say that "X trials that were registered, Y were completed, and Z were reported or published". For instance, registered trials that are "recruiting patients" or "ongoing" are unlikely to have reported result until the study has been completed. If we just present the number of registered, completed, and reported or published studies, it may appear as if they all have the same denominator. In order to increase clarity, while still accurately reporting the results, we limited the numbers of times that we reported results based on different denominators in our abstract:

Page 2, Abstract:

Among the 50 registered and completed studies, 36 (72.0%) had reported results on ClinicalTrials.gov. ~~Among the 65 completed studies, regardless of ClinicalTrials.gov registration, 36 (55.4%) were published in the peer-reviewed literature~~. Among the 65 completed studies, 47 [72.3%] had either reported results or were published ~~Among the 47 studies that either reported results or were published, and the~~ a median ~~time from FDA approval to reported results or publication was~~ of 47 (IQR, 32-67) month after FDA approval. Two-thirds (32 of 47 [68.1%)] of these studies did not report results publicly by the time of their original FDA report submission deadline.

7. Methods – another important trial characteristic is the number of patients to be enrolled. This might be mentioned in the methods.

Response:

Thank you for this comment. In our manuscript, we report the median study duration and estimated sample size, according to ClinicalTrials.gov. As we state in our methods: "Once identified, for each registered prospective cohort study, registry, and clinical trial, one reviewer (JDW) abstracted study characteristics from the ClinicalTrials.gov registration, including: National Clinical Trial (NCT) number; ClinicalTrials.gov status (e.g., Currently recruiting, Completed, Terminated, and Withdrawn);[8] first submission, first results reporting, study start, and primary completion dates…".

Unfortunately, we originally did not record the number of patients to be enrolled as outlined in the postmarketing requirement descriptions. However, based on Review #1's suggestion, we returned to the 134 identified prospective cohort study, registry, and clinical trial descriptions and recorded whether the "number of patients to be enrolled" was provided ("Exact or approximate number provided", "minimum number provided", "minimum number in the treatment arm only provided", or "no information provided"). We found that among the 110 postmarket study descriptions for clinical trials, only 12 provided some information about the number of patients to be enrolled: 5 provided an exact or approximate number of patient to be enrolled, 5 provided a minimum number of patients to be enrolled, and 2 provided a minimum number of patients to be enrolled in the treatment arm only. We have updated the Abstract, Methods, Results, and Discussion sections of our manuscript to reflect this new data.

Page 2, Abstract:

Among the 110 clinical trials, there was not enough information to establish use of randomization, comparator type, allocation, outcome, and number of patients to be enrolled for 38 (34.5%), 44 (40.0%), 62 (56.4%), 66 (60.0%), and 98 (89.1%), respectively.

Page 7-8, Methods:

Using only the information from FDA approval letters hyperlinked in the Drugs@FDA database, we calculated the length of each postmarket study description (word count) and abstracted whether there was information provided about the use of randomization; whether patient allocation was double blind, single blind, open-label, or unclear; whether there was a comparator; whether the comparator was placebo, active control, both, or unclear; and study duration. As a non-prespecified abstraction, we also recorded whether information was provided about the estimated number of patients to be enrolled (Exact or approximate number provided, minimum number provided, minimum number in the treatment arm only provided, or no information provided).

Page 12, Results:

*Among the 110 clinical trials, there was not enough information to establish use of randomization, comparator type, allocation, outcome, and number of patients to be enrolled for 38 (34.5%), 44 (40.0%), 62 (56.4%), 66 (60.0%), and 98 (89.1%) respectively (**see supplementary appendix table 1**).*

We have also added a column to supplementary appendix table 1:

	Number of patients to be enrolled

Prospective Cohort Studies, Registries, and Clinical Trials	Exact or approximate number	Minimum number[a]	None
Prospective cohort studies (n=5)	2 (40.0)	0 (0.0)	3 (60.0)
Registries (n=19)	0 (0.0)	0 (0.0)	19 (100.0)
Clinical Trials (n=110)	5 (4.5)	7 (6.4)	98 (89.1)
Total (n=134)	7 (5.2)	7 (5.2)	120 (89.6)
[a] This includes postmarketing requirement descriptions that outline a total minimum enrollment or a minimum enrollment for the treatment arm only.			

Page 16, Discussion:

The brief descriptions of many postmarket clinical trials often did not contain enough information to establish use of randomization, comparator type, number of patients to be enrolled, and allocation.

8. Methods – when the final status of trials was not available, supplemental letters in the Drugs@FDA database as well as reports from pharmaceutical companies were used to update the available trial status. Given that 3 different data sources were used, it might be useful to comment on whether any inconsistencies were identified and, if so, which report took precedence in classifying the trials. For how many studies (PMRs) did the authors have to consult Google, as described on page 8?

Response:

We would like to thank the review for this suggestion. When there were status inconsistencies across the sources, we selected the status that was the furthest along or most definitive. For example, if the FDA classified a postmarket study as *Ongoing* and a drug sponsor classified the same postmarket study as *Submitted,* we selected *Submitted* as the final status. We used this approach because a report from the Office of Inspector General[7] concluded that the FDA has problems with its data management system, which hinders their ability to track postmarket requirements. In our sample. there were only 9 postmarket studies where the FDA and drug sponsors provided a different status classification. For 8 of these postmarket studies, we used the status provided by the drug sponsors.

We have already provided some of this information in our supplementary content, but acknowledge that this may not have been easy to locate. In particular, under Appendix Table 2, we state "50 postmarketing requirements were classified as fulfilled according to supplemental letters on Drugs@FDA and 106 had a status provided by the drug sponsors." To address this comment, we have updated our Methods and Results sections.

Page 8, Methods:

We then performed additional Google searches using the terms "postmarketing" or "PMR" in combination with manufacturers names to determine whether manufacturers were publicly sharing their own information about postmarketing requirements (e.g., "Pfizer PMRs" or "Pfizer postmarketing requirements"). Lastly, we reviewed the supplemental letters on the Drugs@FDA database to determine whether they included information regarding the fulfillment of postmarketing requirements. When there were status inconsistencies between the FDA and drug sponsor data, we selected the study status that was the furthest along (e.g., Submitted instead of Ongoing) or the most definitive (Fulfilled instead of Unclear).

Page 12, Results:

Drug sponsor data was available for 106 postmarketing requirements. Excluding postmarket studies with an unclear status based on FDA data, there were 9 postmarket studies where the FDA and drug sponsors provided a different status. Most (8 [88.9%]) of these postmarket studies were classified as further along according to drug sponsor data. Overall, there were 131 (30.0%) postmarket studies without enough information in any publicly available source to determine a recent, up-to-date status.

9. Methods – trial registration was assessed for the group of trials comprised of prospective cohort studies, registries, and clinical trials. The authors may want to note in the methods that trial registration is not actually required for observational studies and also report a registration rate for clinical trials alone.

Response:

Thank you for this comment. In our methods section, we have provided a description of "applicable clinical trials", which are subject to mandatory registration and results reporting under FDAAA. Please see our response to the Editors comments above. However, we already reported a registration rate for clinical trials alone. On page 12, we state "among the 110 studies explicitly described as clinical trials, 84 [76.4%] were registered". We have now also included additional information regarding results reporting and publication for clinical trials in the Results section.

Page 15, Results:

Among the 46 clinical trials, which are highly likely to be subject to mandatory registration and results reporting under FDAAA, classified as Completed or Terminated on ClinicalTrials.gov, 35 (76.1%) had reported results. There were 61 registered or unregistered clinical trials, of which 37 (60.7%) were published in the peer-reviewed literature and 46 (75.4%) had either reported results or were published. Among the 35 required clinical trials with reported results on ClinicalTrials.gov, 15 (42.9%) reported results ahead of schedule (median 16 [IQR, 6-23] months before the FDA report submission deadline) and 20 (57.1%) reported results behind schedule (median 15 [IQR, 10-22 months after the deadline].

10. Results – in the results section describing results reporting and publication, reporting rates are provided for completed trials according to different definitions of "completed". I'm not sure this is necessary, but if included, it would be helpful to add some details around the consistency encountered for trial status between ClinicalTrials.gov and the FDA database.

Response:

Thank you for this comment. For results reporting, we only evaluated studies with a *Completed* or *Terminated* status on ClinicalTrials.gov. We do not report different rates of results reporting

according to different definitions of "completed". When we looked for publications, we also included non-registered studies that were classified by FDA as *Submitted, Fulfilled, Released,* or unclear. However, in order to address this comment, we have created two additional Appendix tables, which classify results reporting and publication rates across ClinicalTrials.gov and the FDA statuses. We have also added a sentence to the results section regarding appendix tables 4 and 5.

Appendix table 4. Results reporting by postmarket requirement status source					
		No.			No. (%)
		ClinicalTrials.gov Status			
		Completed	Terminated	Total	Reported results
FDA Status	Unclear	26	4	30	22 (73.3)
	Pending	0	0	0	0 (0.0)
	Ongoing	1	1	2	1 (50.0)
	Delayed	2	1	3	1 (33.3)
	Terminated	0	0	0	0 (0.0)
	Submitted	2	0	2	2 (100.0)
	Released	1	0	1	1 (100.0)
	Fulfilled	11	1	12	9 (75.0)
	Total	47	7	50	36 (72.0)
Among the 30 postmarket studies classified as Unclear according to FDA data, 9 were classified as Fulfilled according to supplementary letters and 10 had an up-to-date status according to drug sponsor data.					

Appendix table 5. Publication by postmarket requirement status source									
		No.							No. (%)
		ClinicalTrials.gov Status						Published	
		Completed	Currently recruiting	Ongoing, not recruiting	Terminated	Not registered	Total	Published[a]	Total published
FDA Status	Unclear	26	1	3	4	3	37	20,1,3,2,0	26
	Pending	-	-	-	-	1	1	-,-,-,-,0	0 (0.0)
	Ongoing	1	-	-	1	1	3	1,-,-,0,0	1 (33.3)
	Delayed	2	-	-	1	-	3	0,-,-,0	0 (0.0)
	Terminated	-	-	-	-	-	-	-	-
	Submitted	2	-	1	-	-	3	1,-,1,-,-	2 (66.7)
	Released	1	-	-	-	-	1	0,-,-,-	0 (0.0)
	Fulfilled	11	-	3	1	2	17	6,-,1,1,0	8 (47.1)
	Total	43	1	7	7	7	65	29,1,4,3,0	37 (56.9)
[a] The values separate by commas represent the publications for each ClinicalTrials.gov status categories (Completed, Currently recruiting, Ongoing, Terminated, Not registered)									

Page 13, Results:

Reporting and publication rates did not differ according to postmarketing requirement authority, therapeutic area, and orphan status. Reporting and publication rates stratified by ClinicalTrials.gov and the FDA statuses are reported in the supporting materials ***(see supplementary appendix tables 4 and 5)****.*

11. Results – it would be helpful for greater granularity on the reasons for the delay in results reporting – is it because the trials themselves are taking a long time or because sponsors are delaying publication of the results? Those two times could be reported separately in the text, even if the existing Kaplan-Meier plots are retained.

Response:

Thank you for sharing this suggestion. We originally did not evaluate potential reasons why sponsors are delaying publication of results. Without access to internal FDA or sponsor data, it is difficult to establish why sponsors are submitting their results before or after the FDA milestones. In order to address this comment, we returned to our data and calculated the time since the primary completion, provided on ClinicalTrials.gov, until final follow-up for all postmarket studies without reported results for which results reporting would be expected. We then also checked the FDA's Postmarketing Requirements and Commitments Database files to determine whether any status explanations were provided for the ongoing postmarket studies.

Among the 50 postmarket studies registered on ClinicalTrials.gov, for which results reporting would be expected, 14 did not report results. We have created a new appendix table (appendix table 6), which includes information on the timing and potential reasons why results may not have been reported. There were 10 postmarket studies classified as *Completed* on ClinicalTrials.gov that did not have results reported a median of 26 months after the primary completion date. We could only locate two FDA status explanations for these studies. There were 4 *Terminated* studies that did not have results reported a median of 39 months after the primary completion date. For one of these studies, there was information on ClinicalTrials.gov outlining why the study was terminated. We have now updated our Results section to reference Appendix Table 6.

In order to further address Reviewer #1's comment, we also created an appendix table outlining the status explanations provided in the Postmarketing Requirements and Commitments Database files for all of the postmarket studies not classified as *Fulfilled.* Most explanations either provided an enrollment update (e.g., "272 patients have been screen; 110 have been randomized") or outlined that a deferral extension had been granted (e.g., "Original Final Report Due Date: 03/30/2018; Deferral Extension granted per FDA letter dated 07/13/2017") (Supplementary appendix table 7). We have also updated our Results section with a reference to appendix table 7.

Appendix Table 6. Timing and reasons for results reporting delays among 14 postmarket studies without posted results

ClinicalTrials.gov Status	***Time since completion (months [Interquartile Range])***	***Number with an explanation***	***ClinicalTrials.gov Explanation***	***FDA Explanation[a]***	***New milestone missed[b]***
Completed (n=10)	*26 (8-43)*	*2*	*NA*	*Recruiting patients (extension granted)*	*Unclear*

			NA	*Multiple completion milestones missed, multiple revised timeline*	*No*
Terminated (n=4)	*39 (14-68)*	*1*	*Terminated (preliminary analysis revealed that the numbers were too low to warrant continuing the project)*	*NA*	*NA*
[a] FDA explanations were abstract from Postmarketing Requirements and Commitments Database files *[b] Based on the most recently FDA explanation and potential revised timelines, has the drug sponsor missed the new milestone data, as of November 2017?*					

Appendix table 7. FDA status explanations provided for ongoing postmarket studies	
Postmarket Studies with a Status Explanation	*No. (%)*
Total	*39*
Protocol due date passed, only partial protocol has been submitted	*1 (2.6)*
Final protocol milestone missed	*1 (2.6)*
Final protocol milestone missed, FDA determined applicant demonstrated good cause for delay	*3 (7.7)*
Enrollment update provided	*8 (20.6)*
NDA product withdrawn from market during investigation of adverse events. Studies on hold	*4 (10.3)*
Ongoing	*1 (2.6)*
Deferral extension granted	*7*
PMR has been released	*1 (2.6)*
PMR has been fulfilled	*1 (2.6)*
Recruitment slow, revised milestones	*4 (10.3)*
Final report submission milestone missed	*1 (2.6)*
Study has not been initiated, but does not meet the criterion for delayed	*5 (12.8)*
Study has been initiated	*1 (2.6)*
Revised timeline agreed upon	*1 (2.6)*

Page 14, Results:

*Among the 14 studies without results reported for which results reporting would be expected, only two had an explanation in FDA's Postmarketing Requirements and Commitments Database files outlining why the studies were delayed. The median times from the primary study completion dates on ClinicalTrials.gov to final follow-up (November 15, 2017) were 26 months (IQR, 8-43) for Completed studies and 39 (IQR, 14-68) for Terminated studies (**see supplementary appendix table 6**). There were 39 postmarket studies that were not classified as Fulfilled by the FDA with a status explanation in FDA's*

*Postmarketing Requirement Database files. Most explanations either provided an enrollment update (e.g., "272 patients have been screen; 110 have been randomized") or outlined that a deferral extension had been granted (e.g., "Original Final Report Due Date: 03/30/2018; Deferral Extension granted per FDA letter dated 07/13/2017") (**see supplementary appendix table 7**).*

12. Results – the ratio of FDAAA studies to PREA ones appears to be larger than those reported in previous analyses. Could the authors confirm that they are studying only FDAAA postmarketing requirements (i.e., excluding postmarketing commitments?)

Response:

Thank you for this comment. In our study, we did not evaluate any postmarketing commitments. As we outline in our manuscript, we focused our analysis on postmarketing requirements outlined at the time of FDA approval for newly approved novel therapeutic agents. Other analyses, including a report by the Office of the Inspector General, evaluated postmarketing requirements from supplemental applications and New Drug Applications, which can also include postmarketing commitments. It could be that a greater proportion of PREA postmarketing requirements are issued in supplemental applications or written requests.

13. Results/Figure – were there any statistically significant differences in the K-M completion curves by authority type?

Response:

Thank you for this question. We did not find any statistically significant differences in the K-M completion curves by authority type. On page 12, we have already included a statement regarding these analyses: "Reporting and publication rates did not differ according to postmarketing requirement authority, therapeutic area, and orphan status."

14. Results/Table – In Table 4, the median duration of PREA trials is listed as 2.8 months, which seems very low. Also in this table, the p-values may not be necessary; there are many comparisons and it ultimately isn't clear which values are significantly different. Any particularly relevant comparisons and differences could be highlighted in the main text.

Response:

Thank you for this comment. In the Methods section of our manuscript, we state that "we recorded the primary end point and corresponding duration provided in the ClinicalTrials.gov registration." Many of the primary outcomes evaluated in the PREA studies were measured after a few days or weeks. For instance, primary outcomes included the change in Children's Depression Rating Scale-Revised Total Score (from baseline to week 8) and number of patients with adverse events (enrollment through end of study Day 38-41), etc.

Thank you for suggesting to remove the *P* values. We agree that there may not be many particularly relevant comparisons and that the table may lack clarity. In order to not deviate from our protocol, we will remove the *P* values from the Table 4 in the full text but will include them in the supplementary materials.

In terms of the discussion and conclusion, these are well-written and appropriate for the results presented. In the "Implications and Recommendations" section, the authors present strong arguments for specific reforms based on the findings presented in this study.

Response: We would like to thank the reviewer for these comments.

Reviewer: 2, Andrew Prayle

Recommendation:

Comments:
This is a timely work. The authors have searched Drugs@FDA for new authorisations, and identified all the relevant postmarketing requirements stipulated by the FDA. They attempted to determine, from the approval letter alone, the study design required. They then cross referenced this with the FDA Postmarketing Study and Clinical Trial Requirements and Commitments Database. Subsequently, they searched ClinicalTrials.gov for trials of the drug, and tried to match these against the FDA requirements for that drug, by using sensible criteria, such as intervention and indications. If a trial was found, and it had completed or terminated according to ClinicalTrials.gov, then they searched for the trial in the peer reviewed literature.

Response: We thank Review #2 for their support and helpful report.

The key findings were that although on average each new drug had 4 studies required, it was often difficult to determine the exact requirements from the publically available information. 38% of the requirements had been fulfilled according to FDA or sponsor data, and 1/3 of human studies (trials, cohorts and registries) were submitted or fulfilled. For 30% of postmarket studies it was not possible to determine the status. Interesting, only ¾ of clinical trials were registered on ClinicalTirals.gov. 76% of these that had completed had reported results. They pooled the studies from the FDA, sponsors and clinicaltrials.gov, and identified 65 studies for which they expected publication, and 55% of these had published in the peer-reviewed literature.

My comments are that this is an important work, which builds upon previous work by (for example) Woloshin et al) in investigating the status of post approval studies, and I congratulate the authors for a well conducted study. The important contribution of this present work is that it is often difficult to ascertain exactly what was requested, and even when the studies have completed, the data are frequently not reported in a manner that would allow us to incorporate the information from the work into clinical practice (for example via meta-anlyeses) as the data are under reported. This is therefore an important issue which the BMJ could use its prominence to usefully highlight. This work highlights a gap in the clinical trials and regulatory enterprise – by definition, the FDA is asking for important work to be done, but it is difficult to find out the results of this work.

Response:

We would like to thank Reviewer #2 for their feedback and support of our work.

My comments are few, and reflect that I think this should be published. They are:

1. It is known that trials often complete but the ClinicalTrials.gov record is not updated, although this is improving over time. Therefore, it would improve the robustness of the work if the authors investigated for this scenario by searching for publications from a sample (or all) trials which are not recorded as completed or terminated on ClincialTrials.gov.

Response:

Thank you for sharing this recommendation. We agree that some trials that are completed may not have an up-to-date status on ClinicalTrials.gov. However, in our pre-specified protocol, we decided that trials that were classified as "ongoing" or "recruiting subjects" on ClinicalTrials.gov would be less likely to have corresponding publications. This decision was based on prior work by our group and others that used ClinicalTrials.gov to characterize results reporting and publication of registered clinical trials.[9-14] Furthermore, searching for publications for trials which are not classified as "completed" or "terminated" on ClinicalTrials.gov could expose the manuscript to criticism. In particular, our paper could be viewed as attempting to make postmarketing requirements look bad if we had included postmarket studies less likely to have been completed and thus have results ready for dissemination, either through results reporting or publication. We considered this decision carefully when initially designing our study and decided to exclude studies that are less likely to be published. Please also see our response to Reviewer #1's comment above (comment #2). We acknowledge some of these concerns in the Limitations section of our manuscript. However, to further address this comment, we have modified some of the language.

Page 19, Limitations of this study:

We looked for publications for all registered studies classified as Completed or Terminated on ClinicalTrials.gov or unregistered studies classified as Submitted, Fulfilled, Released, or unclear according to FDA or drug sponsor data. This decision was based on prior work by our group and others that used ClinicalTrials.gov to characterize results reporting and publication registered trials.[9-14] We acknowledge that additional studies may get published, but were not published at the time of our search. Third, we did not determine whether the results from required 'ongoing' prospective cohort studies, registries, or clinical trials were reported or published. While some 'ongoing' studies may have reported or published results, ongoing studies are less likely to have results reported and publications.

2. In several sections of the paper, consistency and accuracy was verified by a second reviewer – it would be good to have supplementary information on how often the second reviewer disagreed (this must have happened from time to time in such a big piece of work) and how this disagreement was dealt with.

Response:

We appreciate the opportunity to provide this information. As we outlined in our manuscript (Page 10), the senior author (JSR) resolved discrepancies by consensus: "All uncertainties and disagreements were resolved by consensus with input from the senior investigator (JSR)." In our results section, we have now also added the concordance.

The second reviewer (ACE) independently abstract information for 42 postmarketing requirements. A total of 1764 individual excel cells were abstracted in duplicate. Although there were 26 cells with differences, all discrepancies were resolved by JDW and ACE after discussion. In order to reflect this, we have added a sentence to our Results section.

Page 15:

A total of 1764 excel cells were abstracted independently by two reviewers (JDW and ACE) and consensus was reach for all 26 (26 of 1764 [1.5%]) differences.

3. The authors have collected a huge amount of rich data, but all of it is publicly available – I would recommend publishing this as a data supplement to the paper in an online repository, as a robust approach to data sharing.

Response:

Thank you for this recommendation. Once that paper is published, we will publish the data on Dryad. We will update our data sharing statement to reflect this information:

Data sharing: Requests for the dataset can be made to the corresponding author at joshua.wallach@yale.edu. The dataset will be made available via a publicly accessible repository on publication.

4. In the introduction, the authors cite reference 9 as the source for ½ of post marketing studies failing to complete. I am not sure that this reference (Naci et al) supports this statement.

Response:

Thank you for your attention to detail. In our manuscript, we accidently cited the incorrect paper published by Naci et al. We have now included the correct reference (Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration doi:10.1001/jama.2017.9415).

Thank you again for asking me to review this work. I would be happy to review a revised piece.

Andrew Prayle

REFERENCES

1. Food and Drug Administration Amendments Act of 2007. US Public Law 110-85. (2007, Sept 27); 21 USC 301.
2. ClinicalTrials.gov. FDAAA 801 requirements. http://clinicaltrials.gov/ct2/manage-recs/fdaaa -/WhichTrialsMustBeRegistered.
3. Cruz ML, Xu J, Kashoki M, et al. Publication and Reporting of the Results of Postmarket Studies for Drugs Required by the US Food and Drug Administration, 2009 to 2013. *JAMA Intern Med* 2017;177(8):1207-10. doi: 10.1001/jamainternmed.2017.1313
4. Phillips AT, Desai NR, Krumholz HM, et al. Association of the FDA Amendment Act with trial registration, publication, and outcome reporting. *Trials* 2017;18(1):333. doi: 10.1186/s13063-017-2068-3 [published Online First: 2017/07/18]
5. Miller JE, Wilenzick M, Ritcey N, et al. Measuring clinical trial transparency: an empirical analysis of newly approved drugs and large pharmaceutical companies. *BMJ Open* 2017;7(12):e017917. doi: 10.1136/bmjopen-2017-017917 [published Online First: 2017/12/05]
6. Miller JE, Korn D, Ross JS. Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. *BMJ Open* 2015;5(11):e009758. doi: 10.1136/bmjopen-2015-009758 [published Online First: 2015/11/12]
7. Department of Health and Human Services Office of Inspector General. July 2016. FDA is Issuing More Postmarketing Requirements, but Challenges with Oversight Persist. https://oig.hhs.gov/oei/reports/oei-01-14-00390.pdf. Accessed 10 Nov 2017.
8. ClinicalTrials.gov. Glossary of Common Site Terms. https://clinicaltrials.gov/ct2/about-studies/glossary. Accessed 1 April 2017.
9. Chen R, Desai NR, Ross JS, et al. Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers. *BMJ* 2016;352:i637. [published Online First: 2016/02/17]
10. Ross JS, Tse T, Zarin DA, et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012;344:d7292. [published Online First: 2012/01/03]
11. Stockmann C, Ross JS, Sherwin CMT, et al. Rate of asthma trial outcomes reporting on ClinicalTrials.gov and in the published literature. *J Allergy Clin Immunol* 2014;134(6):1443-46. doi: 10.1016/j.jaci.2014.09.019 [published Online First: 2014/10/28]
12. Ross JS, Mulvey GK, Hines EM, et al. Trial publication after registration in ClinicalTrials.Gov: a cross-sectional analysis. *PLoS Med* 2009;6(9):e1000144. doi: 10.1371/journal.pmed.1000144 [published Online First: 2009/09/08]
13. Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012;344:d7373. [published Online First: 2012/01/03]
14. Anderson ML, Chiswell K, Peterson ED, et al. Compliance with results reporting at ClinicalTrials.gov. *N Engl J Med* 2015;372(11):1031-9. doi: 10.1056/NEJMsa1409364