PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reporting of Retrospective Registration in Clinical Trial Publications: a Cross-Sectional Study of German Trials
AUTHORS	Haslberger, Martin; Gestrich, Stefanie; Strech, Daniel

VERSION 1 – REVIEW

REVIEWER	Oddens, Björn Merck & Co Inc
REVIEW RETURNED	06-Nov-2022

GENERAL COMMENTS	This is an important study highlighting the need to prospectively register clinical research, and - if the study is registered retrospectively - to explain this fact as well as the reasons in the resulting study publication. The authors demonstrate that the latter is rarely done, which is an important reminder to all involved in clinical research: (1) why a study is necessary; (2) for transparency of studies that were negative and never reported; (3) to avoid redundancy of research. Nevertheless, (A) the results can be more clearly presented, (B) there are oddities in the numbers, (C) there is room to discuss a main finding (in the Figures), and (D) reading is hampered by the many unexplained abbreviations in all sections including the abstract (found a number of them back in the text [that should not be the case], but still wonder what TRN stands for). Will focus on (A) to (C): (A) Abstract should be clearer that this is not an investigation into how many clinical studies were retrospectively registered or not registered (that was the subject of references 17-18). This follow-up study investigates how retrospective registration (of studies identified in Refs 17-18) was declared/explained in subsequent study publications (cross-referenced by journal (ICJME/not) or funding (industry/academic). The current abstract suggests a broader scope. (B) The text about the sample of studies does not follow the flow chart (Figure 1). Both seem illogical. You would start with 1038 studies --> 5 were erroneous --> 77 were moved to prospective (the latter are now under "prospective" in the flow chart [??]). The text in Results is silent how the 1932 moved to 956. The statistics are not correctly summarized in the abstract: - The sentence about P < 0.001 is non-interpretable (what was compared with what?) - The ICJME versus other journals was not higher when it was not significant - The significant finding for industry vs non-industry is not mentioned (but feel free to add that ~ 60% reported is not what it should be)

	(C) Apart from the call to action to explain retrospective registration, I think it is worthwhile to discuss that the non-registration rate improved over the years to about 25%. A positive note to reinforce that (timely) registration of clinical research is essential helps reminding us to do a better job; not only explaining afterwards why registration was originally not done. This is an important study, requiring a clearer display of the findings to ensure clinical researchers understand their duties to patients and society.

REVIEWER	Taruno, Hiroyuki Japanese Foundation For Cancer Research Cancer Institute Hospital
REVIEW RETURNED	13-Nov-2022

GENERAL COMMENTS	I believe this paper should be submitted. 1. As an advice: how about a bit more regulatory background in the introduction chapter? The Declaration of Helsinki states that "35. All research involving human subjects shall be registered in a publicly accessible database prior to the recruitment of the first subject." I believe that some researchers who start a study after reading only the GCP will register in the database later and write in the paper that they were "unaware" of the database. 2. abbreviations are not shown in the first appearance, which makes some parts difficult to understand. some words are shown only as abbreviations in the Abstract. there is a word limit in the Abstract, but the full term should also be shown, if possible. In the text, it should be indicated in the first appearance. 3. The statistics are performed by Fisher and Chi-square, explain why you use them differently. 4. There is no title and caption for Figure, so it should be shown after the text. 5. In Japan, there is little delay in disclosing information, at least with regard to the specified clinical trials（interventional study） but what is the background for this to happen? Could you please describe this area a little more? 6. Did you consult with the general public when writing this paper? 7. I feel that the judgment of this paper is extremely personal, but what are your thoughts?

REVIEWER	Al-Durra, Mustafa University of Toronto, Centre for Global eHealth Innovation, Techna Institute, University Health Network
REVIEW RETURNED	14-Dec-2022

GENERAL COMMENTS	This paper examined the reporting of retrospective registration of clinical trials in published manuscripts of trials registered in the ClinicalTrials.gov and the Deutsches Register Klinischer Studien (DRKS). This study provided a secondary and cross-sectional analysis of two previously reported projects that were conducted by the same research group. This is an important topic and need a wider attention of the clinical trials community in Germany and beyond. The authors could also benefit from further their analysis by measure the registration bias as defined by Al-Durra et al. 2020 – by measuring and reporting on the duration between late/retrospective registration and the publication date, i.e. to find out if authors may have registered their

	trials late not for the ethical/rights reasons, but more so to increase their chance in result publication. Reviewer Comments: Abstract Section\Objective Sub-Section: - Please call out the “Mitigation of publication and selective reporting bias” as one of the good reasons behind prospective trial registration. Abstract Section\Design Sub-Section: - With respect to "We used a dataset of trials registered on ClinicalTrials.gov or DRKS". What if the trial was registered in both registries? Also, I think 'registered in' would be more appropriate than 'registered on'. Abstract Section\Conclusion Sub-Section: - With respect to "Disclosure of the retrospective nature of the registration would require 1-2 additional sentences in the manuscript...". The number of sentences is not indicated in the ICMJE guidelines. Also, the disclosure, as indicated by the ICMJE, requires both the authors and editors to justify the rationale behind late registration and exceptional acceptance of the manuscript respectively. Perhaps, indicate that "Providing a brief statement to disclose the retrospective nature of the registration could be easily implemented by the authors and editors". Please refer to the ICMJE guidelines here "Because of the importance of prospective trial registration, if an exception to this policy is made, trials must be registered and the authors should indicate in the publication when registration was completed and why it was delayed. Editors should publish a statement indicating why an exception was allowed." https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. Strengths and limitations of this study: - With respect to "...led by German university medical centers, and therefore reflects German or European registration standards.". The postulate the German university medical centers are the best to reflect the German/Eu registration standard is contradictory to this paper's own findings and need to be clarified objectively. In Table 1, this research reported higher compliance (p=.002) in prospective registration of Industry sponsored trials (59.3%) compared to non-industry (48.9%) - it's fair to assume university medical centers are part of the later. In Table 3, the paper also reported no statistically significant difference between Industry and non-Industry sponsored trials for transparent reporting of retrospective registration. Based on these finding, it's clear that German university medical centers are NOT representative of the German or European registration standards. Perhaps, the authors needs to declare this choice as 'convenience sampling' under the limitation section. Introduction Section: - "A number of ethical and legal documents call...". The authors provided a few examples on ethical documents but not to any legal ones? Please indicate and cite clearly the legal requirement if any. - "Some registries, such as DRKS, explicitly mark retrospectively registered entries as such, whereas others, such as

	ClinicalTrials.gov, do not.". It will be important to call out the ICTRP of the WHO (https://trialsearch.who.int/Default.aspx), as they too mark the <Retrospective_flag> in their database (you can find that data element in the xml export from their search portal). - "While some publishers allow retrospectively...". The manuscript need to be clear on what's mean by 'Publishers'...or even better, use the term 'Authors' or 'Editors' instead, as the term 'Publishers' may refer to the journal as publishing business/company and not the corresponding editors. - "Using the data from these two studies on trials registered inwo large...". What is 'inow'? Methods\Data Sources and sample: - "The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany.". This is a wrong statement. DRKS is indeed one of the 17 WHO primary registries: https://www.who.int/clinical-trials-registry-platform/network/primary-registries. CT.GOV is however not a WHO primary registry. It's be enlisted one of the WHO DATA PROVIDERS: https://www.who.int/clinical-trials-registry-platform/network/data-providers. Also, can you please cite the source declaring CT.GOV is a primary registry for German trials? Methods\Eligibility criteria: - There seems to be different fonts used in that paragraph (at least in the HTML version). Please, revise. Methods\Cross-registrations: - With respect to "...EudraCT in the publication as prospective...". Please refer to finding reporting by Al-Durra et al. (https://www.bmj.com/content/369/bmj.m982). That group found that the European Clinical Trials Register (EU CTR) reported the highest compliance in prospective trial registration at 93.1% (81/87), which means 6.9% of the EU CTR trials are not registered prospectively. Please, review the prospective registration of all trials irrespective of the registries and revise your reported findings. - With respect to "...EudraCT in the publication as prospective...". Because EU CTR is yet another registry, the authors need to explain why they are considered trials registered in EU CTR (or most likely in this case it is a multi-registration of the same trial). Results\Sample of retrospectively registered trials: - "77 (7.8%) of the publications provided a EudraCT number, in which case we reclassified the study as prospectively registered": please refer to my previous comment above. Results\Retrospective registration: - "It is important to note here that the information on ICMJE-following is based on journals' requests to be included on the ICMJE website, therefore our results suggest that journals requesting to be featured on the site often do not enforce the recommendations strongly." The language should be cited from source "https://mc.manuscriptcentral.com/bmjopen?DOWNLOAD=TRUE&PARAMS=xik_5WP6BWRSTU2arJBh7i5tZpMgGRxcs28i9byHdrrw

	1CjgzEyJJeNo7f8nu7HRcQ833bTUFRxSr8bRMQRmeHLVhSHLmB3xkEnoQ3Vuakjr1EivuWq3Kn4s8a2RHNUc5My8yzw9UBn33DUn9i3HknkpGAjoQNiFDjPzRF4PftXW5C1m8Np5yzxnbMRFumgAQqG9ToXQb". Perhaps, the authors can elaborate more about the "list" to indicate "list of journals whose editors or publishers have contacted the International Committee of Medical Journal Editors (ICMJE) to request listing as a journal that says it follows the ICMJE's Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals." Discussion - "To our knowledge, only two studies have previously addressed the reporting of retrospective registration...". Please, include and reflect on these two studies; (1) Hunter et al. (https://bmjopen.bmj.com/content/8/3/e019983?ijkey=0206b507c137d7ae81e2386e29e563d3e9ef38f8&keytype2=tf_ipsecsha) and (2) Harriman et al. (https://pubmed.ncbi.nlm.nih.gov/27079379/) - "...in a larger sample representing a more diverse selection of journals and broader time frame.": This is partially a wrong statement. The sample of retrospectively registered trials in this study was (N=956) compared to (N=4205) included in the Al-Durra et al. study. Also, this study did not a more diverse selection of journals. As per Table 1, there were only 28 published papers in ICMJE member journals of prospectively registered trials whereas Al-Durra et al. (see Appendix K) reported on 410 published papers in ICMJE member journals of prospectively registered trials. It's correct however, that this study covered a broader time frame. Limitations - "For example, in Germany, unlike many other countries, there is no legal mandate to register all clinical studies...". Please indicate and cite where legal mandates have been enforced? in which countries? - "In addition, due to Germany’s high research output (23) our results in any case highlight a key transparency issue in a major research environment." This statement can benefit from a proof-reading revision? It isn't clear what was the point that authors tried to make. Conclusion: - "For highly regulated clinical trials this was even codified into law." This needs to be supported by a citation/reference please. - "This study was retrospectively registered at [Registry], [X] days after the trial started because [Reason]". This a great, impactful and well-thought statement. The authors should be commended on providing this important, yet simple, guiding statement and is really the highlight of this research to inform the registration and publication of future clinical trials in Germany and beyond.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Björn Oddens, Merck & Co Inc

Comments to the Author:

This is an important study highlighting the need to prospectively register clinical research, and - if the study is registered retrospectively - to explain this fact as well as the reasons in the resulting study publication. The authors demonstrate that the latter is rarely done, which is an important reminder to all involved in clinical research: (1) why a study is necessary; (2) for transparency of studies that were negative and never reported; (3) to avoid redundancy of research. Nevertheless, (A) the results can be more clearly presented, (B) there are oddities in the numbers, (C) there is room to discuss a main finding (in the Figures), and (D) reading is hampered by the many unexplained abbreviations in all sections including the abstract (found a number of them back in the text [that should not be the case], but still wonder what TRN stands for). Will focus on (A) to (C):

(A) Abstract should be clearer that this is not an investigation into how many clinical studies were retrospectively registered or not registered (that was the subject of references 17-18). This follow-up study investigates how retrospective registration (of studies identified in Refs 17-18) was declared/explained in subsequent study publications (cross-referenced by journal (ICJME/not) or funding (industry/academic). The current abstract suggests a broader scope.

RE: Thank you for making us aware of this ambiguity. We revised the abstract to address the issue you raised.

(B) The text about the sample of studies does not follow the flow chart (Figure 1). Both seem illogical. You would start with 1038 studies --> 5 were erroneous --> 77 were moved to prospective (the latter are now under "prospective" in the flow chart [??]). The text in Results is silent how the 1932 moved to 956.

RE: Thank you for your comment. We revised the first paragraph in “Results” to make our selection clearer. We explain the reasoning for re-classifying studies that are cross-registered in EudraCT as prospectively registered in the methods.

The statistics are not correctly summarized in the abstract:

- The sentence about $P < 0.001$ is non-interpretable (what was compared with what?)

- The ICJME versus other journals was not higher when it was not significant

- The significant finding for industry vs non-industry is not mentioned (but feel free to add that ~ 60% reported is not what it should be)

RE: Thank you for pointing out these inconsistencies. We describe in the main text that we compare retrospectively registered to prospectively registered studies, but this was not evident from the abstract. Regarding the latter two points – thank you for noticing these cases of unintended spin. We hope that the revised abstract resolves the issue.

(C) Apart from the call to action to explain retrospective registration, I think it is worthwhile to discuss that the non-registration rate improved over the years to about 25%. A positive note to reinforce that (timely) registration of clinical research is essential helps reminding us to do a better job; not only explaining afterwards why registration was originally not done.

RE: Thank you for this suggestion! While we agree that this generally positive trend should be commended, there are relatively fewer studies from the later years (120 from 2016-17) in our dataset. Due to the selection of studies (completed until 2017), the studies that were started in 2016-17 show timely reporting and therefore likely generally a higher quality of registration conduct. We added a paragraph describing this in the limitations section.

This is an important study, requiring a clearer display of the findings to ensure clinical researchers understand their duties to patients and society.

RE: Thank you for your kind words and your helpful suggestions.

Reviewer: 2

Mr. Hiroyuki Taruno, Japanese Foundation For Cancer Research Cancer Institute Hospital

Comments to the Author:

I believe this paper should be submitted.

1. As an advice: how about a bit more regulatory background in the introduction chapter? The Declaration of Helsinki states that "35. All research involving human subjects shall be registered in a publicly accessible database prior to the recruitment of the first subject." I believe that some researchers who start a study after reading only the GCP will register in the database later and write in the paper that they were "unaware" of the database.

RE: Thank you for your suggestion. We added references to regulatory documents, as those were previously missing. Regarding researchers being “unaware” - we go into those kinds of justifications, if available, in the results.

2. abbreviations are not shown in the first appearance, which makes some parts difficult to understand. some words are shown only as abbreviations in the Abstract. there is a word limit in the Abstract, but the full term should also be shown, if possible. In the text, it should be indicated in the first appearance.

RE: Thank you for noticing, we revised this.

3. The statistics are performed by Fisher and Chi-square, explain why you use them differently.

RE: We wrote: “To test the strength of the associations between prospective registration and three variables, we used Pearson’s chi-squared independence test or Fisher’s exact test (for small numbers).” We revised this text in the methods part to be clearer and re-calculated the p-value for the association between ICMJE membership and prospective registration as the number of cases (n=28) was not small enough to warrant the Fisher test. The resulting change in p-value from 0.09 to 0.10 does not influence the interpretation of the analysis.

4. There is no title and caption for Figure, so it should be shown after the text.

RE: Thank you for making us aware of this. We added the figure captions at the end of the document. We had entered them in the form provided in the manuscript submission system, but they were not included in the review document.

5. In Japan, there is little delay in disclosing information, at least with regard to the specified clinical trials（interventional study） but what is the background for this to happen? Could you please describe this area a little more?

RE: In Germany and several other European countries only certain drug and device trials are required by law to be prospectively registered. Other interventional trials on surgical or behavioral interventions, etc. should of course follow the registration principle as addressed in the Declaration of Helsinki but they often do not. Over the past ten years we see a steady increase of prospective registration also for non-drug/device trials. One background reason is journals’ requirement for (prospective) registration.

6. Did you consult with the general public when writing this paper?

RE: We did not consult with the public when writing the paper. However, we prepared a publicly available dashboard that present the underlying data for trial transparency across all 35 German university medical centers. This publicly available dashboard is accepted for publication in PLOS Medicine and will be published in the next weeks.

7. I feel that the judgment of this paper is extremely personal, but what are your thoughts?

RE: We are sorry that our conclusion seems to be very personal. We went over the conclusion to make sure that we describe only what we intended to describe from the beginning: We show empirical results in our study that an important rule (“reporting about the retrospective nature of trial registrations in journal publications”) is inadequately followed and we point out the relevant guidance.

Reviewer: 3

Mr. Mustafa Al-Durra, University of Toronto, University of Toronto

Comments to the Author:

This paper examined the reporting of retrospective registration of clinical trials in published manuscripts of trials registered in the ClinicalTrials.gov and the Deutsches Register Klinischer Studien (DRKS). This study provided a secondary and cross-sectional analysis of two previously reported projects that were conducted by the same research group.

This is an important topic and need a wider attention of the clinical trials community in Germany and beyond. The authors could also benefit from further their analysis by measure the registration bias as defined by Al-Durra et al. 2020 – by measuring and reporting on the duration between late/retrospective registration and the publication date, i.e. to find out if authors may have registered their trials late not for the ethical/rights reasons, but more so to increase their chance in result publication.

RE: Thank you for this good suggestion. We describe the rationale behind “selective registration bias” in the description of themes identified from full-text screening, but added a reference to your previous description of the phenomenon, and added numbers on the number of retrospectively registered papers registering after study completion and the median time to publication.

Reviewer Comments:

Abstract Section\Objective Sub-Section:

- Please call out the “Mitigation of publication and selective reporting bias” as one of the good reasons behind prospective trial registration.

RE: We describe this in the first two paragraphs of the introduction.

Abstract Section\Design Sub-Section:

- With respect to "We used a dataset of trials registered on ClinicalTrials.gov or DRKS". What if the trial was registered in both registries? Also, I think 'registered in' would be more appropriate than 'registered on'.

RE: For trials that were registered in both registries we kept the earlier entry. We added this in the methods section.

Abstract Section\Conclusion Sub-Section:

- With respect to "Disclosure of the retrospective nature of the registration would require 1-2 additional sentences in the manuscript...". The number of sentences is not indicated in the ICMJE guidelines. Also, the disclosure, as indicated by the ICMJE, requires both the authors and editors to justify the rationale behind late registration and exceptional acceptance of the manuscript respectively. Perhaps, indicate that "Providing a brief statement to disclose the retrospective nature of the registration could be easily implemented by the authors and editors". Please refer to the ICMJE guidelines here "Because of the importance of prospective trial registration, if an exception to this policy is made, trials must be registered and the authors should indicate in the publication when registration was completed and why it was delayed. Editors should publish a statement indicating why an exception was allowed." https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html.

RE: Thank you for your comment. With the sentence you refer to we did not mean to reference ICMJE guidance, but give a suggestion how the retrospective nature of a registration could be reported. We modified this slightly and included a more explicit reference to the relevant statements on retrospective registration in the ICMJE guidance in our introduction.

Strengths and limitations of this study:

- With respect to "...led by German university medical centers, and therefore reflects German or European registration standards.". The postulate the German university medical centers are the best to reflect the German/Eu registration standard is contradictory to this paper's own findings and need to be clarified objectively. In Table 1, this research reported higher compliance (p=.002) in prospective registration of Industry sponsored trials (59.3%) compared to non-industry (48.9%) - it's fair to assume university medical centers are part of the later. In Table 3, the paper also reported no statistically significant difference between Industry and non-Industry sponsored trials for transparent reporting of retrospective registration. Based on these finding, it's clear that German university medical centers are NOT representative of the German or European registration standards. Perhaps, the authors needs to declare this choice as 'convenience sampling' under the limitation section.

RE: We included any study that had a university medical center (UMC) as the lead center – “Lead” is defined as either being the lead sponsor of a study or hosting the lead PI. The vast majority of publications on interventional clinical studies are published by UMCs. In our sample 14.3% of studies are industry-sponsored, which is indeed less than would be expected. This might be due to a combination of different factors: for example, in the total dataset of all UMC-led German trials (of which the data used in this analysis are a subset), 26.4% (999/3788) are industry-sponsored. Significantly more of those industry-sponsored trials report results only in the registry, but not in a publication ($p < 2.2e-16$; Chi-sq. test). Since the main unit of analysis for this paper is the trial publication, a larger number of industry-sponsored trials was filtered out.

Introduction Section:

- "A number of ethical and legal documents call...". The authors provided a few examples on ethical documents but not to any legal ones? Please indicate and cite clearly the legal requirement if any.

RE: Thank you for spotting this. We added the EU regulation 536/2014 which calls for prospective registration.

- "Some registries, such as DRKS, explicitly mark retrospectively registered entries as such, whereas others, such as ClinicalTrials.gov, do not.". It will be important to call out the ICTRP of the WHO (https://trialsearch.who.int/Default.aspx), as they too mark the <Retrospective_flag> in their database (you can find that data element in the xml export from their search portal).

RE: Since we used DRKS and CT.gov, we give those two examples, but added ICTRP now.

- "While some publishers allow retrospectively...". The manuscript need to be clear on what's mean by 'Publishers'...or even better, use the term 'Authors' or 'Editors' instead, as the term 'Publishers' may refer to the journal as publishing business/company and not the corresponding editors.

RE: Thank you for pointing out this imprecise phrasing. To be clearer, we changed this to “while some journals…”.

- "Using the data from these two studies on trials registered inwo large...". What is 'inow'?

RE: Thank you for noticing this error. We corrected it to “in two large …”.

Methods\Data Sources and sample:

- "The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany.". This is a wrong statement. DRKS is indeed one of the 17 WHO primary registries: https://www.who.int/clinical-trials-registry-platform/network/primary-registries. CT.GOV is however not a WHO primary registry. It's be enlisted one of the WHO DATA PROVIDERS: https://www.who.int/clinical-trials-registry-platform/network/data-providers. Also, can you please cite the source declaring CT.GOV is a primary registry for German trials?

RE: This might be a grammatical misunderstanding as we’re not native English speakers. Since “which is the WHO primary trial registry for Germany” is singular, we assume that it relates only to DRKS. We modified the text to prevent misunderstandings.

Methods\Eligibility criteria:

- There seems to be different fonts used in that paragraph (at least in the HTML version). Please, revise.

RE: Thank you for pointing this out – we hope the issue is now resolved.

Methods\Cross-registrations:

- With respect to "...EudraCT in the publication as prospective...". Please refer to finding reporting by Al-Durra et al. (https://www.bmj.com/content/369/bmj.m982). That group found that the European Clinical Trials Register (EU CTR) reported the highest compliance in prospective trial registration at 93.1% (81/87), which means 6.9% of the EU CTR trials are not registered prospectively. Please, review the prospective registration of all trials irrespective of the registries and revise your reported findings.

RE: Before trials can recruit patients, they need to be approved by the national competent authorities (NCAs), which for Germany is the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) or Paul Ehrlich Institut (PEI). To apply for approval, sponsors need a valid EudraCT number for the trial (https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/klin-pr/Leitfaden%20zur%20Antragstellung.pdf?__blob=publicationFile; resource in German).

Therefore, we defined any trial registered in EudraCT (based on reported registration numbers) as prospectively registered, even if there was another retrospective registration in another registry. There are known problems with the reliability of registration dates in EudraCT as the speed with which different NCAs process trial applications differs between countries (see https://www.clinicaltrialsregister.eu/doc/14-03-26%20FLS%20-%20Response%20to%20Paolo%20Daniele%20Siviero%20-%20to%20whom%20it%20may%20concern.pdf). A registration that appears retrospective in EUCTR will in most cases be registered with the NCA prospectively. This is an automatic process in Germany. You cannot submit your documents to a German authority or ethics committee without an EudraCT number.

See also the study by Denneny et al. 2019 (https://doi.org/10.1136/bmjopen-2018-026840) that accepted the ethics approval of drug trials as sufficient to assume that these trials have an EudraCT number as required by law and the relevant automatic submission processes.

- With respect to "...EudraCT in the publication as prospective...". Because EU CTR is yet another registry, the authors need to explain why they are considered trials registered in EU CTR (or most likely in this case it is a multi-registration of the same trial).

RE: We did not initially consider trials registered in EudraCT. We reclassified trials that report two registration numbers (one EudraCT; one DRKS or CT.gov) and were initially classified as retrospectively registered. We assume, as EudraCT registration dates are sometimes incorrect, but it is implied in the approval process that they go through regulatory approval and the regulator is responsible for entering the data, that they are not retrospectively registered (see letter cited above).

Results\Sample of retrospectively registered trials:

- "77 (7.8%) of the publications provided a EudraCT number, in which case we reclassified the study as prospectively registered": please refer to my previous comment above.

RE: see above

Results\Retrospective registration:

- "It is important to note here that the information on ICMJE-following is based on journals' requests to be included on the ICMJE website, therefore our results suggest that journals requesting to be featured on the site often do not enforce the recommendations strongly." The language should be cited from source "https://mc.manuscriptcentral.com/bmjopen?DOWNLOAD=TRUE&PARAMS=xik_5WP6BWRSTU2arJBh7i5tZpMgGRxcs28i9byHdrrw1CjgzEyJJeNo7f8nu7HRcQ833bTUFRxSr8bRMQRmeHLVhSHLmB3xkEnoQ3Vuakjr1EivuWq3Kn4s8a2RHNUc5My8yzw9UBn33DUn9i3HknkpGAjoQNiFDjPzRF4PftXW5C1m8Np5yzxnbMRFumgAQqG9ToXQb". Perhaps, the authors can elaborate more about the "list" to indicate "list of journals whose editors or publishers have contacted the International Committee of Medical Journal Editors (ICMJE) to request listing as a journal that says it follows the ICMJE's Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals."

RE: Unfortunately, the provided link does not link to a reference. Did you mean to paste the ICMJE website (https://icmje.org/journals-following-the-icmje-recommendations/)? The ICMJE states:

> "The following is a list of journals whose editors or publishers have contacted the International Committee of Medical Journal Editors (ICMJE) to request listing as a journal that says it follows the ICMJE's Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Although these journals are not "members" of the ICMJE itself, nor does their inclusion indicate "certification" by the ICMJE, maintenance of such a list may help to promote improvements in the quality of medical science and its reporting by indicating the standards many editors indicate they work to uphold.
>
> **The ICMJE cannot verify the completeness or accuracy of this list.**
>
> - There may be some journals that follow the ICMJE recommendations, but have never requested listing.
> - There may be some listed journals that do not follow all of the many recommendations and policies in the document."

We are not aware that any more complete list of ICMJE-following journals is available anywhere. The closest approximation is the list provided on the ICMJE website, which we use in our study. However, some journals are missing, e.g. all PLOS journals except PLOS Medicine (which is a ICMJE member journal).

Discussion

- "To our knowledge, only two studies have previously addressed the reporting of retrospective registration...". Please, include and reflect on these two studies; (1) Hunter et al. (https://bmjopen.bmj.com/content/8/3/e019983?ijkey=0206b507c137d7ae81e2386e29e563d3e9ef38f8&keytype2=tf_ipsecsha) and (2) Harriman et al. (https://pubmed.ncbi.nlm.nih.gov/27079379/)

RE: Thank you for pointing out these references, which are valuable additions to our discussion.

- "...in a larger sample representing a more diverse selection of journals and broader time frame.": This is partially a wrong statement. The sample of retrospectively registered trials in this study was (N=956) compared to (N=4205) included in the Al-Durra et al. study. Also, this study did not a more diverse selection of journals. As per Table 1, there were only 28 published papers in ICMJE member journals of prospectively registered trials whereas Al-Durra et al. (see Appendix K) reported on 410 published papers in ICMJE member journals of prospectively registered trials. It's correct however, that this study covered a broader time frame.

RE: We agree that in some ways, our sample is less diverse than the Al-Durra sample. However, for the purposes of the presented study, we consider our sample “more diverse” in some ways: the sampling in Al-Durra et al. is based on MEDLINE-indexed publications using a title keyword filter, with registry entries identified automatically based on the publications. Our dataset includes all trials registered in the two large registries relevant in Germany, with publications identified through multiple manual searches in different databases. The primary aim of our analysis was to assess the reporting of retrospective registration. While Al-Durra et al. start from a very large sample of 10500 publications, the full-text analysis of retrospectively registered trials is based on 286 publications, resulting in the identification of eight justifications for the retrospective registration. The assessed publications were exclusively from the 12 ICMJE member journals, which enforce higher standards for reporting than other journals, evidenced by, e.g., higher proportions of registration number reporting, etc. We assess 956 publications published any journal and investigate whether ICMJE membership/”following” has influence on retrospective registration and the transparent reporting thereof, as well as the development of these practices over a timespan of nine years.

Limitations

- "For example, in Germany, unlike many other countries, there is no legal mandate to register all clinical studies...". Please indicate and cite where legal mandates have been enforced? in which countries?

RE: Thank you for pointing out this imprecise statement and missing reference. There are some countries, such as Switzerland (see e.g., https://www.kofam.ch/upload/downloads/humanforschungsgesetzgebung/Erlauternder_Bericht_20130821.pdf; resource in German), that have a stricter policy than Germany, which implements the EU regulation. However, this example is not essential to the discussion, so we deleted it.

- "In addition, due to Germany’s high research output (23) our results in any case highlight a key transparency issue in a major research environment." This statement can benefit from a proof-reading revision? It isn't clear what was the point that authors tried to make.

RE: This statement was meant to contextualize the limitation that the sample is based on German trials only. However, it is not necessary, as it is completely obvious, and has been deleted in the revision.

Conclusion:

- "For highly regulated clinical trials this was even codified into law." This needs to be supported by a citation/reference please.

RE: Thank you for pointing this out, we added some relevant references. We also noticed that this sentence was somewhat pleonastic, so we modified it slightly.

- "This study was retrospectively registered at [Registry], [X] days after the trial started because [Reason]". This a great, impactful and well-thought statement. The authors should be commended on providing this important, yet simple, guiding statement and is really the highlight of this research to inform the registration and publication of future clinical trials in Germany and beyond.

RE: Thank you. We expanded this slightly, pointing to the fact that this would simply be proper implementation of ICMJE guidance.

Reviewer: 1

Competing interests of Reviewer: Reviewer is employed by and owns stock in pharmaceutical industry, in casu Merck & Co.

Reviewer: 2

Competing interests of Reviewer: There are no conflicts of interest with the author.

Reviewer: 3

Competing interests of Reviewer: NA

VERSION 2 – REVIEW

REVIEWER	Oddens, Björn Merck & Co Inc
REVIEW RETURNED	11-Mar-2023

GENERAL COMMENTS	The reviewers' comments have been adequately addressed. Thank you!

REVIEWER	Taruno, Hiroyuki Japanese Foundation For Cancer Research Cancer Institute Hospital
REVIEW RETURNED	11-Mar-2023

GENERAL COMMENTS	This paper adequately addresses my points. I believe this paper should be approved.

REVIEWER	Al-Durra, Mustafa University of Toronto, Centre for Global eHealth Innovation, Techna Institute, University Health Network
REVIEW RETURNED	14-Mar-2023

GENERAL COMMENTS	The authors have provided an adequate response to all my review points. A courtesy reminder to the authors to revise this statement "To our knowledge, two studies have previously quantified the reporting of retrospective..." in the discussion section. I have provided two additional studies that addressed the rerporting of retrospective registraiton; (1) Hunter et al. (https://bmjopen.bmj.com/content/8/3/e019983?ijkey0206b507c137d7ae81e2386e29e563d3e9ef38f8&keytype2=tf_ipsecsha) and (2) Harriman et al. (https://pubmed.ncbi.nlm.nih.gov/27079379/). In acknowledging this addition, there should be four studies that previously quantified the reporting of retrospective.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Mr. Hiroyuki Taruno, Japanese Foundation For Cancer Research Cancer Institute Hospital

Comments to the Author:

This paper adequately addresses my points.

I believe this paper should be approved.

RE: Thank you for your positive feedback.

Reviewer: 1

Dr. Björn Oddens, Merck & Co Inc

Comments to the Author:

The reviewers' comments have been adequately addressed. Thank you!

RE: Thank you for your positive feedback.

Reviewer: 3

Mr. Mustafa Al-Durra, University of Toronto, University of Toronto

Comments to the Author:

The authors have provided an adequate response to all my review points.

A courtesy reminder to the authors to revise this statement "To our knowledge, two studies have previously quantified the reporting of retrospective..." in the discussion section.

I have provided two additional studies that addressed the rerporting of retrospective registraiton; (1) Hunter et al. (https://bmjopen.bmj.com/content/8/3/e019983?ijkey=0206b507c137d7ae81e2386e29e563d3e9ef38f8&keytype2=tf_ipsecsha) and (2) Harriman et al. (https://pubmed.ncbi.nlm.nih.gov/27079379/).

In acknowledging this addition, there should be four studies that previously quantified the reporting of retrospective.

RE: Thank you for your positive response. Regarding your reminder, we're happy to clarify: In response to your comment in the first review, we revised the manuscript text from "addressed the reporting…" to "quantified the reporting…". Hunter et al. conducted a survey of trialists of retrospectively registered studies, but did not extract reasons for retrospective registration provided in publications. Harriman et al. included an analysis of the timepoints of registration in relation to journal publication, i.e., if retrospective registrations occurred before or after journal submission. We include both studies in the discussion of reasons for retrospective registration, but not earlier, as none of the two studies quantify the reporting of retrospective registration in publications. We changed the text slightly to make this point clearer: "To our knowledge, two studies have previously quantified the transparent reporting of retrospective registration in journal publications."

Reviewer: 2

Competing interests of Reviewer: The content of this paper, including its author, is not in conflict of interest with mine.

Reviewer: 1

Competing interests of Reviewer: BJO is a paid employee and stock holder of Merck & Co, a pharmaceutical company

Reviewer: 3

Competing interests of Reviewer: NA