PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Characteristics and trends of clinical studies primarily sponsored by China in WHO primary registries between 2009 and 2018: A cross-sectional survey
AUTHORS	Xu, Yang; Dong, Min; Liu, Xuemei

VERSION 1 – REVIEW

REVIEWER	Simon Kolstoe University of Portsmouth UK I teach and conduct research into Integrity, Ethics and Governance processes. I chair a number of Research Ethics committees for UK government departments, and have conducted audits in collaboration with the UK Health Research Authority.
REVIEW RETURNED	23-Mar-2020

GENERAL COMMENTS	This is a fascinating review of Chinese trials outlining impressive growth in registrations over the last few years, but the paper is not really able to "...help us... better understand the current state of trials registration..." (p9, line 38 & 39). Likewise the main claim in the conclusion (p11 lines 48 & 29) that "Prospective registration has accounted (for) over half and continued to rise..." cannot be justified. This is because the methods chosen only reviews those trials that HAVE been registered, but has no way of identifying the overall number of trials that are being conducted and are NOT registered. To expand - the manuscript claims in a number of places that "63% of Chinese sponsored trials are registered prospectively", but I think this is in comparison to 37% registered retrospectively. As such there is no indication of what the total number of trials are, and thus total registration rates are likely to be significantly lower overall. Although the authors do mention this in section 4.5, they need to make this very clear throughout the manuscript. The interesting data here is not an increase in the proportion of trials registered (the authors have no way of measuring this) but rather the absolute increase in the number of trials registered - the authors need to make this very clear throughout, and especially caveat the 63% figure wherever it is mentioned. Another area that needs expanding is the definition of a clinical trial. It would be helpful to know whether there is Chinese legislation defining this, and whether registration is a legally required prerequisite for conducting some types of research (as it is in the EU). Also is there a specific definition as to what

	constitutes an "observational" clinical trial (as mentioned in section 2.1) - for instance who defines this? The text could do with some careful proof reading and copy-editing from a native English speaker, although on the whole is pretty good.

REVIEWER	Karmela Krleza-Jeric MedILS, IMPACT Observatory; Croatia and Canada
REVIEW RETURNED	01-Apr-2020

GENERAL COMMENTS	This is a very interesting and timely study. It can be expected that it will lead to more trial registration of clinical trials especially of Phase 2 and 3 trials sponsored by China, and more IPD sharing. Please find my comments in the attached file below. Pls note that beside my attached comments, the whole manuscript needs language editing. Karmela Krleza-Jeric.MD., M.Sc., D.Sc. MedILS - IMPACT Observatory Peer review of the manuscript: Yan Xu, Min Dong, Xuemei Liu. The clinical trials registry profile of China in a global context: Characteristics and trends of clinical trial registration primarily sponsored by Chinese institutions between 2009 and 2018, Submitted to BMJ Open Comments to authors This is a very interesting and timely study. It can be expected that it will lead to more trial registration of clinical trials especially of Phase 2 and 3 trials sponsored by China, and more IPD sharing. The connection you made btw the focus of registered trials and morbidity in China is particularly valuable. I suggest you indicate that important element of your study in the abstract, objectives and conclusion. Language editing of the whole manuscript is needed. Some sentences would merit to be broken in two; some are not clear, while some need basic editing. Example: Abstract/ Objectives: To analyse metrological . Example: Pg 4 line 4-6: the sentence starting with “We only recruited….” you probably mean that you analysed. Following are my detailed comments and suggestions Introduction Page 4 • Line 3-4: you state: ….and the registration of clinical trials in China is not compulsory at present…, while on page 9. 4.1. Trial activity, lines 56 and on you state: As for drug clinical trials sponsored or funded by Chinese industries, compulsory registration is required on CHINADRUGTRIALS platform. Please explain/ clarify. By the way I tried to visit this CHINADRUGTRIALS platform it seems to be in Chinese only. • Line 20: It is not clear what do you mean by stating that the concept of trial registration was established in 1997. Please verify, explain or edit. As far as I know, and we wrote

	about it, the call for trial registration was first issued by RJ Simes in 1986. Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol [Internet]. 1986 Oct [cited 2016 Jul 14];4(10):1529–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3760920 Since Simes' call for trial registration, the understanding of the importance of trial registration developed gradually. It took setting of few registries, analysing publication and reporting bias, and more. The next major push took place in 2004, following the New York against Glaxo, which inspired the ICMJE Clinical Trial Registration Statement, followed by the Ottawa statement and the development of the International standards for trial registration by the WHO. Etc. It might be useful for readers if you devote few sentences to history of trial registration and sharing of IPDs. You have it a bit here and there, but it might be good to give it in one place. • Line 43-44: remove the sentence: Clinical trial in this study means… Namely using the word "Clinical trial" to include both interventional and observational studies is confusing and incorrect. Clinical trials are interventional. Furthermore, your study seems to be about clinical trials (CTs) only: in the abstract you did not mention the inclusion of observational studies, only interventional ones ie CTs. Also, in your analysis and results you did not present any info about the registration of observational studies: you keep talking about the CTs, analyse them by phase and by disease (focus), and country/ies of recruitment. The term "clinical studies" includes both interventional studies (CTs) and observational studies, as you indicated in the first sentence in the & 2.1 .Clinical Trial data… (line 42). Page 5 • Line 26, 3.1. Trial activity: I suggest changing the title of this & to read: Trial registration dynamics, or Trial registration activity Page 6 • Line 50, 3.1.2. Distribution of country(ies)….: I suggest you list several more countries of China sponsored registered trials, not just China and USA; at least add Australia, Germany and Taiwan to be comparable with the list of countries for the global MCTS. Page 8 • Line 3, 3.1.3. Industry involvement … Please specify the industry: Namely it is not clear whether the industry involvement means involvement of China based industry or it also includes international companies esp when there is "some kind of industry involvement" and when combined with other sources of funding.

	The same &: line 9: “Over the decade, 14% of China sponsored” you probably mean: 14% of registered China sponsored…, if so please edit • Line 43, DATA NOTES under the Table 5: The type was defaulted to non-industry… “ I have a problem with this default. Unless you can explain the reason, I would rather see them in the non specified category or at least to provide the number/% within the nonindustry category. Also pls edit: I reckon that you wanted to say …non-industry in 135 entries if “primary sponsor”…. and not as primary sponsor • Line 48, 3.2.1. Health condition studied: Can you explain the reason of decreasing of number of trials studying certain health conditions? Page 8 and 9 • Page 8, Line 61, and page 9 line 1-7, 3.2.2, Phase of study: It is rather strange that there are many phase 4 trials and small % of phase 2, and 3. Analysing this phenomenon might be the topic of another study. Namely phase 4 trials study drugs that are in use/on the market, meaning that phase 2 and 3 had to be done previously. These numbers indicate that either phase 4 are analysing the drugs developed elsewhere and now in use in China or that phase 2 and 3 were not registered. The info what drug is analysed in each phase 4 trial might be available in the registry; if so, please provide as least for a sample of phase 4 trials. This is especially interesting in the context of the statement on page10, line 19 “in recent years China has strengthened the independent innovation”. Namely this might mean that a substantial number of Phase 2 and 3 might have been taking place in China but were not registered on ICRTP registries. Namely, on page 9, last paragraph (lines 56-on) you provide the number of industry funded trials as over 7300 and only 80 are also registered on ICRTP. If possible pls provide the number of China publicly funded trials and % registered. Page 9 • 3.3. Trial registration: suggest you change the title of this & to read : Trial registration and plan to share IPD • Line 12, 3.3.1 Prospective vs retrospective registration: can you provide any explanation why prospective trial registration rose so sharply in 2013? • Line 41, 4.1. Trial activity. I suggest that you change the title of the this & to read: Trial registration dynamics or Trial registration activity • Line 47 Please edit the sentence: After more then ten years of development, the number of China sponsored trials… to read: ,….: “After more then ten years of development, the number of registered China sponsored trials…. Namely I reckon that you talk about the number of registered China sponsored trials, not all

	China sponsored trials. Please edit the order of references: the reference 21 appears in the texts after the ref 22. • Line 55: thank you for citing one of our publications (24: Krleza-Jeric PloS med 2005), as indeed it informs trial registration discussion, as do few more that you might wish to consult, including Ottawa statement (all are open access) but we did not state in that paper that the main body of clinical research is universities and hospitals. I reckon that this reference is meant to be added to the 21-23 on line 27. OR the sentence should be edited to read something like: This is not surprising considering the resistance of industry to trial registration details as discussed in an earlier study (24). By the way, the main body of clin research is certainly done in universities and hospitals no matter who sponsors them. Line 58 over 7300 industry funded trials are registered in CHINADRUGTRIAL platform, out of which only 80 registered on ICRTP. Could this explain the low % of phases 2 and 3? Can you comment/provide the reason why are industry trials registered in that platform, and not on ChiCTR. Also, does this platform contain the same/similar info about trials, and is the information on this platform publicly accessible? Page 10 • Line 23, 4.2. Trial focus. Thank you for providing this interesting and important correlation. If possible, I suggest that you present this info on a graph/picture. • Line 24: I reckon you are talking about DALY in China, right? If so, please precise. • Line 49: 4.3 Trial Registration I would argue that WHO international standards and WHO/ICRTP are essential international enablers and triggered trial registration, supported by the ICMJE statements and I suggest and even suggested earlier to clarify that and provide the relevant refences as advised earlier (pls see my comments re page 4 above). Page 11 • Line10: … Please verify and edit the sentence Even in the highest year of 2006… You probably mean 2016, i.e. that the largest number of trialists indicated YES for IPD sharing in 2016 Line 35, 4.5. Limitations • Line 38-39: please clarify: why would inclusion of CHINADRUG TRIALs platform limit the level of comprehensive understanding…? • Line 41: Please clarify the compulsory part. Namely here you again state that the registration is not compulsory while you stated earlier that it was • Line 44: “official website” you mean ChiCTR? If so pls specify as it might confuse with

	CHINADRUGTRIALS that is also official albeit it seems it functions only within China. • Line 46, 5. Conclusions • Overall pls consider add conclusions on disease burden and focus of registered trials. Conclusions also need editing, for example: • Line 48: What do you mean by: prospective registration has accounted for over half…..half of what? Of all registered? • Line 49: edit the sentence: While there are… either by connecting it to the previous sentence with comma or start the sentence with However instead of while. • Line 49 and 50: The low number of MRCT and the low proportion of phase 2 and 3…The conclusion re phase 2 and 3 stands only if all publicly funded trials were registered. As we do not know the number of publicly funded China trials, and we do not know which proportion of these publicly funded trials are registered. If you do not have the numbers needed, consider editing to read: … the low proportion of registered 2 and phase 3 trials might implicate… • Line 53: Do you mean that the accessibility of Participant level data of China registered trials merits improvement?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Simon Kolstoe
Institution and Country:
University of Portsmouth
UK
Please state any competing interests or state 'None declared':
I teach and conduct research into Integrity, Ethics and Governance processes. I chair a number of Research Ethics committees for UK government departments, and have conducted audits in collaboration with the UK Health Research Authority.

Please leave your comments for the authors below

1. This is a fascinating review of Chinese trials outlining impressive growth in registrations over the last few years, but the paper is not really able to "...help us... better understand the current state of trials registration..." (p9, line 38 & 39). Likewise the main claim in the conclusion (p11 lines 48 & 29) that "Prospective registration has accounted (for) over half and continued to rise..." cannot be justified. This is because the methods chosen only reviews those trials that HAVE been registered, but has no way of identifying the overall number of trials that are being conducted and are NOT registered.

To expand - the manuscript claims in a number of places that "63% of Chinese sponsored trials are registered prospectively", but I think this is in comparison to 37% registered retrospectively. As such there is no indication of what the total number of trials are, and thus total registration rates are likely to

be significantly lower overall. Although the authors do mention this in section 4.5, they need to make this very clear throughout the manuscript. The interesting data here is not an increase in the proportion of trials registered (the authors have no way of measuring this) but rather the absolute increase in the number of trials registered - the authors need to make this very clear throughout, and especially caveat the 63% figure wherever it is mentioned.

Reply:Thank you for this important suggestion. This is the limitation of this study, and we mention this limitation in the limitation section of the paper. We have made it more clearly by adding 'registered' before every 'China sponsored studies'.

2. Another area that needs expanding is the definition of a clinical trial. It would be helpful to know whether there is Chinese legislation defining this, and whether registration is a legally required prerequisite for conducting some types of research (as it is in the EU). Also is there a specific definition as to what constitutes an "observational" clinical trial (as mentioned in section 2.1) - for instance who defines this?
Reply: A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials (also called interventional studies) and observational studies. And both interventional and observational studies can be registered on ICTRP source registries(https://www.who.int/ictrp/en/,https://www.clinicaltrials.gov/ct2/about-studies/learn#ClinicalTrials). Observational studies are also included in this study except for analyzing study phase. Using the word "Clinical trial" to include both interventional and observational studies is confusing. To avoid this confusion, we have changed almost all 'clinical trials' to 'clinical students'. The registration of clinical studies on ICTRP source registries in China is not compulsory at present. Industry drug clinical trials for new drug application in China are legally required registration on Platform for Registry and Publicity of Drug Clinical Trials in China (ChinaDrugTrials.org) run by Center for Drug Evaluation, National Medical Products Administration (NMPA). The types and scope of the trial resisted on ChinaDrugTrials.org are limited to the drug clinical trials for new drug application (including bioequivalence test, pharmacokinetics test, phase I-IV test, etc.) which have been approved by National Medical Products Administration (NMPA) and carried out in China. This study did not include trials registered on ChinaDrugTrials.org. For clinical studies conducted by academic research institutions in China, it is not compulsory to register clinical studies in public registries at present, although ICMJE requires the prospective registration of clinical trials as a condition for publication.

3. The text could do with some careful proof reading and copy-editing from a native English speaker, although on the whole is pretty good.

Reply: We have asked a native English speaking colleague's assistance on copy-editing.

Reviewer: 2 **Additional comments are attached to this email**

Reviewer Name: Karmela Krleza-Jeric
Institution and Country: MedILS, IMPACT Observatory; Croatia and Canada
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is a very interesting and timely study. It can be expected that it will lead to more trial registration of clinical trials especially of Phase 2 and 3 trials sponsored by China, and more IPD sharing.
Please find my comments in the attached file below. Pls note that beside my attached comments, the whole manuscript needs language editing.

Karmela Krleza-Jeric.MD., M.Sc., D.Sc. MedILS - IMPACT Observatory
Peer review of the manuscript: Yan Xu, Min Dong, Xuemei Liu. The clinical trials registry profile of China in a global context: Characteristics and trends of clinical trial registration primarily sponsored by Chinese institutions between 2009 and 2018, Submitted to BMJ Open
Comments to authors
This is a very interesting and timely study. It can be expected that it will lead to more trial registration of clinical trials especially of Phase 2 and 3 trials sponsored by China, and more IPD sharing.
The connection you made btw the focus of registered trials and morbidity in China is particularly valuable. I suggest you indicate that important element of your study in the abstract, objectives and conclusion.
Language editing of the whole manuscript is needed. Some sentences would merit to be broken in two; some are not clear, while some need basic editing. Example: Abstract/ Objectives: To analyse metrological . Example: Pg 4 line 4-6: the sentence starting with “We only recruited….” you probably mean that you analysed.
Following are my detailed comments and suggestions
Introduction
Page 4
? • Line 3-4: you state: ….and the registration of clinical trials in China is not compulsory at present…, while on page 9. 4.1. Trial activity, lines 56 and on you state: As for drug clinical trials sponsored or funded by Chinese industries, compulsory registration is required on CHINADRUGTRIALS platform. Please explain/ clarify.
By the way I tried to visit this CHINADRUGTRIALS platform it seems to be in Chinese only.

Reply: As for clinical trials for new drug application, it is compulsory to register and publicize information on Platform for Registry and Publicity of Drug Clinical Trials in China (website: www.chinadrugtrials.org.cn, abbreviated as ChinaDrugTrials.org) run by Center for Drug Evaluation, National Medical Products Administration (NMPA). Those clinical trials for new drug application are funded by pharmaceutical enterprises. There are 7,345 trials registered and publicized information on ChinaDrugTrials.org up to 2018, and only 75 trials were registered simultaneously on ICTRP source registries. ChinaDrugTrials.org is only in Chinese. The main purpose of this platform is to serve publicize the drug clinical trials of new drug applications.
For clinical studies conducted by academic research institutions in China, it is not compulsory to register clinical studies in public registries at present, although ICMJE requires the prospective registration of clinical trials as a condition for publication.
We revised the sentence to “the registration on ICTRP source registries is not compulsory in China at present, which would limit the level of comprehensive understanding of clinical trial in China, especially those trials for new drug application sponsored by industries.

• Line 20: It is not clear what do you mean by stating that the concept of trial registration was established in 1997. Please verify, explain or edit. As far as I know, and we wrote about it, the call for trial registration was first issued by RJ Simes in 1986. Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol [Internet]. 1986 Oct [cited 2016 Jul 14];4(10):1529–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3760920
Since Simes’ call for trial registration, the understanding of the importance of trial registration developed gradually. It took setting of few registries, analysing publication and reporting bias, and more. The next major push took place in 2004, following the New York against Glaxo, which inspired the ICMJE Clinical Trial Registration Statement, followed by the Ottawa statement and the development of the International standards for trial registration by the WHO. Etc.
It might be useful for readers if you devote few sentences to history of trial registration and sharing of IPDs. You have it a bit here and there, but it might be good to give it in one place.

Reply:.https://www.clinicaltrials.gov/ct2/about-site/history#CongressPassesLawFDAMA
1997: Congress Passes Law (FDAMA) Requiring Trial Registration
The first U.S. Federal law to require trial registration was the Food and Drug Administration Modernization Act of 1997 (FDAMA) (PDF). Section 113 of FDAMA (FDAMA 113) required the National Institutes of Health (NIH) to create a public information resource on certain clinical trials regulated by the Food and Drug Administration (FDA). Specifically, FDAMA 113 required that the registry include information about federally or privately funded clinical trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for patients with serious or life-threatening diseases or conditions. The information in the registry was intended for a wide audience, including individuals with serious or life-threatening diseases or conditions, members of the public, health care providers, and researchers.

We have re-written the introduction section and added a few sentences about the history of trial registration: In 1970, the United States formally proposed the concept of clinical trial registration to reduce the publication bias of clinical trial results. 4 In 1977, the American Cancer Institute launched the world's first clinical trial registry, the Cancer Clinical Trial Registry. In February 2000, ClinicalTrials.gov was launched by the United States FDA, the National Institutes of Health and the National Library of Medicine. The next major move forward took place in 2004, following the case of New York against Glaxo, which inspired the Clinical Trial Registration Statement by the International Council of Medical Journal Editors (ICMJE), followed by the Ottawa statement and the development of international standards for trial registration by the World Health Organization (WHO). 5 Subsequently, the United Kingdom, China, Japan, the Netherlands, Germany, Iran, Sri Lanka, South Korea and other countries launched clinical trial registration platforms. In 2007, the World Health Organization International Clinical Trial Research Portal (ICTRP) was launched to provide a searchable database containing the trial registration data sets provided by source registries around the world. An increasing number of clinical studies have been registered on ICTRP source registries worldwide.

? • Line 43-44: remove the sentence: Clinical trial in this study means… Namely using the word "Clinical trial" to include both interventional and observational studies is confusing and incorrect. Clinical trials are interventional. Furthermore, your study seems to be about clinical trials (CTs) only: in the abstract you did not mention the inclusion of observational studies, only interventional ones ie CTs. Also, in your analysis and results you did not present any info about the registration of observational studies: you keep talking about the CTs, analyse them by phase and by disease (focus), and country/ies of recruitment. The term "clinical studies" includes both interventional studies (CTs) and observational studies, as you indicated in the first sentence in the & 2.1 .Clinical Trial data… (line 42).

Reply: This sentence was inappropriate and was deleted. Both interventional studies and observational studies can be registered on ICTRP source registries, so observational studies are included for analysis in this study except for analysis of study phase. To avoid this confusion, we have changed almost all 'clinical trials' to 'clinical students'.

Page 5
? • Line 26, 3.1. Trial activity: I suggest changing the title of this & to read: Trial registration dynamics, or Trial registration activity
Reply: We changed the title to 'Trial registration activity'.

Page 6
? • Line 50, 3.1.2. Distribution of country(ies)….: I suggest you list several more countries of China sponsored registered trials, not just China and USA; at least add Australia, Germany and Taiwan to be comparable with the list of countries for the global MCTS.

Reply: We revised the sentence as: After China, the United States was the second most commonly cited country/region of recruitment for the registered trials sponsored by China, followed by Australia, Germany, and Taiwan (a province of China).

Page 8
? • Line 3, 3.1.3. Industry involvement … Please specify the industry: Namely it is not clear whether the industry involvement means involvement of China based industry or it also includes international companies esp when there is “some kind of industry involvement” and when combined with other sources of funding.

The same &: line 9: “Over the decade, 14% of China sponsored” you probably mean: 14% of registered China sponsored…, if so please edit

Reply: China sponsored trials can also be funded by global industry. Industrial institutions include China based industry and also global industry. If China sponsored trials were funded by industry, no matter China based industry or global industry, they had industry involvement.
China sponsored trials are all indicate registered China sponsored trials, we have revised it.

? • Line 43, DATA NOTES under the Table 5: The type was defaulted to non-industry… “ I have a problem with this default. Unless you can explain the reason, I would rather see them in the non specified category or at least to provide the number/% within the non-industry category. Also pls edit: I reckon that you wanted to say …non-industry in 135 entries if “primary sponsor”…. and not as primary sponsor

Reply: We checked the data again and identified 132 entries with absent ‘primary sponsor’ and ‘source support’ value, they were excluded from the analysis for industry involvement.

? • Line 48, 3.2.1. Health condition studied: Can you explain the reason of decreasing of number of trials studying certain health conditions?

Reply: With the total number of registrations increases, the trials targeted some specific diseases showed a downward trend as a proportion of clinical trials registered each year in spite of a rapidly growing absolute number.

Page 8 and 9
? • Page 8, Line 61, and page 9 line 1-7, 3.2.2, Phase of study: It is rather strange that there are many phase 4 trials and small % of phase 2, and 3. Analysing this phenomenon might be the topic of another study. Namely phase 4 trials study drugs that are in use/on the market, meaning that phase 2 and 3 had to be done previously. These numbers indicate that either phase 4 are analysing the drugs developed elsewhere and now in use in China or that phase 2 and 3 were not registered. The info what drug is analysed in each phase 4 trial might be available in the registry; if so, please provide as least for a sample of phase 4 trials.

This is especially interesting in the context of the statement on page10, line 19 “in recent years China has strengthened the independent innovation”. Namely this might mean that a substantial number of Phase 2 and 3 might have been taking place in China but were not registered on ICRTP registries. Namely, on page 9, last paragraph (lines 56-on) you provide the number of industry funded trials as over 7300 and only 80 are also registered on ICRTP.
If possible pls provide the number of China publicly funded trials and % registered.

Reply: For answering this question, we analysed phase of study for the drug trials registered on

ChinaDrugTrials.org as of December 2018 (Table 1), and found that bioavailibility test is the most common trial type (30.4%), followed by phase 1 trial (including phase 1/2 trial, 26.1%), phase 3 trial (including phase 3/4 trial, 19.7%), and phase 2 trial (including phase 2/3 trial, 15.2%). The trials in phase 2 and phase 3 together accounted 34.9%, which is also obviously lower than that proportion for global registrations (53%). These numbers might indicate that phase 4 trials are analysing the generics drugs or the drugs developed elsewhere and now in use in China. Bioequivalence tests are usually classified as phase 1 clinical trials or trials without specified phase. Both the high proportion of phase 4 trials in China sponsored trials registered on ICTRP source registries, and high proportion of bioequivalence tests on ChinaDrugTrials.org, might suggest lack of innovation capacity in clinical research and pharmaceutical industry.

Table 1: Phase of study for trials registered and publicized on ChinaDrugTrials.org as of December 2018
Date of first publicity Phase 1+1/2 Phase 2+2/3 Phase 3+3/4 Phase 4 Not specified Bioavailibility test Total
2013 88 96 69 36 51 340
2014 377 430 434 41 171 136 1,589
2015 299 187 243 44 64 104 941
2016 265 105 185 30 57 172 814
2017 352 139 236 29 70 578 1,404
2018 537 160 279 28 64 1,189 2,257
Total 1,918(26.1%) 1,117(15.2%) 1,446(19.7%) 172(2.3%) 462(6.3%) 2,230(30.4%) 7,345

Page 9
? • 3.3. Trial registration: suggest you change the title of this & to read : Trial registration and plan to share IPD
Reply:We change the title to ‘Trial registration status and plan to share IPD’

? • Line 12, 3.3.1 Prospective vs retrospective registration: can you provide any explanation why prospective trial registration rose so sharply in 2013?

Reply: I think it may be related to the sharply increase demand for publishing SCI academic articles by China’s institutions around 2013 year.

? • Line 41, 4.1. Trial activity. I suggest that you change the title of the this & to read: Trial registration dynamics or Trial registration activity
Reply:We changed the title to: Trial registration activity
? • Line 47 Please edit the sentence: After more then ten years of development, the number of China sponsored trials… to read: ,….: “After more then ten years of development, the number of registered China sponsored trials….

Namely I reckon that you talk about the number of registered China sponsored trials, not all China sponsored trials.
Please edit the order of references: the reference 21 appears in the texts after the ref 22.

Reply: We revised all China sponsored trials to registered China sponsored trials.
The reference was wrongly labeled and we have revised it.

? • Line 55: thank you for citing one of our publications (24: Krleza-Jeric PloS med 2005), as indeed it informs trial registration discussion, as do few more that you might wish to consult, including Ottawa statement (all are open access) but we did not state in that paper that the main body of clinical research is universities and hospitals. I reckon that this reference is meant to be added to the 21-23

on line 27. OR the sentence should be edited to read something like: This is not surprising considering the resistance of industry to trial registration details as discussed in an earlier study (24). By the way, the main body of clin research is certainly done in universities and hospitals no matter who sponsors them.

Reply: Thank you. We used the sentence and quote like this: This is not surprising considering the resistance of industry to trial registration details as discussed in an earlier study.24

Line 58 over 7300 industry funded trials are registered in CHINADRUGTRIAL platform, out of which only 80 registered on ICRTP. Could this explain the low % of phases 2 and 3? Can you comment/provide the reason why are industry trials registered in that platform, and not on ChiCTR. Also, does this platform contain the same/similar info about trials, and is the information on this platform publicly accessible?

Reply:As shown in Table 2 below, the phase 2 and phase 3 trials together accounted 34.9% in 7,345 trials registered on ChinaDrugTrials.org up to 2018, not considering the source of sponsor or funder. This proportion is a little higher than that of China sponsored trials registered on ICTRP source registries (30%). Industry trials for new drug application in China were registered on ChinaDrugTrials.org by legally requirement of Center for Drug Evaluation, NMPA. The trial registration by pharmaceutical enterprises is mainly based on the demand of new drug application, but not the demand of publishing academic papers. ChinaDrugTrials.org contains the same/similar information about trials in accordance with WHO requirements and international practices, and is also publicly accessible, but has not recognized by ICTRP and ICMJE.

Table 2: Main similarities and differences between two clinical trial registration platforms in China
ChiCTR ChinaDrugTrials.org
Launched year 2005 2013
Sponsor Led by a nonprofit organization: The Chinese Cochrane Center of West China Hospital Led by a government organization: Center for Drug Evaluation, National Medical Products Administration (NMPA)
Voluntary or Compulsory Voluntary registration; the requirements of ICMJE for clinical trial report Compulsory registration by government
Language Chinese and English Chinese
Scope of registration The types and scope of the trial are extensive, mainly registration of academic research subjects; drug clinical trials for new drug application are also included. Including trials for drugs, also non-drug trials such as surgical treatment, radiotherapy, behavioral therapy, etc. The trials are conducted mainly in China, also can be any other countrie or regions. The types and scope of the trial are limited to the drug clinical trials for new drug application (including bioequivalence test, pharmacokinetics test, phase I-IV test, etc.) which have been approved by Center for Drug Evaluation, National Medical Products Administration (NMPA) and carried out in China
Purpose For the purpose of information disclosure. ICMJE required relevant clinical trials must be registered on ICTRP source registries before they can be considered for acceptance. For the purposes of regulation and information disclosure. Cannot meet the needs of publishing reports (ChinaDrugTrials.org is not cooperate with ICMJE)
Funder type of registered trials 11% of trials register on ChiCTR had industry involvement Almost 100% of trials register on ChinaDrugTrials.org were funded by China based industry or global industry.

Page 10
? • Line 23, 4.2. Trial focus. Thank you for providing this interesting and important correlation. If possible, I suggest that you present this info on a graph/picture.

Reply:We presented it in a new graph/picture to show the yearly changes of proportion and total proportion of trials targeted some specific disease condition (Figure 1).
Figure 1. Top 15 conditions by number of registered China sponsored trials and their trends by proportion of registrations per year, 2009–2018 (N=31,853)

? • Line 24: I reckon you are talking about DALY in China, right? If so, please precise.
Reply: Yes, we have made it precise. “In China, among top 10 causes of disability-adjusted life years (DALYs) in 2017,”

? • Line 49: 4.3 Trial Registration I would argue that WHO international standards and WHO/ICRTP are essential international enablers and triggered trial registration, supported by the ICMJE statements and I suggest and even suggested earlier to clarify that and provide the relevant refences as advised earlier (pls see my comments re page 4 above).
Reply: We added a few sentences about the history of trial registration in the introduction part.
Page 11

? • Line10: … Please verify and edit the sentence Even in the highest year of 2006… You probably mean 2016, i.e. that the largest number of trialists indicated YES for IPD sharing in 2016

Reply: We have corrected 2006 to 2016.

Line 35, 4.5. Limitations
? • Line 38-39: please clarify: why would inclusion of CHINADRUG TRIALs platform limit the level of comprehensive understanding…?

Reply: We have revised the wrong sentence. ‘First, we only recruited ICTRP source registries and did not include trials registered on ChinaDrugTrials.org. This would limit the level of comprehensive understanding of clinical trials in China, especially those trials for new drug applications sponsored by industry.’

? • Line 41: Please clarify the compulsory part. Namely here you again state that the registration is not compulsory while you stated earlier that it was

Reply: For new drug application, it is compulsory required to register and publicize information on ChinaDrugTrials.org by Center for Drug Evaluation, National Medical Products Administration. Whereas the registration of clinical studies on ICTRP source registries is not compulsory in China at present. We have made it clear.

? • Line 44: “official website” you mean ChiCTR? If so pls specify as it might confuse with CHINADRUGTRIALS that is also official albeit it seems it functions only within China.
Reply: We revised the words: ‘website of primary registries’.

? • Line 46, 5. Conclusions
? • Overall pls consider add conclusions on disease burden and focus of registered trials.

Reply: We added disease

VERSION 2 – REVIEW

REVIEWER	Simon Kolstoe University of Portsmouth, UK I teach and conduct research into Integrity, Ethics and Governance processes. I chair a number of Research Ethics committees for UK government departments, and have conducted audits in collaboration with the UK Health Research Authority.
REVIEW RETURNED	23-Jun-2020

GENERAL COMMENTS	The authors have suitably addressed my earlier main methodological/reporting concerns by i) better defining a clinical trial and ii) making it much clearer that this manuscript is only describing registered trials and thus is not making any estimation of total registration rates. However the English could still be improved by closer proof reading.

REVIEWER	Karmela Krleza-Jeric MedILS, IMPACT Observatory, Croatia and Canada
REVIEW RETURNED	08-Jul-2020

GENERAL COMMENTS	Karmela Krleza-Jeric.MD., M.Sc., D.Sc. MedILS - IMPACT Observatory 2020-07-06 Peer review of the revised version of the manuscript: Yan Xu, Min Dong, Xuemei Liu. The clinical trials registry profile of China in a global context: Characteristics and trends of clinical trial registration primarily sponsored by Chinese institutions between 2009 and 2018, Submitted to BMJ Open as a revised version in June 2020. Comments to authors Thank you for revising the manuscript. This is much improved version and I have only few comments. As I already mentioned in the initial peer review this is a very interesting and timely study. It can be expected that it will lead to more registration of clinical trials, more IPD sharing and improving the quality information of registered studies. 1 Introduction Thank you for adding the history. Allow me to suggest few edits: Page 4 of 38 Line 13: suggest to add btw " National Library of Medicine.:' and the sentence that starts with 'The major move…: " that in the same year the ISRCTN was launched in the UK. If you wish to verify pls see: https://www.isrctn.com/page/about Actually you might even add this link either in text or as reference.. Line 20 add ref 2 after "…ICMJE…" to read "…ICMJE (2)…" Line 20: add the reference after" ….the Ottawa statement…."Here it is: Krleža-Jerić K., Chan A-W., Dickersin K., Sim I., Grimshaw J., Gluud C., Principles for international registration of protocol information and results from human trials of health-related interventions: Ottawa statement (part 1). BMJ. 330:956-958, 2005 (doi: 10.1136/bmj.330.7497.956) Line23: edit: remove the United Kingdom- The ISRCTN which is based in the UK, already existed; see comment above line 17. Actually you may wish to add Australia to the list of countries as ANZCRTR joined the WHO primary registries in 2007. By the way

	both ISRCTN and ClinicalTrials.gov participated in the development of the WHO International standards. Line 28: Suggest edit: between the sentence ending with "…worldwide." and the next one beginning with "As of January 2017.." insert the information that clinical trial registries gradually started registering observational studies. 3. Results: 3.1.1. Number of studies Please clarify: It is not clear from this text, from the Methods, and Tables 1 and 2, whether 478,261 registered studies worldwide (globally) include 32,557 studies sponsored by China's institutions. 3.1.2. Distribution of countries or regions of recruitment Please verify and edit, as necessary, by replacing the word "study" with "trials when appropriate. Namely as the story about Multiregional trials is about trials only it does not include observational studies. In that case …" accounting for 0.4% of registered"… refers to trials only. Also following sentence starting with " After China…." Seems to be about trials only. I therefore suggest that you replace the word "studies" with "trials". 3.3.2 Plan to share Individual Participant data You might wish to limit discussion on the IPD sharing to Clinical trials . 4.4. Registration quality: thank you for pointing to quality issues. It will inform all involved and it might be expected expect that it will lead to improvements of registration quality. 4.5 Limitations The last statement "In addition…" is in fact not a limitation of this study. It is rather the recommendation and as such it might better fit in Conclusions. One possibility is to finish the sentence at ChiCtr registration data and move the rest of the sentence, starting with "further…" to Conclusions. While moving it, you may wish to edit that sentence to read something like: comparisons of data in ICTRP and WHO Primary registries are needed to learn about eventual discrepancies.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Simon Kolstoe
Institution and Country: University of Portsmouth, UK
Please state any competing interests or state 'None declared':
I teach and conduct research into Integrity, Ethics and Governance processes. I chair a number of Research Ethics committees for UK government departments, and have conducted audits in collaboration with the UK Health Research Authority.

Please leave your comments for the authors below
The authors have suitably addressed my earlier main methodological/reporting concerns by i) better defining a clinical trial and ii) making it much clearer that this manuscript is only describing registered trials and thus is not making any estimation of total registration rates. However the English could still be improved by closer proof reading.
Reply: Thank you for your suggestion. We have got the language in the manuscript edited by American Journal Experts on last revision.

Reviewer: 2
Reviewer Name: Karmela Krleza-Jeric

Institution and Country: MedILS, IMPACT Observatory, Croatia and Canada
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Karmela Krleza-Jeric.MD., M.Sc., D.Sc.
MedILS - IMPACT Observatory
2020-07-06
Peer review of the revised version of the manuscript: Yan Xu, Min Dong, Xuemei Liu. The clinical trials registry profile of China in a global context: Characteristics and trends of clinical trial registration primarily sponsored by Chinese institutions between 2009 and 2018, Submitted to BMJ Open as a revised version in June 2020.
Comments to authors
Thank you for revising the manuscript. This is much improved version and I have only few comments. As I already mentioned in the initial peer review this is a very interesting and timely study. It can be expected that it will lead to more registration of clinical trials, more IPD sharing and improving the quality information of registered studies.

1 Introduction
Thank you for adding the history. Allow me to suggest few edits:
Page 4 of 38
Line 13: suggest to add btw " National Library of Medicine.:' and the sentence that starts with 'The major move…: " that in the same year the ISRCTN was launched in the UK.
If you wish to verify pls see: https://www.isrctn.com/page/about
Actually you might even add this link either in text or as reference..
Reply: Thank you for your correction. We added this sentence: "and that in the same year the International Standard Randomized Controlled Trial Number (ISRCTN) was launched in the UK."

Line 20 add ref 2 after "…ICMJE…" to read "…ICMJE (2)…"
Reply: We added the reference 2.

Line 20: add the reference after" ….the Ottawa statement…."Here it is:
Krleža-Jerić K., Chan A-W., Dickersin K., Sim I., Grimshaw J., Gluud C., Principles for international registration of protocol information and results from human trials of health-related interventions: Ottawa statement (part 1). BMJ. 330:956-958, 2005 (doi: 10.1136/bmj.330.7497.956)
Reply: Than you for your suggestion. We added this paper as reference 5.

Line23: edit: remove the United Kingdom- The ISRCTN which is based in the UK, already existed; see comment above line 17. Actually you may wish to add Australia to the list of countries as ANZCRTR joined the WHO primary registries in 2007. By the way both ISRCTN and ClinicalTrials.gov participated in the development of the WHO International standards.
Reply: We added Australia to the list of countries and removed the UK.

Line 28: Suggest edit: between the sentence ending with "…worldwide." and the next one beginning with "As of January 2017.." insert the information that clinical trial registries gradually started registering observational studies.
Reply: We added the sentence "and clinical trial registries gradually started registering observational studies." Meanwhile we added reference 8: Williams RJ, Tse T, Harlan WR, Zarin DA. Registration of observational studies: is it time?. CMAJ. 2010;182(15):1638-1642. DOI:10.1503/cmaj.092252

3. Results:
3.1.1. Number of studies
Please clarify: It is not clear from this text, from the Methods, and Tables 1 and 2, whether 478,261

registered studies worldwide (globally) include 32,557 studies sponsored by China's institutions.
Reply: We revised the sentence to "We identified 478,261 global registrations as of 31 December 2018, in which 32,557 registrations were primarily sponsored by China's institutions"

3.1.2. Distribution of countries or regions of recruitment
Please verify and edit, as necessary, by replacing the word "study" with "trials when appropriate. Namely as the story about Multiregional trials is about trials only it does not include observational studies. In that case …" accounting for 0.4% of registered"… refers to trials only. Also following sentence starting with " After China…." Seems to be about trials only. I therefore suggest that you replace the word "studies" with "trials".
Reply: The data used as the denominator covered all registered studies sponsored by China, so the word "studies" was not replaced with "trials" in the case of the sentence about proportions. In other cases the word "trials" was used when appropriate.

3.3.2 Plan to share Individual Participant data
You might wish to limit discussion on the IPD sharing to Clinical trials .
Reply: Yes, we replaced the word "study" with "trials" in this section when appropriate.

4.4. Registration quality: thank you for pointing to quality issues. It will inform all involved and it might be expected expect that it will lead to improvements of registration quality.
Reply: Thank you for your encouragement.

4.5 Limitations
The last statement "In addition…" is in fact not a limitation of this study. It is rather the recommendation and as such it might better fit in Conclusions. One possibility is to finish the sentence at ChiCtr registration data and move the rest of the sentence, starting with "further…" to Conclusions. While moving it, you may wish to edit that sentence to read something like: comparisons of data in ICTRP and WHO Primary registries are needed to learn about eventual discrepancies.
Reply: We added the sentence in the Conclusions as "Furthermore, comparisons of data in ICTRP and WHO primary registries are needed to learn about eventual discrepancies."

Your professional advice helped me a lot. Special thanks to you for your good comments, again.

VERSION 3 – REVIEW

REVIEWER	Karmela Krleza-Jeric MedILS, IMPACT Observatory, Croatia and Canada
REVIEW RETURNED	22-Aug-2020

GENERAL COMMENTS	Congratulations. Well done