Author’s response to reviews

Title: Scarce quality assurance documentation in major clinical trial registries for approved medicines used in post-marketing clinical trials

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"Scarce quality assurance documentation in major clinical trial registries for approved medicines used in post-marketing clinical trials"

Reviewer reports:

Reviewer #1: An interesting paper on an important but neglected subject.

Background

Reviewer 1 comment a/:

Suggest to refer to WHA 2017 definitions of medicine quality - substandard and falsified. Degraded are included in substandard category in these definitions

Author’s response to comment a/:

Author agrees with Reviewer that new definition has been reported since the WHA 2017. Substandard and Falsified (SF) medical products was adopted as new term with 3 categories of SF medicines.
The manuscript has been adjusted to integrate the new definitions (substandard medicines, unregistered/unlicensed medicines, and falsified medicines) as set in WHA 2017.

Reviewer 1 comment b/

the last sentence of the penultimate para of first page of Background seems incorrect. DRAs are also key for addressing falsified medicines

Author’s answer to comment b/:

Author agrees with the reviewer’s comment. Adjustment has been made, accordingly as seen bellow.

Previous wording: Although falsified medicines are addressed by law and security enforcement authorities, the latter two types of medicines are assessed by drug regulatory authorities (DRAs) based on criteria determining their quality as shown in Box I.

Current wording:

While solely falsified medicines are addressed by law and security enforcement authorities, all three type of SF medicines are assessed by drug regulatory authorities (DRAs) based on criteria determining their quality as shown in Box I.

Reviewer 1 comment c/

use of term ‘substandard quality’ is confusing in relation to the WHA 2017 substandard category - suggest to use the term substandard and falsified that is what reference 8 referred to

Author’s answer to comment c/:

Author agrees with Reviewer. ‘substandard quality’ is changed to ‘substandard medicines” throughout the manuscript.
Reviewer 1 comment d/

my understanding from reference 16 is that the clopidogrel was not used in 2007 as an IMP - it was thankfully detected before it could be used. Suggest to change.

Author’s answer to comment d/:

Author agrees with Reviewer’s comment. The manuscript has been adjusted, accordingly to clarify that the clopidogrel was in fact not used as an IMP. the new wording is as follow:

“Another report indicates that clopidogrel of brand Plavix which prevents heart attacks and strokes, could not be used in the US as an IMP comparator in 2007 after quality testing detected only 50-80% of the active ingredient in the product”.

Reviewer 1 comment e/

Page 7, line 32 - not clear to me who suggested this previously?

Author’s answer to comment e/:

On page 2 of the paper of Newton NN et al. (2015), it is noted that: “If drugs used in the trial were not manufactured in a country with an SRA or without such approval the researchers should provide independent chemical analysis results (including dissolution if appropriate), and the analytical methods and results should be given in the supplementary material.”

To our opinion, if a drug is manufactured in a country with SRA but without a registration by a SRA, product quality issues cannot be excluded since reports exist on quality defects of US-approved products of trusted and reputable global manufacturers.(ref: 26) A quality testing might therefore also be applicable for drugs manufactured in country with SRA but without a SRA-approval before their use in a trial.

However, to avoid misinterpretations by the reader, the author has amended the manuscript by deleting the wording: “In contrast to what was previously suggested”.
Reviewer 1 comment f/
I could not see mention of CONSORT guidelines - feel that they should be included

Author’s answer:
the manuscript is amended to integrate a statement on CONSORT guidelines.
“The CONSORT guidelines were followed for the reporting of this study.

Reviewer 1 comment “References”

Ref 18, 20, 21, 23 need a web page address

Author’s answer to comment “references”:
A web page for all references including 18, 20 22 (22 instead of 21), and 23 which are online available reports were added in the manuscript

Reviewer 1 comment on Box 1 –
should the product Lot Number be given too?

Author’s answer to Reviewer 1 comment on box 1:
Lot number is indeed an important aspect of factor determining the quality of a medicine. However, since the lot number is part of the packaging and it is described in the product label, the author assessed that an explicit mention of the lot number might not be relevant for Box 1.

Reviewer #1 comment on vaccine quality:
Should mention be made explicitly of vaccine quality for vaccine trials?
The author would like to have the opportunity to refer to the design of this study which assessed Clinical Trial registries irrespective of the pharmaceutical which was used as IMP. This manuscript therefore addresses all types of pharmaceuticals including vaccines. Hence, vaccines were not explicitly mentioned in this manuscript.

Reviewer #1 comment:

The paper could be shortened.

Author’s answer:

The manuscript was edited and shortened where possible.

Reviewer #2: This paper is a crucial piece for public health and is well written, easy to understand. The authors have discussed on a crucial issues found in Phase IV trials, based on a concrete assessment of CTR and I hope this paper will be largely communicated to advocate for a change in regulation.

Key messages are well written and understood and I have no major comment to make.

I only have one minor comment:

In the Background (second page) L11-13: 'in infants'

Author’s answer to Reviewer’s #2 comment: we have rewritten the sentence as follow: “… a clinical trial in Tanzanian infants”

Editor’s comments

In addition to the above comments from the peer reviewers, I would be grateful if you could address the following:
• In the last paragraph of your cover letter you state that an abstract of this research was approved by the WHO Collaborating Centre for Drug Policy and regulation of the University of Utrecht. And that the results were shared in the winter meeting of the UU-WHO held on the 9-10 January 2018. Please ensure that you have cited both the abstract if published and if the presentation was included in conference proceedings then this should also be cited.

Author’s answer:

The author would like to clarify that the WHO Collaborating Centre for Drug Policy and regulation of the University of Utrecht and the UU-WHO are a same institution. Although an abstract of this research was approved by the WHO-UU and shared at the WHO-UU winter meeting 2018, neither the abstract nor the presentation were made publicly available. Hence, a reference could not be provided in the manuscript.

• Please ensure the references are cited as per the guidance on the BMC Trials website. In particular please ensure all web links and URLs are included.

Author’s answer: the references have been updated, accordingly.

• Please remove the reference to BMJ policy under the competing interests section and update to BMC Trials.

Author’s answer:

“BMJ policy” was deleted and replaced by “BMC Trials” in the manuscript.

Additional

A specific mention was added to specific a shift in affiliation during the conduct of this research as follow:

“YJ Doua was affiliated to the Benelux Pharmacovigilance department, Janssen Global Medical Organisation of Johnson&Johnson as deputy Cluster safety team lead at the start of this research.”
He shifted later to the Janssen Infectious diseases and Vaccines, Crucell Holland BV in June 2018”.

Thank you, Joachim