14 November 2014
Joint response to public consultation

WHO Statement on Public Disclosure of Clinical Trial Results: A welcomed commitment on transparency but one that should capitalise on best practices

Comment Form: WHO Statement on Public Disclosure of Clinical Trial Results

Comment as individual or on behalf of agency or institution?:
On behalf of several non-governmental organisations.

Commenter's Name in Full, Title, Institution, City, Country, Tel., Email address:

- Ancel.la Santos; Policy advisor; ***Health Action International (HAI) Europe***; Overtoom 60/II 1054 HK Amsterdam, The Netherlands; ancel.la@haieurope.org
- Jörg Schaaber, President; ***International Society of Drug Bulletins (ISDB)***; August-Bebel-Str. 62, 33602 Bielefeld, Germany. president@isdbweb.org
- Pierre Chirac, Coordinator: ***Medicines in Europe Forum (MiEF)***; Prescrire 83 boulevard Voltaire 75 558 Paris Cedex 11, France
- Peter Gøtzsche, ***Nordic Cochrane Centre***; Copenhagen, Denmark; pcg@cochrane.dk
- Burcu Kilic, ***Public Citizen***; Washington, D.C., USA; bkilic@citizen.org

General comments:

● We **welcome** and **strongly support** this comprehensive WHO statement on public disclosure of clinical trial results. Granting public access to clinical trial results is a scientific, ethical, and moral responsibility.

● This WHO statement is particularly important in the current context of transparency, in which global standards are being set to support public disclosure of clinical data. This is in the interest of furthering science and protecting patients.

● We support the WHO position that the details of clinical trials are to be registered in a publicly available, freely accessible and searchable **clinical trial registry** before any clinical trial is initiated. We also agree that **updating** clinical trial registries is crucial, and insist that such registries should be user-friendly to maximise their potential.

● We also support the **proposal to set reporting timeframes** for clinical trial results. In addition to the reporting modality proposed by the WHO regarding publication in a **peer reviewed journal** within 18 months from the study completion, we recommend that **all outcomes are posted on an open registry** within 12 months and **all clinical trial data** are made publicly available (e.g. in the form of **clinical study reports**) within 30 months from the end of the trial. The WHO statement should capitalise on the significant advancements on data transparency that have been made in the European Union (EU) with the implementation of the new EU Regulation on clinical trials (Regulation (EU) No 536/2014). We also suggest **centralising the posting of results on the WHO clinical trial registry** to avoid results being split on several websites as proposed in the statement. In addition, we propose that public access to clinical trial data from **all past clinical trials** is ensured.

● In our specific comments, we also insist on the positive impact of public disclosure of clinical trial results to public health and provide evidence. A clear statement that clinical data cannot be considered commercially confidential information should be added.[1]

● The WHO should be the principal institution that sets global standards and encourage Member States to develop and implement mechanisms that ensure public access to clinical trial data. It would also be useful to **add a new section to the statement that lists best practices on data disclosure by different countries, medical journals and publishers** (e.g. requesting that the data are made publicly available as a condition for publishing an article). Such standards should include dissuasive sanctions for non-adherence to these standards.

Specific comments:

Locator **(Page & Line No or section heading, footnote number)**	**Comment**	**Suggested amendment to WHO's statement** **(our additions are in *ital. and bold*; our deletions are in ~~*ital., bold and crossed-out*~~)**	**Internal Use Only [blank]**
Page 1, lines 10-13	Publication bias, in which studies are selectively published depending on their results, as well as the selective non-reporting of results within published studies jeopardise evidence-based medicine and risk patients' safety. Reporting bias, a common phenomenon in biomedical literature, results in the overestimation of a treatment's benefits and the underestimation of its harms.[2] [3] [4]	However, concerns have been raised ~~***that there may be***~~ ***about widespread practices of*** selective publication of trials dependent on their results, with particular concern that trial results which may be viewed as "negative", are less likely to be submitted, or accepted, for publication in the scientific literature or made public in other ways. ***This results in an overestimation of an intervention's benefits and***	

[1] See for example, the EU Ombudsman's ruling in 2010 in a complaint over the EMA submitted by the Nordic Cochrane Centre (Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011;342:d2686).
[2] Dwan K, Altman DG, Arnaiz JA et al. Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. PLoS ONE, 3:8 (2008) http://www.plosone.org/article/
[3] McGauran N, Wieseler B, Kreis J et al. Reporting bias in medical research - a narrative review. *Trials* 11:37 (2010) http://www.trialsjournal.com/content/11/1/37
[4] Gøtzsche PC. Why we need easy access to all data from all clinical trials and how to accomplish it. Trials, 12:249 (2011) doi: 10.1186/1745-6215-12-249.

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	It has been found that one of the main reasons for the non-publication of negative studies is non-submission, rather than rejection by medical journals.[5]	***an underestimation of its harms.***[6] [7] [8]	
Page 1, line 18 (new sentence after 'Handler et al. 2013')	Publication bias and reporting bias are recurring practices in biomedical research.	***In fact, it is estimated that only half of all studies first presented as abstracts are published in full, and that positive outcomes are more likely to be published than negative results.***[9] [10]	
Page 1, line 25	Publishing only the summaries of the results of clinical trials can still result in selective reporting of study outcomes, where a medical treatment's benefits are overrated and its harms are downplayed. Full access to clinical trial data, including the study protocol, statistical methods used, detailed trial results -e.g. in the format of clinical study reports (CSR)- and anonymised patient data listings, is a prerequisite to rigorous systematic reviews. Independent reviews can bring additional knowledge about a medical treatment's effects and strengthen evidence-based medicine.	***As it has been demonstrated that published trial results are often unreliable, t~~T~~***here is an ethical imperative to report the ***study protocol and subsequent amendments, the statistical analysis plan and full*** results of all clinical trials***, including de-identified subject level data allowing other researchers to check the analyses.***	
Page 1, lines 26-28	Estimates indicate that there are 197,000 deaths per year in the EU from Adverse Drug Reactions (ADRs), representing the fifth most common cause of hospital death.[11] According to the Institute of Safe Medication	Furthermore poor allocation of resources for product development and financing of available interventions, and suboptimal regulatory and public health recommendations may occur where decisions are	

[5] See reference 2
[6] See reference 2
[7] See reference 3
[8] See reference 4
[9] Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database of Systematic Reviews,* 2:MR000005 (2007) doi:10.1002/14651858.MR000005.
[10] Song F, Parekh S, Hooper L et al. Dissemination and Publication of Research Findings: An Updated Review of Related Biases. *Health Technology Assessment*, 14:2 (2010) doi:10.3310/hta14080.
[11] Raine JM. PRAC's perspective on implementation: strengthening public health protection. Presentation at EMA's Seventh Stakeholders' forum on the implementation of the new pharmacovigilance legislation. September 27, 2013.

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	Practices, in the United States the number of annual deaths due to ADRs is 128,000.[12] To optimise public health outcomes, prescribers and patients must be able to make informed decisions on treatment. Many adverse reactions, including deaths, could be avoided if the general public knew more about adverse reactions and harms caused by pharmaceutical products and medical devices. For example, the inclusion of previously unpublished trial data in an independent meta-analysis of trials for *rosiglitazone* (Avandia°) was critical in demonstrating that its use was associated with a significant increase in the risk of myocardial infarction. The European Medicines Agency recommended the suspension of the marketing authorisation for *rosiglitazone* in September 2010.[13]	based on only a subset ***of all data and*** of all completed clinical trials. ***The lack of access to complete information on the true effects of pharmaceutical products and medical technologies puts patients' safety at risk and causes otherwise preventable harm.***	
Page 1, lines 30-31	To maximise their potential, trial registries must be user-friendly. Their use must also be promoted. New research shows that clinical trials registry searches are not regularly included in systematic reviews published in major medical journals. According to the study results, only 35% of authors used trial registries in their search strategy.[14] A routine use of trial registries can help to better identify	Before any clinical trial is initiated (at any Phase) its details are to be registered in a publicly available, free***ly*** ~~***to***~~ access***ible***, searchable ***and user-friendly (e.g. downloadable in multiple forms)*** clinical trial registry.	

[12] Moore TJ, Cohen MR, Furberg CD. QuarterWatch 2011 Quarter 4: FDA direct report rankings as risk index. 2012.
[13] European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. (Press release, EMA/585784/2010 September 23, 2010).
[14] Jones CW, Keil LG, Weaver MA et al. Clinical trials registries are under-utilized in the conduct of systematic reviews: a cross-sectional analysis. *Systematic Reviews*. 2014, 3:126.

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	publication bias and the selective reporting of trial results.		
Page 2, lines 38-52 (new paragraphs added. Proposal to replace modalities 1 and 2 by new points 1-5).	The newly adopted EU Regulation on clinical trials on medicinal products for human use[15] represents a significant advancement in data transparency. The Regulation requires clinical trial sponsors to publish: • The summary of results of all clinical trials conducted in the EU within 12 months from the end of the trial, accompanied by a summary written in a manner that is understandable to a layperson • Clinical study reports that are submitted for marketing authorisation within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application. The Regulation explicitly states that **clinical trial data should not be considered commercially confidential** once the procedure for granting the marketing authorisation has been completed, or the application withdrawn. This is aligned with previous findings of the **European Ombudsman**, according to which **trial protocols and clinical study reports are not commercially confidential information**.[16]	***Clinical trial data are of utmost importance to public health and thus, cannot be considered commercially confidential.*** ***Full*** clinical trial results are to be reported within 30 months of the study completion date as defined above. Reporting is to occur in ~~***BOTH of***~~ the following ~~***two***~~ ***five*** modalities: ~~***1. The main findings of clinical trials to be submitted for publication in a peer reviewed journal within 18 months of study completion and are to be published through an open access mechanism unless there is a specific reason why open access cannot be used, or otherwise made available publicly at most within 30 months of study completion.***~~ ***1. All outcomes are to be made publicly available within 12 months from the end of the trial by posting to the results section of the primary clinical trial registry and the WHO registry.*** ***2. All clinical trial data (e.g. in the form of clinical study reports or another comparable format in terms of details), even if not submitted for marketing authorisation, has to be made publicly***	

[15] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use. OJ L 158/1. Recital 68b and Article 37.

[16] European Ombudsman. Decision of the European Ombudsman closing his inquiry into complaint 2560/2007/BEH against the European Medicines Agency. November 24, 2010.

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	In addition, the EU is currently reviewing the regulatory framework for medical technologies. The European Parliament endorsed key pro transparency provisions to ensure public access to clinical study results.[17] [18] At a minimum, the WHO should take into account positive regulatory developments on clinical data transparency in the EU. As the foremost international organisation on public health, the WHO should always aim at setting best practices that maximise the public health interest.	***available within 30 months from the study completion on the primary registry and the WHO registry.*** ***3. Irrespective of point 2, clinical trial data submitted for marketing authorisation has to be made publicly available on the competing regulatory agency registry within 30 days after the decision-making process has been completed.*** ***4. The results of previously unpublished clinical trials have to be made publicly available at least in all primary registries within 2 years from the adoption of this WHO statement.*** ~~***2.In addition the key outcomes are to be made publicly available by posting to the results section of the primary clinical trial registry. Where a registry is used without a results database available, the results should be posted on a free-to-access, publicly available, searchable institutional website of the Regulatory Sponsor, Funder or Principal Investigator.***~~ ***5. The main findings of clinical trials should be submitted for publication in a peer reviewed journal within 18 months of the study completion***	

[17] Report on the proposal for a regulation of the European Parliament and of the Council on in vitro diagnostic medical devices (COM(2012)0541 – C7-0317/2012 – 2012/0267(COD)), Article 51.

[18] Report on the proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (COM(2012)0542 – C7-0318/2012 – 2012/0266(COD)) Article 53.

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		and be published through an open access mechanism. It is noted that journals such as Public Library of Science (PLoS) journals and Trials allow open access publication of the findings of all clinical trials without any prejudice against the publication of negative trials. These ***12,*** 18 ~~***month***~~ and 30 month timeframes represent the longest possible acceptable timeframe for reporting and shorter timeframes are strongly encouraged. It should be possible in most instances for reporting to occur in shorter timeframes.	
Page 3, lines 61-66	De-identified subject level data needs to be disclosed in ways that ensures subject confidentiality as well as the robustness of the data.	The benefit of sharing research data and the facilitation of research through ~~***greater***~~ access to primary datasets is a principle which WHO sees as important. ~~***This statement is not directed towards sharing of primary data. However***~~ WHO is actively engaged with multiple initiatives related to data sharing, and supports ~~***sharing***~~ ***disclosure*** of ~~***health research***~~ ***de-identified subject level data*** ~~***datasets whenever appropriat***~~ ***in ways that ensure subject confidentiality and the robustness of the data.*** WHO will continue to engage with partners in support of ~~***an enabling environment***~~ ***policies that*** ~~***to allow***~~ ***require the disclosure of de-identified subject level*** data **in order** ~~***sharing***~~ to maximise the value of health research data.	

About us

HAI Europe. Health Action International (HAI) Europe is a non-profit, European network of consumers, public interest NGOs, health care providers, academics, media and individuals working to increase access to essential medicines and improve their rational use through research excellence and evidence-based advocacy. More info: www.haieurope.org. Contact: ancel.la@haieurope.org

ISDB. The International Society of Drug Bulletins, founded in 1986, is a worldwide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently ISDB has around 80 members in 41 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org.

MiEF. The Medicines in Europe Forum (MiEF) was launched in March 2002 including more than 70 member organisations in 12 Member States, representing four key players on the health field, i.e. patient groups, family and consumer bodies, social security systems, and health professionals. It is a testament to the importance of European medicines policy. Medicines are not merely consumer goods, and the European Union represents an opportunity for European citizens to seek further guarantees of efficacy and safety. Contact: pierrechirac@aol.com

NCC. The Nordic Cochrane Centre is part of the Cochrane Collaboration, an international not-for-profit international network of more than 30,000 dedicated people from over 100 countries preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care. More information: www.cochrane.org. Contact: pcg@cochrane.dk

Public Citizen. Public Citizen is a public interest group based in the United States (U.S.), which has worked for over 40 years conducting research and advocacy aimed at ensuring consumer access to safe and effective drugs, medical devices, and other health products. More info: www.citizen.org. Contact: bkilic@citizen.org.