Response to the UK Parliamentary Committee to inquire into clinical trials and disclosure of data

Healthy Skepticism UK (HSUK) and Health Action International (HAI) Europe joint submission

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1. Healthy Skepticism UK and Health Action International (HAI) Europe value this opportunity to provide evidence why access to clinical trial results are of great importance to patients for the effective and safe use of medicines. For that reason, this response will focus only on the evidence in support of access to data and the practical means by which data disclosure can be introduced to facilitate the practice of evidence-based medicine and rational healthcare decisions.

2. What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?

2.1 The HRA is a very young organisation and our knowledge of it is limited to that which can be obtained from their publications. HSUK and HAI Europe strongly support the last point of HRA's vision statement: 'clinical trials get registered and research results get published'. In HRA's first annual report, it is stated that HRA has 'carried out a process review of the entire research project journey: from initial idea, development, funding, approval, conduct, compliance, inspection, publication and translation' (1), although there is no mention of the review findings. Therefore, we are unable to judge how effective HRA has been in achieving its aims.

2.2 The HRA seem to focus their efforts on the ethical involvement of patients in studies from the outset, analysing important issues such as the risk/benefit balance of participation, as well as communication and understanding between participants and researchers. HSUK and HAI Europe would argue that in order for studies to be ethical, the participants must be assured that the information obtained from their involvement will be used for the purpose outlined and furthers insight into treatments, whether viable or not. We would welcome more obvious work into this area.

3.1 What evidence is there that pharmaceutical companies withhold clinical trial data?

3.1.1 Clinical trial data can be withheld in many different ways. Besides the obvious withholding of information, as will be demonstrated below with the example of Oseltamivir, there are also more subtle and/or indirect means of restricting access to information. Examples of these are outlined clearly by the Cochrane handbook and reproduced below (2):

- Publication bias: The publication or non-publication of research findings, depending on the nature and direction of the results.
- Time lag bias: The rapid or delayed publication of research findings, depending on the nature and direction of the results.
- Multiple (duplicate) publication bias: The multiple or singular publication of research findings, depending on the nature and direction of the results.
- Location bias: The publication of research findings in journals with different ease of access or levels of indexing in standard databases, depending on the nature and direction of results.
- Citation bias: The citation or non-citation of research findings, depending on the nature and direction of the results.
- Language bias: The publication of research findings in a particular language, depending on the nature and direction of the results.
- Outcome reporting bias: The selective reporting of some outcomes but not others, depending on the nature and direction of the results.

3.1.2 The current medical research model encourages the dissemination of study results through publication in peer-reviewed journals – the gold standard of information accessibility in academia. However, the seven sources of bias outlined in the Cochrane handbook demonstrate that the information that is published in academic literature can not only misrepresent the actual results or conclusions of that study, but also skew the larger body of evidence. Scargle illustrates this point in his paper ‘Publication Bias: The “File-Drawer” Problem in Scientific Inference’ by stating that ‘apparently significant, but actually spurious, results can arise from publication bias, with only a modest number of unpublished studies’. (3)

3.1.3 Studies have investigated the phenomenon of publication bias and demonstrated that data is not published and therefore not accessible. Moreover, ssummaries and analyses of clinical trial data may be published in peer reviewed journals, but regardless of whether an article is published, much of the raw data is currently never made public. Scherer et al. (4) found that ‘only about half of all studies first presented as abstracts were published in full following presentation at meetings or publication as a summary report’ whilst Song et al. (5) furthered this by concluding that ‘positive trial data is twice as likely as negative trial data to be published’.

3.1.4 Examples of specific medicines demonstrate the above points:

3.1.4.1 Oseltamivir or Tamiflu, was purchased for thousands of pounds by the UK government

amid concerns about its effectiveness at easing influenza symptoms. The therapy was marketed by Roche in 2005 as being able to provide a '67 percent reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals' (6). Numerous requests for the raw data substantiating these claims from entities including the Cochrane review and the UK government, have been met with the answer 'The files appear to have been discarded' from the study authors and the statement "Following discussions with our medical teams both in the UK and Basel, unfortunately we are unable to send you the data requested as a similar meta-analysis is currently commencing with which there are concerns your request may conflict" from Roche (7). Despite the company's promise to publish the raw data in 2009, it is still unclear whether it has been made publicly available. Godlee of the British Medical Journal writes that 'there are at least 123 trials of oseltamivir and that most (60%) of the patient data from Roche's phase III completed treatment trials remain unpublished' (8). The sheer quantity of unpublished data illustrates the size of the problem of publication bias. Nonetheless, Oseltamivir is still used by thousands of patients in spite of the fact there is no publically available conclusive evidence of its efficacy.

3.1.4.2 Rosiglitazone is another example of a drug that demonstrates publication bias. First used in 1999 and originally developed to treat diabetes, Rosiglitazone, has since been shown to have serious adverse effects on the heart. In 2004, the manufacturer, GlaxoSmithKline, was obligated to publish all of the trial results by a court of law. Data from 35 of the 42 studies had remained unpublished until then (9).

3.2 What impact does this have on public health?

3.2.1 The current situation of limited access to a fraction of trials results, coupled with widespread promotional messages, ultimately drives prescribers and consumers to make choices based on inaccurate or unbalanced information. Poorly informed decisions lead to the increased risk of otherwise preventable adverse reactions and to the waste of public resources on inappropriate or unnecessary medicines. Worse yet, poorly informed treatment decisions lead to increased hospitalisation and the concomitant costs involved or even in death.

3.2.2 Without complete access to research results, further investigations into medicines of genuine therapeutic advance may be neglected. Greater trials data disclosure could ease unnecessary bottlenecks in research & development and reduce wasteful repetition of trials – all of which potentially delay the development of life-saving medicines.(17)

3.2.3 Trial data secrecy is an abuse of participants' trust that the risk they've taken contributes to medical advances. 'Most trial participants give consent to the risks involved in an experimental study under the assumption that they are making a contribution to science. If that study remains unpublished, their contribution is for nought' (4). Trials to investigate public health advances depend on patients, and if their contribution is kept secret, then patients' trust in trials and willingness to participate may one day be lost.

3.2.4 The increasing tendency to outsource clinical trials to low and middle income countries exacerbates the potential for vulnerable populations to be inadequately informed and protected. Cases documented by Nina Lakhani in the Independent demonstrate that trial participants from these countries (e.g., India) may not be empowered to give informed consent. (18)

3.2.4.1 Participants profiled by Lakhani were reported to be included in clinical studies despite their prior exposure to environmental toxins, making it nearly impossible to dissociate the effects

of the trial medicine with those of the patients' toxic exposure. Lakhani has stated that these trial medicines have since been approved to be marketed in Europe.

3.2.4.2 Unethical clinical testing is by definition unscientific medical research. Full access to the raw data at the patient level would enable regulatory authorities and public watchdogs to identify whether a medicine has been tested in unethical circumstances, for instance, when a medicine had been tested on vulnerable populations and if the participating patients had previous harmful exposures.

3.2.5 By withholding information, including the original methodology and raw data, the possibility to re-analyse study results is undermined. Several drug disasters illustrate why all results should be publicly available and trials should be followed up in the longer term. In one example, it took nearly one year to make the link between rare and unusual limb defects reported in children and the medicine Thalidomide. In a second example, evidence of adverse events such as heart attacks resulting after using the medicine Rofecoxib, Vioxx, was not reported in its entirety in peer-reviewed publications, according to a timeline by National Public Radio (NPR). NRP reports that research published in the Lancet estimates that "…88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died" (19). Access to all study data enabled timely, retroactive research that can establish links between therapies and adverse effects, and ultimately save lives.

4. How could the occurrence and results of clinical trials be made more open to scrutiny? And who should be responsible?

4.1There are two natural time points at which the disclosure of trials information could be introduced and effectively enforced, while limiting the administrative burden on trial sponsors and authorities.

4.2 Time point one: A study investigator or sponsor submits an application to the relevant body for approval to conduct a trial in the UK.

4.2.1 First, an accurate and complete record (i.e. list) of all clinical trials submitted for approval should be maintained on a publicly accessible website. Clinical trials registration is a prime example of such record keeping in which basic details of the study are recorded and made publicly accessible. Registration must be done at the point of application for approval (i.e. prior to decision) and before the first patient is recruited to participate in the trial.

4.2.2 Second, trial sponsors should submit a list of all known clinical trials already undertaken on the product to be tested and the clinical trial protocol for the study in question. This information can greatly reduce the number of so-called 'missing trials' whose occurrence has not been properly documented and whose study structure and results can not be independently analysed.

4.2.3 The EU Database foreseen in the EU Clinical Trials Regulation proposal is one potential EU-wide registry in which the above information could be submitted and published. The current proposal foresees that all data and information submitted by the applicant in the process of seeking approval to conduct a clinical trial would be contained in the EU Database, which is to be maintained by the European Commission. (10) Therefore, the disclosure of these additional documents would seem unlikely to impose a serious additional administrative burden, as a public submission portal is already foreseen in European legislation.

4.2.4 The EU Database would only be an effective registry if the information above is correctly and accurately recorded and published openly and in a timely manner in respect of the

principles in EU Regulation (EC) 1049/2001 on Access to Documents.(11) Evidence shows that even mandatory trial registration may not always be respected.(12) Therefore, the monitoring and enforcement of registration is an essential element of any trials register (see point 5).

4.2.5 Approval bodies should only review the trial application after the above criteria have been fulfilled and the relevant documents are publicly available to download from the EU Database. Approval bodies should also pro-actively publish on their website(s) the criteria by which trial applications will be evaluated.

4.3 Time point 2: Companies submit evidence from clinical trials in support of their market authorization applications to UK or European regulators. If authorised, the product may be marketed for the approved indication.

4.3.1 First, applicants should submit proof of trial registration in primary or partnered registry of the international clinical trials registry platform of the World Health Organization (13) for all evidence supporting its product. Regulators should only review applications that contain evidence from registered trials.

4.3.2 Second, applicants should submit a list of all known clinical trials already undertaken on the product. Products seeking market approval in Europe or the UK may not be the same as those tested in trials in the UK, therefore a list of all known clinical trials on a given product should be submitted at both time points (i.e. approval to test, approval to market). This requirement is a step towards ensuring the proper documentation of all trials conducted globally.

4.3.3 Third, applicants should submit both clinical study reports from trials supporting their application and the corresponding raw, anonyomised data at the patient level to the regulators.

4.3.4 All the above information should be proactively disclosed by the regulators on established, publicly-accessible websites they maintain. For example, technical adaptations to existing registries, such as the EU Clinical Trials Register, could enable the online publication of these documents.

4.3.5 Following the recommendations of the European Ombudsman (14), and in line with the EU Regulation on Access to Documents, the European Medicines Agency currently releases clinical study reports on request (15) and is in the process of developing a proactive publication policy for these and other documents (16). Yet, these trials only represent a fraction of all clinical trials taking place, some of which may not be used in a market authorisation application in the EU and therefore will not be in the Agency’s possession. Therefore, it is crucial that disclosure requirements be applied at both the point of approval to start a trial and the approval to market a medicine.

5. Can lessons about transparency and disclosure of clinical data be learnt from other countries?

5.1 Robust disclosure policies fall by the way-side without monitoring and enforcement mechanisms. In 2008, the Food and Drug Administration Amendments Acts (FDAAA) introduced mandatory rules whereby any drug that is already licensed by the FDA must publish the results of all their studies within one year of completion. A detailed study (12) of 738 trials that were subject to this legislation found that only 22% produced results within one year, the missing 78% of studies were conducted on drugs in use on humans and not produced within the time scale for open scrutiny. It was however an increase on those who were not subjected to the legislation, of which 10% produced their results within one year. Considering these results, fines

or anther means of liability for missing or incomplete registrations may be a useful penalty mechanism to ensure compliance.

This submission was compiled by:

Healthy Skepticism UK (HSUK) aims to improve health by reducing harm from inappropriate, misleading or unethical marketing of health products or services, especially misleading pharmaceutical promotion in the UK. In addition, we aim to support evidence-based health care, provided according to need, to optimal health outcomes in the UK. Both aims are equally important as misleading pharmaceutical promotion and non-evidence based-medicine can harm health and waste limited resources. www.healthyskepticismuk.com contact: ward.emily87@gmail.com

Declaration of interests: HSUK is a network of concerned and motivated health professionals and other interested individuals who work together to improve the health of the UK population. HSUK does not accept funding from the pharmaceutical industry.

Health Action International (HAI) is working towards a world where all people, especially those who are poor or marginalised, are able to exercise their human right to health. Our goal is to achieve universal and equitable access to affordable essential medicines of assured quality and to ensure that those medicines are used rationally to promote the highest standards of health throughout the world. www.haieurope.org contact: Katrina@HAIEurope.org

Declaration of interests: HAI is an independent global network of health, consumer and development organisations working to increase access to essential medicines and improve their rational use. HAI receives funding from public entities including the UK Department for International Development and the EU Health programme, as well as from non-profit, private foundations. A complete statement of HAI's income sources can be found online at: http://haieurope.org/wp-content/uploads/2012/08/List-of-donors-2006-2011.pdf HAI does not accept funding from the pharmaceutical industry.

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