Brussels, 4 April 2014
Joint Response

Clinical trial data disclosure protects the public from preventable harm

This consultation represents an opportunity for the IOM to develop guidelines for full transparency and access to clinical data held by drug regulatory authorities.

Public access to clinical trial data is particularly important to protect public health as it allows for independent analysis, enhancing knowledge about the real effects of medicines and allowing comparative effectiveness reviews.

We welcome the opportunity to contribute to the Institute of Medicine (IOM) consultation on the *Discussion Framework for Clinical Trial Data Sharing, Specific Topics for Public Feedback.*

In our response, we will first focus on the general principles underpinning the need for clinical data disclosure and then provide insight into aspects relating to privacy and confidentiality, unfounded claims of potential data misuse, as well as how to enhance incentives and measure impact.

At present, there is a lack of full public access to the body of available scientific evidence about the effects of medicines on human health. This undermines evidence-based medicine, hinders informed choice and leaves citizens at risk of otherwise preventable harm.

The above signatory organisations **encourage the IOM to commit to the active implementation of a data sharing policy that ensures full public access to clinical data** and puts public health ahead of commercial interests.

A consultation amidst a particularly sensitive context

During the legislative process for a new European Union Regulation on Clinical Trials, both the European Parliament's Committee on the Environment, Public Health and Food Safety (ENVI) and the EU Council, agreed to support a set of provisions that will significantly improve the transparency of clinical trial data. The new Regulation on Clinical Trials was adopted by the European Parliament's plenary session on 2 April 2014. Once the bill is implemented in the Europe Union from mid-

2016 onwards, not only will the summaries of the results of all trials be made publicly available - as it is already the case in the USA - but **clinical study reports (CSRs) will also be published** once a decision on marketing authorisation has been completed or the application has been withdrawn.

The agreed legal provisions are in line with the **EMA's 2010 policy on access to documents** and with the **European Medicines Agency's commitment towards the proactive publication of clinical trial data** (i).

During the current negotiations between the European Union and the United States of America on the Transatlantic Trade and Investment Partnership (TTIP), the pharmaceutical industry is advocating for uniform and far-reaching protection of commercial confidences and trade secrets, while seeking a levelling down of European transparency requirements (ii).

Against the backdrop of these developments and given the overarching structure brought by such a partnership agreement, **the IOM has the opportunity to take stock of the Clinical trials' regulation discussions and to support the advances made during the revision of the European Union's legislative framework on clinical trials**. In this response, we call on the IOM to recommend the adoption of **an ambitious US framework for open public access to clinical trial data and in line with the recent European transparency achievements**.

1. Access to clinical data (efficacy and safety data) protects public health from preventable harm

Public access to full clinical data, including raw data, is particularly important in **protecting public health** as it allows for **independent analysis**, enhancing knowledge about the real effects of medicines and **allowing comparative effectiveness reviews** (iii).

For instance, the identification of cardiovascular risks associated with *rosiglitazone* (Avandia°) in 2007 relied mostly on unpublished data (iv). Similarly, the review of previously unpublished data submitted to the FDA together with published summary-level data and research abstracts were used to demonstrate an increased risk of heart attacks among *rofecoxib* (formerly Vioxx°) users (v). In contrast, the manufacturer had sponsored several "ghost-written" articles in peer-reviewed publications. These articles contained errors in the presentation of cardiovascular events with *rofecoxib* (downplaying the cardiovascular risk), and were written for marketing purposes (vi) (a).

2. Clinical data is scientific data that belongs to the public, not to pharmaceutical companies

In Europe, the clinical data held by medicines regulatory authorities is related mainly to clinical trials conducted under the auspices of the World Medical Association's Declaration of Helsinki. The Declaration of Helsinki explicitly refers to the **ethical obligation** in disclosing the results derived from research and insists on the completeness and accuracy of such reports (articles 30 and 33) (vii). Moreover, science has to be reproducible and researchers are ethically obliged to write a report under any circumstances. The **reliability and reproducibility of research are two paramount principles in science**.

Patients taking part in clinical trials are willing to put themselves at risk in the hope that their participation will benefit society through the advancement of science (b).

Yet **science is hampered when data** from these studies **are never made public**, which is often the case especially when their results do not favour the sponsor's product- (a common practice in "negative" trials known as "publication bias" which leads to overrating a drug's benefits while underestimating its harms) (viii, ix). Since publication bias and the selective reporting of positive study results are widespread in biomedical research, (x) failure to make all the data available greatly diminishes the social value of research.

Moreover, industry-funded research often benefits from **publicly funded research bodies** (access to investigators and research teams at publicly research sites; public funding for basic research through government grants and state funding; public-private partnerships; etc.). It is therefore more than reasonable to expect that all data from biomedical research is made publicly available.

3. A precise and narrow definition of "commercial confidentiality" is needed

In line with the US Freedom of Information Act (FOIA), particularly in what concerns scientific data, **transparency should be applied by default.** If there is a claim that certain information is to be considered "commercially confidential", then companies must be required to provide detailed documentation that shows that the release of that information would truly harm their interests and that non-disclosure would not be detrimental to public health.

All data with a bearing on human health, notably clinical data, should, as a principle, be excluded from the definition of "commercial confidentiality". This includes, as a minimum, pre-market clinical trial data, post-market safety and

effectiveness data, as well as the sales volume (needed to assess exposure levels in adverse drug reactions). It is important to note that the European Ombudsman has conducted an assessment on the disclosure of clinical trial data and concluded that neither trial protocols nor Clinical Study Reports nor Periodic Safety Update reports (PSUR) contained information that could be classified as commercially confidential (xi) (c).

Any exception to disclosure should only involve the removal of specific elements of information within a document and never be applied to an entire section or certain types of documents.

4. Practical consideration: Patient confidentiality should not be used as a pretext to prevent clinical data disclosure

Specific topic: What measures should be deployed to minimize the privacy and confidentiality risks to trial participants? For example, are current anonymisation or de-identification methodologies sufficient?

According to good clinical practice, **patients' personal data** (identity, address, and other specific information allowing further identification) **are duly anonymised** (e.g. using codes or identification numbers) (xii). In order to allow re-analysis, anonymisation methods have to be applied so that patients' confidentiality is protected and data robustness is preserved.

A recent study published in *BMJ Open* confirms that clinical study reports (CSRs) contain only anonymised individual data (xiii). This is in line with previous findings from the European Ombudsman: "*Neither the requested documents nor other information in the public domain appeared to allow a link to be made between a given identification number and a particular patient, thus making it possible for him/her to be identified*" (xiv). Moreover, the European Medicines Agency has acknowledged that the applied **de-identification methods uphold the protection of participants' data**: *"there are established ways and means to anonymise data and protect patients from retroactive identification"* (1).

We agree with the IOM *Discussion Framework for Clinical Trial Data Sharing* statement that "*Individuals with rare conditions are among the underserved groups from which data sharing might accelerate research*". In very specific cases (i.e., rare diseases), when, after all available means, re-identification is possible, additional measures should be implemented to prevent this from occurring. Taking into account that rare diseases are often under-researched, it is all the more important to make sure that available scientific data is shared (xv). Lastly, it should be noted that a **mere hypothetical scenario cannot be invoked against the disclosure of**

anonymised patient-level data. "Unlikely to happen" events need to be weighed against the current situation, where millions of otherwise avoidable adverse drug reactions are occurring because anonymised data is not disclosed (xvi).

5. Mitigating Risks? Claims of data misuse and misinterpretation are unfounded

Specific topic: What might be done to minimize the risks to patients and to public health from the dissemination of findings from invalid analyses of shared clinical trial data?

Claims that the disclosure of clinical trial data would lead to the misinterpretation of data and to the dissemination of skewed information that would scare the public reflect **outdated paternalism** and are **not evidence-based**.

Proportionality in ethics has to be taken into account. There is overwhelming evidence of drug-induced harm being routinely hidden by pharmaceutical companies to the detriment of public health, while **there is no example of misinterpretation of data and misuse from the last 2.5 years during which the European Medicines Agency released clinical data on request.** There is no evidence of data manipulation as a result of data sharing/open data.

On the contrary, if data is publicly available, full scientific evaluation of any analysis is possible, and the reasons for differences between a primary and secondary analysis can be openly discussed. **Open science stimulates advances in methods.** Everyone is better protected against data manipulation when a climate of openness prevails.

The publication of anonymised individual-patient data is good research practice and in line with current developments. Indeed, in an attempt to promote transparency, **an increasing number of authors are publishing the anonymised individual-patient raw data along with the scientific article.** This is currently done on a voluntary basis but should apply to all clinical trials.

6. Enhancing incentives & measuring impact: following up the policy's implementation and tracking progress

Specific topic: What would be the appropriate measures to assess the usefulness of different models of clinical trial data sharing and how can they be used to guide improvements in data sharing practices?

The signatory organisations call upon the IOM to develop an ambitious *Open Access framework for clinical trial data sharing* and to **monitor the policy's implementation**

by publishing an annual report. This report should describe:

- Quantitative and qualitative information about documents accessed from the publicly available database managed by a competent authority;
- The information deemed commercially confidential information both quantitatively (numbers) and qualitatively (identifying section in documents);
- The data proactively shared online by the Agency during that given year;
- A list of the documents being withheld, including an abridged summary of their contents, when information is not being disclosed by the agency.

Specific topic: What incentives and protections might be established to encourage investigators to continue to conduct clinical trials in the future, without unduly restricting the sharing of certain types of data?

While the disclosure of clinical trial data should be an obligation for all marketing authorisation holders, we would encourage the IOM to develop guidelines to establish an incentive strategy to stimulate clinical trial sponsors and clinical investigators, such as a **Transparency Recognition system**, which acknowledges the most proactive and transparent pharmaceutical companies, and highlights others with persistent shortcomings in disclosure (that unduly classify documents as CCI in order to prevent access).

The IOM should propose guidelines to enact and enforce **financial sanctions when non-compliance of transparency measures occurs**. Whilst, the publication of clinical trial results is compulsory in the United States, unfortunately this provision is not complied with, nor respected (xvii). Therefore, financial sanctions must be sufficiently strong to deter clinical trials sponsors and investigators from not disclosing clinical trial data.

7. Beware of conflicts of interest

We would like to highlight that **by claiming ownership of clinical trial results, pharmaceutical companies are arguing for the right to keep secret information** that could harm their products' sales but **that if disclosed could also save lives and advance biomedical research** (e.g. making data of earlier trials available could avoid the repetition of similar trials, reduce harm and decrease both private and public expenditure). Bearing in mind this insurmountable conflict of interest, it is injudicious for the Institute of Medicine to accept having 17 pharmaceutical companies as study sponsors, as indicated in the consultation document (xviii).

Endorsing organisations

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 the pharmaceutical industry. Currently ISDB has about 80 members representing 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 and reaches 12 European Member States. It includes more than 70 member organisations representing the four key players on the health field, i.e. patient groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is unique in the history of the European Union and is testament to the importance of European medicines policy. Contact: pierrechirac@aol.com

TACD. The Transatlantic Consumer Dialogue (TACD) is a forum of US and EU consumer organisations which develops and agrees on joint consumer policy recommendations to the US government and European Union to promote the consumer interest in EU and US policy making. More information: www.tacd.org. Contact: tacd@consint.org or hammerstein.david3@gmail.com

Notes from the editor

a) Evidence that emerged during court proceedings in the United States has shown that the manufacturer had influence over all aspects, including data analysis, safety monitoring and reporting.

b) The World Health Organization's Informed Consent Form Template for Clinical Studies clearly states that benefits are to include: "benefits to the individual, benefits to the community in which the individual resides, and benefits to society as a whole as a result of finding an answer to the research question" . WHO Informed Consent Template Form. Available at: http://www.who.int/rpc/research_ethics/InformedConsent-clinicalstudies.doc

c) The Ombudsman concluded that Clinical Study Reports did not fall within the scope of the commercial interests exception. "It followed that their disclosure could not undermine commercial interests. Even if one were to assume that certain information contained in the requested documents could fall within the scope of the commercial interests exception, there appeared to be nothing to suggest that disclosure would specifically and actually undermine commercial interests."

d) See for example, one article published in the BMJ Open. The full data set was published in Dryad http://datadryad.org/resource/doi:10.5061/dryad.h435m/1

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