

# Points to Consider about Clinical trial data and transparency

January 2013

## Background information

### What is changing? Individual patient data to be publicly accessible

On 22/11 the European Medicines Agency (EMA) organised a conference with Gerhard Grill (representing the European Ombudsman), Giovanni Buttarelli (representing the European Data protection supervisor), Peter Gøtzsche (from the Cochrane collaboration), Ben Goldacre and Virginia Barbour (editors of medical journals), Susan Forda and Neil Weir (representing the European Federation of Pharmaceutical Industry Associations), and François Houyez (representing EURORDIS and all patients). The debates were moderated by Sir Mark Walport, currently Director of the Wellcome Trust, and who will start as UK Government Chief Scientific Adviser on 1 April 2013.

Since late 2010, the Agency has been releasing clinical-trial reports on request as part of its access-to-documents policy and is now working towards its goal of publishing clinical-trial data proactively for the medicines it has assessed. In his opening remarks, Guido Rasi, Executive Director of the EMA, explained that this decision is irreversible.

In the context of two appeals, Mr Nikiforos Diamandouros, the European Ombudsman, concluded in May 2010 that the Agency has to grant access to adverse drug reaction reports and clinical trial data, including the patient data from clinical trials submitted for the evaluation of the benefit/risk (marketing authorisation): this means not only the results of the trials, but also all individual patient data. The EMA therefore updated its transparency policy and in December 2010 the European Ombudsman applauded this revision (Press release no. 22/2010, 01 December 2010, <http://www.ombudsman.europa.eu/en/press/release.faces/en/5498/html.bookmark>).

Mr Nikiforos Diamandouros commented: "EMA plays a crucial role in the approval and monitoring of medicines placed on the market. Since its work has a direct impact on the health of European citizens, it is of utmost importance for EMA to give the widest possible access to documents and also to pursue a pro-active information policy for the benefit of citizens" as provided by EU transparency rules (Regulation 1049/2001).

As explained by Hans-Georg Eichler and other regulators "The potential benefits for public health of independent (re-)analysis of data are not disputed and, in an open society, trial sponsors and regulators do not have a monopoly on analysing and assessing drug"<sup>1</sup>.

<sup>1</sup> Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G (2012) Open Clinical Trial Data for All? A View from Regulators. PLoS Med 9(4): e1001202. doi:10.1371/journal.pmed.1001202



The panel discussion on YouTube can be found here:

<http://www.youtube.com/watch?v=upinaTryTho&feature=share&list=PL7K5dNgKnewYrjJQQSTTr2rdy3SlmxCdZ>

### **However, a number of policy and practical issues need to be resolved before this goal becomes a reality**

EURORDIS fully acknowledges the importance for regulators to access the full individual patient data, and for third parties to also access the data used to evaluate the medicines. The question is less whether this should be done, than how to do it the right way. For patients' organisations, the right way is the way that best respects the people who participate in clinical trials, without who no medical progress can be made. Clinical trial participants are voluntary research partners.

Questions that remain unaddressed:

- How to ensure patient safety is protected?
- In rare diseases, are the risks of breaching patient privacy greater?
- Who can have access to the data? And how?
- Should the data be stored in a database where everybody can have access, or should access be controlled to ensure that potential users are qualified to analyse the data?
- Should participants in clinical trials be informed? Should they specifically give their consent for third parties to access the data?

After consulting with Therapeutic Action Group and Drug Information Transparency and Access task force, and internal discussions with some patients' representatives involved in clinical trials, these are our points-to-consider and recommendations.

### **Benefit-risk of sharing/transferring data to third parties**

We certainly acknowledge the interest of different experts having a second look at the same data. An example is provided by the public hearings organised by the Food and Drug Administration (FDA) where both the marketing authorisation applicant and the FDA experts conduct their analyses of the trial patients' data. For example the subjects' disposition can differ, participants can be re-included in the analysis when they were excluded and should not have been. It makes sense to verify the accuracy of the analysis based on all data. It can only benefit all concerned.

The first set of risks involve data privacy.

### **Different diseases, different opinions**

In rare diseases, parents often testify that when one, two, three or more of their children born with a rare disease, live with the disease, die with the disease, and no or little research has been conducted, then these parents may have the feeling of a "huge waste": waste of body tissues that could have been bio-banked for future research, waste of data that could have been collected for a research team to investigate on the disease. Patients with rare diseases are eager to share their data, their information, with anyone willing to express interest to conduct research on the disease, to discover more about the natural evolution, genes, and to analyse collected data etc. The desire for visibility and recognition is such that patients with rare diseases are



*advocating for Centres of Expertise to be created. Research is the priority, even if this can mean less data protection.*

*In other diseases, such as HIV/AIDS, the context is very different, and the opinion of the patients may differ. People living with HIV, for example, asked their medical departments to stop using any kind of “Infectious department Hospital” stamp on their documents such as sick leaves etc. Stigma is so strong vis-à-vis HIV infection and AIDS that people living with the virus insist that their data are fully protected. As opposed to patients living with a rare disease, attempts to create specialised centres for HIV/AIDS in European hospitals have been turned down by patients’ organisations. Here, research is also a priority, but not to the detriment of data protection.*

*The French national database DMI2 is another illustration: it aimed at including all HIV patients visiting hospitals but in fact it is not 100% exhaustive. In particular, patients with no legal documents, and even more, patients whose profession is in computer science often refuse to consent and to be in the database. They do not trust that confidentiality will be respected.*

*As we can see, different diseases carry different stigma, different risks when data protection is not ensured, and different opinions.*

### ***Some risks are greater than data protection breach.***

*There is nothing worse, from the communication point of view, than when different “authorities” or “official circles” communicate completely diverging information to the public.*

*The situation regarding the communication with genetically modified organisms (GMO) and research is an illustration of what should not happen with clinical trials: whenever a team publishes a study results, another team that has access to the data may apply a different statistical method, sometimes not appropriate, and publish different results. They emphasize the fact that their analysis was conducted independently from the industry, as opposed to the other team. The average reader cannot distinguish between statistical method A or B and cannot make up their mind on whether or not it is accurate. But the reader can understand that one team was funded by industry, and the other one was not, and often this is all that the reader remembers. Is this helpful for society?*

*We do not want to end up in a similar situation with the results of clinical trials. The proposal for a Regulation on clinical trials states that the scientific and ethical review of protocols should evaluate the anticipated benefits and also the risks and inconvenience for the subjects. If patient data are to become accessible to other parties than the trial team, then the risk of discrepancies and any confusion around the results need to be mentioned. The consent form should inform the potential trial subject about this risk. If the potential participant refuses to take this risk, then he/she can refuse to take part in the trial.*

### ***Avoid confusion; avoid miscommunication***

*The risk is not just theoretical. There are precedents.*



*From 1988 to 1993, the Medical Research Council in the UK and the Agence Nationale de Recherches sur Le Sida in France conducted the Concorde trial<sup>2</sup>, a multicentre collaborating trial with 35 centres, 3 year-duration, and 1739 patients. After analysis of the results, academics and the Marketing Authorisation Holder diverged on the conclusions, and communicated their positions without reaching an agreement. To add to the confusion, the general press communicated a third version of the trial results, largely wrong. Patients, among them those who participated in the Concorde trial, were puzzled, confused, and finally, harmed. The public place is not the best forum for scientific controversies to be discussed.*

*When a team of physicists working at CERN hit a snag - a staggering extent of a particle moving faster than light - they wrote an article to share their findings with other scientists. Having understood that media coverage might become important, scientific institutions took the precaution to warn journalists, giving them all the information in advance, allowing them to contact other scientists. The result was generally good, journalists published articles which were balanced, and concluded them with the following warning: "The results shall only be considered as reliable when confirmed by independent experiments". In fact the measurement resulted from a subtle mechanical problem, thus demonstrating the correctness of this approach.*

*What we would like to recommend:*

- *As done for the access to individual patient data in the EudraVigilance database<sup>3</sup>, any third party interested to use the patient data from a specific clinical trial should request access to the data from the European Medicines Agency "study protocols of research organisations will be subject to prior review by the Agency";*
- *With this request, the third party should explain the purpose (meta-analysis, counter-analysis..) and the proposed analytic method;*
- *The third party should explain how it protects data privacy;*
- *The third party should disclose any financial interest in relation with the sponsor(s) of the trial;*
- *The third party should demonstrate having the necessary expertise and qualification to conduct the proposed analysis;*
- *The third party should agree to disclose their results first with the EMA (a public hearing may be proposed) before going public;*
- *Failure to adhere to these principles would lead the third party in question to be blacklisted for future access to clinical trial data;*
- *If patient data are to be disclosed to third parties, a probation period for the implementation of this policy of 3 or 5 years could be proposed to evaluate the impact of the disclosure;*
- *Clinical trials consent forms should mention the possibility that individual data are shared with third parties, beyond the research team;*
- *Explicit consent to share data with third parties should be obtained prior to the release of such data to third parties in question;*

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<sup>2</sup> Sébastien Dalgarrondo « Savoir thérapeutique et logique commerciale » *Annales. Histoire, Sciences Sociales* 2/2007 (62e année), p. 299-326. URL : [www.cairn.info/revue-annaes-2007-2-page-299.htm](http://www.cairn.info/revue-annaes-2007-2-page-299.htm).

<sup>3</sup> EudraVigilance access policy for medicines for human use  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2011/07/WC500108538.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108538.pdf)



- *For past trials, where the consent did not include the information on the possibility to share individual data with third parties, and where it is no longer possible to obtain the explicit consent, then data should not be released.*

### ***Patient data protection is an obsession: yet, double standards, two sets of rules.***

*Clinical trials are intensively regulated and patient protection at large is ensured, risks are rather limited. In social media and/or medical applications that are more and more frequently used by the patients to report on their health status, data protection seems to be completely absent: you can appear online, seen by any visitor, with a photograph of your face, family name, diagnosis, prognosis, treatment, etc. It is assumed that by using these sites or applications the user is, de facto, consenting to the terms of use. However it is quite certain that no information is provided regarding the risks. This is a domain where data protection no longer exists and action is needed.*

*Most Terms of Services of social media are long and contain legal jargon only lawyers are supposed to understand. An initiative to be mentioned is “Unhosted”, a movement to create web apps that give users control over their valuable user data and privacy, since “I have read and agree to the Terms” is the biggest lie on the web”. This is where the biggest threat to data protection currently lies.*

### ***Conclusion***

*The working relations established since 1996 with the European Medicines Agency, where patients and consumers can witness all internal scientific processes, raise issues, dialogue with experts, be members of scientific committees and management boards, comment on the agency governance, make their voices heard, review documents intended for the public, contribute to guidelines, operating procedures, participate in the decision making, ensure greater trust and transparency in the medicines regulatory process, at the European level. This has benefited patients and public health, represents progress. This is also a model we recommend for research organisations willing to access our individual data: we hope this will provide an opportunity to establish similar working relations, for transparency purpose and in the interest of public health.*

*People who participate in clinical trials, healthy volunteers or patients, condemn attempts to label them as passive subjects, which implies helplessness, and dependence upon others. Researchers on the involvement of patients in clinical research showed that “patients do not see themselves as passive research subjects but feel they made an active contribution<sup>4</sup>”. Clinical trial participants are research partners, and one underlying condition for a successful partnership is mutual respect. Respect no longer exists when participants realise that things other than what they consented to are being done without their agreement, or even without them being informed.*

*Yet research participants do not have many opportunities to “keep control” on what is being done. This is, for example, illustrated by the agreement with the ANRS, the French research agency for HIV/AIDS: for all trials, the trial participant information must mention not only the volume of blood taken at each blood test, but also the number of tubes and their size, to make sure no additional tubes are collected, for other purposes than the research in question.*

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<sup>4</sup> Kerrison S, Laws S, Cane M, Thompson A. The patient's experience of being a human subject. *JRSM* 2008;101(8):416.



*In most cases volunteers will consent: compared to all patients, trial volunteers are active patients, almost militant activists. To them, medical progress is important, and they are more likely to accept some risks (e.g. data disclosure).*

*Recommendations already exist in different but not so distant domains, e.g. the International Society of Pharmacoepidemiology ISPE entitled “Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health”, 1 September 1997, amended 19 August 1998, see appendix 1, and could be applied here (see also <http://www.pharmacoepi.org/resources/privacy.cfm>).*

*For internal use only:*

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## Appendix 1: Principles for protecting data privacy

These principles are taken from a report prepared at the request of the US Secretary of Health and Human Services. The report was delivered in May, 1997 by Dr. William W. Lowrance as background for public policy discussions relating to US and international data privacy legislation, policy and practice. The International Society for Pharmacoepidemiology (ISPE) endorses these principles, and insofar as they do not conform with the existing legal situation in different countries, ISPE encourages the revision of existing laws.

"The following principles are recommended for organizations that conduct, sponsor, or regulate health research involving personally identifiable data. They can be transposed into professional guidelines, standard operating principles, regulations, or laws. Criteria and procedures should be established that are specific to the context.

"Overall in health research, cultivate an atmosphere of respect for the privacy of the people whose health experience is being studied.

- Collect or use personally identifiable data only if the research is worthwhile and identifiability is required for scientific reasons.
- Urge Institutional Review Boards and other ethics review bodies to become fully engaged with the privacy, confidentiality, and security aspects of subject protection, in secondary research on data as well as in direct experimentation.
- Respect such standard fair-use practices as announcing the existence of data collections, allowing data-subjects to review data about themselves, and the like. If for scientific reasons exceptions have to be made to normal practice, this should be discussed as part of the informed consent process before the study starts.
- Attend sensitively to informing data-subjects and gaining informed consent.
- Safeguard personal identifiers as close to the point of original data collection as possible.
- Enforce a policy of "No access to personally identifiable information" as the default--then base exceptional access on need-to-know.
- Generally limit the cordon-of-access to personally identifiable data. Allow access for formally justified research uses and to appropriate researchers. Maintain and monitor access "audit trails."
- Remove data-subjects' personal identifiability as thoroughly as is compatible with research needs. If key-coding, aggregating, or otherwise removing personally identifying information, do so with adequate rigor.
- Maintain proper physical safeguards and cybersecurity measures. Periodically challenge them, to test their adequacy.
- Develop policies on seeking or allowing secondary use of personally identifiable data, and on the associated conditions and safeguards.
- Before either (a) transferring data to other researchers or organizations, or (b) using data for new purposes, make conscientious decisions as to whether to proceed and what the privacy protections should be. Then if proceeding, implement appropriate protections.
- Sensitize, train, and certify all personnel who handle personally identifiable data or supervise those who do. Make data stewardship responsibilities clear. Maintain internal and external accountability."

Reference: Privacy and Health Research: A Report to the US Secretary of Health and Human Services from William W. Lowrance. May, 1997. (Web site: <http://aspe.hhs.gov/datacncl/phr.htm>)

