Report on the EMA Workshop on clinical trial data and transparency

Susan Bhatti

Regulatory Affairs and Medical Writing, Premier Research Germany Ltd, Darmstadt, Germany

Correspondence to:

Susan Bhatti
Executive Director
European Regulatory Affairs and Medical Writing
Premier Research Germany Ltd
Europaplatz 5
64293 Darmstadt
Germany
Susan.Bhatti@premier-research.com

Abstract

Access to patient data gathered in clinical trials is a highly controversial and complex issue that needs to balance three aspects: the public right to transparency regarding data used to approve new medicines, protection of the data privacy rights of patients involved in the studies, and commercial confidentiality concerns of the trial sponsors. In response to an increasing number of formal complaints about restrictive practices in publicising clinical data, the European Medicines Agency has started an initiative to enable access to patient-level study data. In November 2012, they organised a workshop to bring the stakeholders together to discuss and establish the way forward.

Keywords: Clinical trials, Data access, European Medicines Agency, Data protection

In November 2012, the European Medicines Agency (EMA) hosted a workshop to discuss how data collected during clinical trials should be made available to the public. The Agency clearly stated at the beginning of the workshop that it is committed to making patient-level clinical trial data publically available following the decision on marketing authorisation, irrespective of whether the decision is positive or negative, with the goal of increasing transparency and thus confidence in the system for approving new medicines in Europe. The aim of the EMA workshop was to create a dialogue among representatives from health agencies, data protection institutions, the pharmaceutical industry, academia, the press, physicians, patient groups, and other stakeholders on *how* public access to clinical trial data can be implemented.

What led up to the workshop

Discussions on the right of access to clinical trial data were initially triggered by complaints to the Office of the European Ombudsman about the EMA refusing to grant access to documents in the possession of the Agency. Four main reasons were given for the EMA's refusal:

- TRIPS agreement[1]
- Disproportionate effort required to prepare and release documents for publication and disclosure
- Data protection issues
- Commercial interest prevailing unless outweighed by public interest

The Agency was unable to convincingly show that the first three arguments were valid, and they also failed to establish the existence of a specific commercial interest that would be undermined by disclosure of the data concerned. Therefore, the EMA agreed to grant access to the documentation.

In his introduction Gerhard Grill (Director of the of the European Ombudsman office) pointed out that the Treaty of Lisbon has now extended the right of public access to information to all EU institutions, including the Medicines Agency. The treaty stipulates that the widest possible access should be granted, that exceptions should be interpreted strictly, and that justification must be provided. (As a side note, legal action against the EMA has recently been taken by some of the companies involved.)

Differing perceptions of the evaluation of clinical trial data

During the meeting, it became clear that there is considerable discrepancy between how academic research institutions, the press, and the pharmaceutical industry perceive the evaluation of clinical trial data used in the marketing authorisation process. Although the meeting was set up as a workshop, in some aspects, it resembled a public hearing: panel members from academia (Peter Gøtzsche) and the press (Virginia Barbour and Ben Goldacre) presented the prosecution

DOI: 10.1179/2047480613Z.000000000104

case that industry is withholding and manipulating clinical data in order to coerce the regulators into approving new medicines, while industry representatives (Susan Forda and Neil Wier) filled the role of defendants and a patient representative (François Houÿez) acted as expert witness.

Peter Gøtzsche, Director of the Nordic Cochrane Centre and cofounder of Cochrane Collaboration, kicked off the discussion. He stated that because the pharmaceutical industry is acting as judge of its own data collected in clinical trials this results in bias in the data analysis. He believes that access to both results and raw data should be available to everyone and anyone for re-analysis. Even when access is currently granted to documents in possession of the Agency, it is not available in electronic and searchable form. As the data are provided freely by patients, it belongs to all of us and industry must be obliged to provide access so that it can easily be re-evaluated by others. Gøtzsche propounded that the third biggest cause of death in USA is the harmful effects of drugs and that this is partly because we do not know what harm many drugs can cause because data analysis is inadequate. He demanded open access to clinical data for everybody and publishing of data on a public website.

Industry was represented on the panel by Susan Forda, Chair of the European Federation of Pharmaceutical Industries and Association (EFPIA) Scientific, Regulatory Manufacturing Policy Committee, and Neil Wier, who sits on the EFPIA's Research Directors Group and is also Senior Vice President of Discovery at UCB Pharma. Wier pointed out that the pharmaceutical industry is now looking to develop personalised medicines and so future clinical trials will include patients' genetic information, increasing data confidentiality issues. He also pointed out that new products must yield an appropriate commercial return on investment. Forda agreed that public access to clinical data is important, but this should be handled on a case-by-case basis with consideration of intellectual property rights and personal data. She was not in favour of making clinical data available for products where applications are withdrawn or product development is cancelled. In her view, an appropriate and balanced approach to data access is required to protect the legitimate interest of the trial sponsors.

Ben Goldacre gave a typically emotive speech on how public engagement in clinical research in his view can only be positive and that having many eyes perform assessment of safety and efficacy of medicines would be beneficial. He called for industry to meet all requests to release data on clinical trials, which should be publicly available to academia and competitors alike, with a public record of all such requests. He cited a UK general practitioners research database that enables doctors to access the full health records of 3 million patients as a valuable tool for physicians. He does not see patient data protection issues as an insurmountable hurdle. He also called for full details of study protocols to be publically posted, as there is not enough detail in current trial registries. He pointed out that not all studies on medicines are posted on the clinical trial databases and said that all trials for all drugs should be made public.

Not surprisingly, Chief Editor of PLoS Medicine, Virginia Barbour, stated that clinical research data should be published to ensure it is reliable and reproducible. Suppression of research results should be combatted and technology used to enable transparency. Subject data that support a successful marketing authorisation application should be made publicly available at the time the authorisation is granted and in the longer term data from unsuccessful applications should also be made available. To enable reproducibility, the data and the analysis must be made available in such a way that others can reassess the data, so data must be stored in a readily accessible format, with datasets and links to specific protocols. Anonymisation standards are required to protect the personal data of trial participants. She also thinks that funding and incentives are required to enable data access, which could be in a separate repository or an independent web-portal.

Interestingly, François Houÿez, representing patient organisations, described his experience of collaboration between patient groups and the EMA as being very open and positive. He thought that FDA hearings are a good model for enabling transparency in the decision-making process for drug approval and that something similar might be worth considering in Europe. With regard to data privacy, he perceived that while some patients may be willing to forgo data privacy rules if it can benefit future generations (e.g. for rare diseases in children), they are greatly concerned about access to individual data in areas like transmittable diseases or those with social stigma (e.g. HIV patients). He does not support data access for everyone, because, in his view, uncontrolled reanalysis of data can also lead to confusion and undue concern, citing the situation with research on genetically modified organisms, where contradictory evaluation of data has resulted in less rather than more transparency about the real risks. Houÿez suggested that third parties wishing to have access to data must be required to state the purpose and need for access, to describe the analytical methods to be used, demonstrate the necessary expertise to

perform such analyses, and ensure that the data will be adequately protected. Results of such reanalysis should then be disclosed to the EMA before being made public. In his view, if clinical data are to be shared with any third parties, this needs to be clearly stated in the informed consent form provided to the patients.

With regard to adequate data protection of subjects involved in clinical trials, Giovanni Buttarelli, Assistant European Data Protection Supervisor, pointed out that data protection is not incompatible with full transparency, but the fundamental rights of patients must be respected. The intention is to allow access to full data sets for interested parties, but what is covered by the notion of 'public interest' in this context must be determined, and as a general rule, sensitive data on individual patients may not be published. If access is restricted to selected groups or individuals via a platform, it is critical to identify who has access and when, as well as who controls access and their level of competency, i.e. would the EMA be the only competent body to decide on data access or should someone else be involved?

Is there a risk of bad analysis of data?

Interestingly, the only consensus within the panel was in response to the question asked by Chairman Mark Walport '*Is there a risk of bad analysis of data*?' All agreed that there is, although Gøtzsche commented that 'the argument about bad analysis is a bit amusing, as the situation cannot be worse than it is today where the only people who have seen all the data are the people working in the company that is going to earn a lot of money from these products'. Weir responded that clinical experts are almost always involved in the evaluation of the data; however, Gøtzsche denied this, stating, 'Clinical investigators are never allowed to see all the data, if they ask for the raw data they are turned down every time'.

What is in the public interest as far as disclosure of clinical data is concerned?

Responding to the question, '*What is in the public interest as far as disclosure of clinical data is concerned*?' Houÿez sympathised with groups who express an interest to see the patient data but pointed out there is an ethical problem if you do not know who has access to the data. In his view patients 'would feel safer if those who do the secondary analysis or look at the data are clearly identified and have the skills and come with a method to analyse the data'. He suggested that an independent body could review the request and decide on whether to grant access to the data. Barbour replied that flaws in the patient consent forms cause problems with access to data and this can be avoided using correct wording in the form. She did not agree that who can access the data should be pre-specified, stating, 'it is much better to have many eyes on data than few eyes'.

In Goldacre's view, the trust placed by patients in the trial sponsor is often misplaced since 'the main analyses conducted by the trialists themselves are often flawed'. He remarked that 'we know that people very commonly, for example, switch their primary outcome between protocol and analysis without even adequately declaring that' and added 'we know that the results of clinical trials are often not disclosed to doctors and patients'. On the issue that patients should prospectively consent before sharing the clinical data, he pointed out that this would prevent access to data from trials that have already been conducted and delay transparency for at least 5 years. In his view, 'the problem of bad analysis is best solved by requiring fully published protocols and analytic strategies from everybody before they start'. With regard to peer review of secondary analyses, he did not think that journals are the best place to publish clinical trials. Secondary analysis should, however, only be regarded as evaluable if the analysis plan is published beforehand.

How are we going to minimise the potential harm to a population from data being published that is wrong or misinterpreted?

The next question, posed by Mark Walport, was '*How are we going to minimise the potential harm to a population from data being published that is wrong or misinterpreted?*'

According to Gøtzsche, 'primary publications are by and large pretty unreliable, and have cost the lives of hundreds of thousands of people … We need to be much more open about this – it's very simple'. Forda suggested that a 'Good Practice of Analysis' should be implemented along with a public forum where the analysis plan can be published and reviewed by others before the analysis is conducted, as this would help to minimise harm. She recommended that third parties who want to do analyses approach the companies directly for data and publicly post this request. Ben Goldacre remarked, 'we have an on-going reality, right now, of bad quality analyses by industry and academics of their own data'. He believes

that fixing this requires public posting of protocols and public sharing of data so that everybody can cross-check everybody else's work. 'We fix this by making sure that primary and secondary data analyses are both conducted as transparently and properly as possible'. In Barbour's view 'by sharing data and by sharing analyses, people do much smarter things than the original investigators ever thought of, and that is the democratisation of data that I think we want to see'.

Houÿez commented that if his organisation wishes to reanalyse data then they approach the person conducting the study and confront them before going public with the data, and he thinks this is a model that could be applied. The EMA will soon have public hearings on safety and therapeutic benefits of product, which would provide a public arena for different results to be confronted. He noted the risks of confusion among the public and miscommunication as well as disclosure of information that can identify patients. For him, it is important to discuss on a case-by-case basis which data-sets can be made public. 'The problem is that when privacy is breached, it is done and then you cannot recall the information – it is released and any harm which is done is done'. Mark Walport agreed that any data released must maximise the privacy of the trial participants and Giovanni Buttarelli commented that a new data protection package is soon to be released in the EU, although it will keep the current definition of what is personal data.

Practical suggestions as to how to share data

Forda agreed that, in principle, the data can be made available but warned that inappropriate analysis could lead to media scare stories that lead doctors to stop prescribing beneficial products (think Measles, Mumps, Rubella vaccine scare). 'If we're going to have additional analyses, these should be somehow prospectively defined and they should be reviewed, and people should have an opportunity to comment'. Gøtzsche, though, could not see immense practical problems with making data available and was not in favour of requiring a declaration of the purpose of the reanalysis. Goldacre repeated his previous comment, 'there is currently a serious problem of misleading analyses already by industry on their own trials, so this is an existing problem that needs to be addressed'. At worst, he would be happy with a two-tier system where the public can access data held by the EMA and any newer data can be requested from the company. Everybody's requests and all rejections should be posted in public immediately.

Barbour suggested that incentives are required for drug companies to provide data access and emphasised that the data must be made available in an open-access format so that it is readable using automated systems, otherwise we will not be much further forward. Houÿez commented that there are already opportunities to invite additional experts to EMA meetings when applications are being reviewed, so this could be an opportunity to invite external parties to review the data as well. Neil Weir's final comment was the need to consider who bears the costs of making data publicly accessible, as the translation of data into searchable form is not trivial and it is not a trivial cost.

Concluding the workshop, Hans-Georg Eichler (EMA) invited stakeholders to collaborate with the Agency to develop policies in five different areas:

- Protecting patient confidentiality
- Clinical-trial data formats
- Rules of engagement
- Good analysis practice
- Legal aspects

The EMA has committed to publish a draft policy on data access for public consultation by 30 June 2013 and to have the final version implemented by January 2014 – so watch this space!

References

1. TRIPs Agreement: Agreement on Trade-Related Aspects of Intellectual Property Rights. The TRIPS Agreement is Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994. Available from: http://www.wto.org

Author information

Susan Bhatti has worked in regulatory affairs for over 15 years and spent the past 6 years in clinical research, where she is involved in setting up and obtaining approval for clinical studies throughout Europe. Discussions with Ethics Committees in connection with data collected during clinical trials and the need for adequate data protection for patients are part of her daily work.