More transparency for clinical trial data

The decision by the European Medicines Agency to make clinical trial reports publicly available could provide a boon for biomedical research

Philip Hunter

The reporting of the results of clinical drug trials follows the current trend in publishing towards more transparency and open access after the European Medicines Agency (EMA) brought into force a policy to proactively publish clinical trial reports on any drug that receives marketing approval in the European Union (EU) on 1 October 2014. EMA is the first major regulatory agency to take a significant step towards full transparency for the processes involved in developing and approving medicines. The new policy will make it easier for academic institutions to reanalyse data from previous trials or compare data from different ones as part of their research into new possibly unrelated therapies. EMA also plans to extend this policy to medical devices and diagnostic tests.

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The move is the culmination of developments that took place during the past decade or more. It included various well-published misdemeanours of major pharmaceutical companies, the effect of which has been increasing pressure to clean up their act and improve their public image. Not all companies have embraced EMA's move, however. During the public consultations over the past 2 years, two pharmaceutical companies, AbbVie and Intermune, sought and obtained

injunctions to prevent EMA from releasing clinical trial data about their drugs, specifically the former's anti-inflammatory drug Humira and the latter's Esbriet (pirfenidone) for treating idiopathic pulmonary fibrosis. This resistance was heavily criticised by clinical trial openness advocates such as AllTrials (<http://www.alltrials.net/>); at different times during 2013, both withdrew their legal challenge, which cleared the way for EMA's new policy of publishing such data whether or not there is a request.

EMA's commitment to proactive publication of clinical data has itself helped persuade the big pharma companies to bend with the winds of change rather than fight a futile rear-guard action such as AbbVie and Intermune, according to its Executive Director Guido Rasi. “When we announced in 2012 that we would commit to the proactive publication of clinical data, the Agency spurred a broad debate worldwide”, he said. “I welcome this debate, which has led in my view to certain stakeholders shifting their position towards greater transparency. In fact, since then we have witnessed that a number of pharmaceutical companies and the organisations representing them have made their own proposals and set up their own schemes to grant access to clinical data on their medicines”.

While denying that they have been influenced specifically by the EMA's new policy, major pharma companies have come out in support of the objectives. “Roche welcomes the move towards greater transparency in clinical trial data publication”, said Sabine Atzor, Head of EU Regulatory Policies at Swiss based F. Hoffmann-La Roche. “Overall

we believe that researchers and industry can benefit from data transparency through learning from each other in the ultimate interest of patients and society”. Roche announced its own clinical trial data sharing policy in 2013 and began making Clinical Study Reports (CSRs) and other summary reports available upon request. “In addition, in January 2014 we began making analysable patient-level datasets available via the shared multi-sponsor portal (www.clinical-studydatarequest.com)”, Atzor added.

Meanwhile, the reputation of pharma giant GlaxoSmithKline (GSK) with data transparency advocates has been transformed after the company has taken a leadership position in embracing data sharing and openness. According to Ben Goldacre, co-founder of the AllTrials campaign, GSK has done far more than simply promising to share information on its own drugs, by “showing leadership, and formally recognising that transparency matters for patient care, at a time when others in the industry are hoping the issue can be dodged”.

Goldacre added that GSK has actually been shining a torch for the EMA, which, he argues, has made too many concessions to the pharma industry: provisions that allow companies to withhold certain data deemed to be commercially sensitive and insufficiently protected by patents, which could, for example, be information on a particular assay to assess the activity of a target drug. The results from the assay would be released but not the technique itself. Critics argue that such information might be necessary to repeat an experiment, but Peter Bogaert, managing partner of the legal firm Covington & Burling, argues that these measures are reasonable. “It is obvious that

providing full access to all data that were submitted with a marketing authorisation application, to the public at large, including actual or potential competitors, can undermine the commercial interests of the pharmaceutical company involved”, said Bogaert, who represents pharmaceutical companies. The EU legislation on access to information recognises that access should be refused when it would undermine the protection of commercial interests including intellectual property rights, but adds that access may in certain cases still be warranted when there is an “overriding public interest”, he added. “This illustrates that this is always a balancing exercise and this can, for instance, also include the application of terms of use that can restrict the use of the information that is made available. In my experience, the EMA has been very careful in trying to strike the balance correctly and I have not seen signs where the agency would have deviated from this by giving way to industry pressures”.

Yet, GSK itself now argues that commercial confidentiality is something of a red herring when it comes to publication of clinical trial data. “We believe there will rarely be commercially confidential information in CSRs for authorised medicines”, said David Daley, GSK’s Director for Global External Communications. “As we’re providing access to data after a medicine has been approved or its development terminated, we believe risks to negatively impacting innovation through a detrimental effect on intellectual property are minimal”.

Notwithstanding details about commercially sensitive data, the real problem for granting unfettered access to clinical trial data is patient confidentiality. EMA and other regulatory bodies were still struggling over how to strike the balance between patients’ rights to privacy or anonymity of their data and the needs of researchers to have access to it, according to François Houyez, who currently leads the *Drug Information, Transparency and Access* task force at EURORDIS, a European non-governmental alliance of patient organisations and individuals involved in rare diseases. “We have difficulties finding the right balance between protection and sharing data between researchers as patients themselves exhibit contradictory behaviour”, said Houyez, who pioneered patient advocacy at the EMA before joining EURORDIS in 2003.

On the one hand, people were keen to ensure that data, tissues and genetic information from relatives or loved ones who had died are widely available for research. On the other hand, many people complain if information about their own or a relative’s condition becomes publicly available as a result of inadequate data security. “They don’t want that information put say in a transparent envelope where it can be seen by a neighbour or a post person, even when it is freely available on the Internet and not at all anonymized”, explained Houyez.

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The minimum requirement to make health and biological data anonymous is removing those names, addresses and other individual identifiers, along with other information that might enable a patient’s identity to be determined. The latter might include textual narrative data detailing a patient’s medical history, including treatments prescribed, outcomes and perhaps adverse reactions, which could in principle be correlated with other sources of information to yield a patient’s identity. Complete transformation therefore removes all association between a trial participant and the clinical data generated in the trial. Anonymised data might just lack names, addresses and identifiers.

Yet, loss of such contextual information can significantly diminish the value of the data for research, for even knowledge of the postcode where a patient lived can be useful for analysis. Goldacre argues that scientists who perform epidemiological studies at population levels have been involved in anonymising data for years, and so the techniques are already there, but this ignores the fact that more sophisticated tools and techniques are now available for probing data sets. The only remedy may be, as Houyez indicated, to give researchers access to data that have been only lightly anonymised rather than heavily transformed, upon special request. This issue is more acute for studies involving rare diseases, which may

only affect a handful of patients in a given region or even a whole country, making it harder to provide robust protection against re-identification. The same applies to a lesser extent for studies of medical devices, which tend to be smaller than full phase 3 drug trials.

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Another related issue is the risk of public confusion and trust when two or more study groups come to radically different conclusions about the results of clinical trial data that are published in respected journals. That has happened in the past, but it would be more likely with open access, especially to individual data. “The danger here is that patients will lose trust in clinical research if different teams find different results”, said Houyez. “So the whole process of accessing data needs to be defined in a way that prevents that happening. For that reason we are very interested by the concept of Safe Harbour”.

Safe Harbour would be an independent repository for past and present clinical trial data and may include research protocols to ensure that contradictory results are in some way reconciled before being published. “One provision could be to require a second study team to discuss further with the first study team in the event they come up with completely different results, before creating controversy”, said Houyez. “We are not open to completely open access to data with no rules or regulations”.

The idea of Safe Harbour does raise a number of issues though, such as who will decide on requests for access and how to avoid unconstructive controversies without imposing constraints on innovation and academic freedom. For these reasons, EMA only provides access to clinical reports for now and not personalised data. To be able to handle the latter, EMA will require the legal powers to back up its recommendations comparable to the US Food and Drug Administration (FDA). “The new EMA policy will

serve as a useful complementary tool ahead of the implementation of the new EU Clinical Trials Regulation that will come into force not before May 2016", noted Rasi. "The Clinical Trials Regulation provides, for the first time, a direct legal basis for the release of clinical trial results. It is foreseen that under the new legal provisions, the first clinical reports will become publically available not before 2019/2020".

This will also include improved access to other important sources of study data, according to Roche's Atzor. "We will certainly see more transparency in other fields, such as medical devices and in vitro diagnostics", he said. "New legislation in the EU is under way which will establish transparency provisions similar to those for medicines". Atzor also highlighted the importance of other data sources that are not fully accessible to researchers. "This includes information from registries and real world data. It is important to establish that these data can be used in the interest of science and ultimately the patients. However, this should only happen while ensuring patient integrity and their right to decide on the use of their data".

Meanwhile, the FDA is also examining how to improve its transparency rules. While the EMA may be first to introduce proactive access to clinical study data, the FDA has long conducted its own analyses of trial data through its Data Monitoring Committees (DMCs), the role of which is to monitor whether studies are conducted safely from the perspective of participants. DMCs, comprising FDA statisticians and medical experts, also help to ensure that studies remain scientifically valid, taking account of changes in understanding of the disease, in standard treatments used outside the trials and technical advances. This approach has the advantage that the secondary analyses conducted by the FDA are in line with what study participants have consented to, as Houyez acknowledged. The downside is that they do not cater for the needs of independent researchers. "All the questions other researchers would like to raise would not be satisfied", said Houyez. "So I think the way

it will go in Europe and has already started is that individual data will be accessed by third parties".

The FDA has acknowledged the potential value of allowing other scientific and clinical experts to review clinical trial data and share insights. "This could ultimately lead to safer and more effective treatment options for patients", agreed FDA spokesperson Tara Goodin. However, the FDA intends to move forward more quickly than the EMA in making non-summary personalised data available. "The FDA's concept [...] is to develop a framework to make publicly available non-summary safety and effectiveness data that has been de-identified and masked", said Goodin. "In June 2009, the FDA launched its Transparency Initiative, through which it solicited public comments on transparency and the Agency's public disclosure policies. As part of the Initiative, the FDA Transparency Task Force issued a report in 2010 containing 21 draft proposals, including one related to non-summary safety and effectiveness data from medical product applications". Goodin indicated the FDA would soon be well placed to move ahead with its framework for de-identified data.

In addition to patient advocacy groups, drug companies and regulators, the other key stakeholders in the open trial data initiative are the journals and their publishers. Here too, some have taken lead roles in pushing for data sharing and trial transparency, notably the *British Medical Journal* and PLoS (Public Library of Science), the non-profit open access publisher. Since January 2013, BMJ requires all authors of drug or device clinical trials to provide detailed scientific study data to anyone with a reasonable request, whether or not the work is funded by the pharmaceutical industry. They followed the lead set by PLoS, whose founding co-editor Virginia Barbour, now Medicine Editorial director, had stated that journals should insist on data sharing as a pre-condition of publication, just as funders should for funding.

Barbour is cautiously optimistic that obstacles to open access and data sharing can eventually be overcome, not least

because some have been overexaggerated, as in the case of patient data privacy. "The issue of confidentiality of de-identified individual patient data is something of a red herring, in that it has been thrown up as insuperable, even though it is not, but nonetheless does have to be handled sensitively", she explained. "Since we don't yet even have full access to all clinical study reports, there is a way to go before access to appropriately handled individual patient data becomes the norm".

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Balfour now believes that FDA and EMA are playing an increasingly important role in setting the framework for data sharing and publication, which helps to close the gap between regulators, the pharmaceutical industry and open access advocates. "Much of this is due to sheer weight of public pressure, such as that drawn together by the AllTrials Campaign, that has systematically engaged politicians, companies and other organizations in the debate, as well as continued academic research in this area, along with journal advocacy, such as by the PLOS journals and BMJ", she explained. "There have also been pharmaceutical companies who have been leaders here and that will be critical in bringing other companies along. The key I think is repeated constructive discussion in public on the benefits of access and the harms caused by lack of access".

Which exactly seems to be the key issue of the whole debate about making data from clinical trials available for independent research groups: the growing consensus that lack of access is not sustainable and poses greater obstacles for future medical research than possible constraints based on public fears about data usage or concerns over commercially sensitive data.