

FINAL REPORT

EFGCP Multi-Stakeholder Roundtable Meeting on Sharing Clinical Trial Data in the Interest of Patients and Research

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European Forum for Good Clinical Practice

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1. The workshop and its aim

This report summarises the discussion and conclusions of a workshop organised by the European Forum for Good Clinical Practice at the headquarters of the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels, Belgium, with the further support of the British Medical Journal, the German Society for Haematology and Medical Oncology (DGHO), the European Federation of Pharmaceutical Industries and Associations (EFPIA), Finsbury International Policy and Regulatory Advisers (FIPRA), the Innovative Medicines Initiative (IMI) and software company SAS.

The meeting was held in the context of the debate on data transparency in clinical trials triggered by the new Clinical Trials Regulation being prepared by the European Commission and the policy proposals of the EMA. One aspect of the new Regulation will be requirements for the sharing of clinical trial data, but this is an issue where – so far – the interests of the different stakeholders have sometimes seemed to diverge sharply.

So the idea of the workshop was to seek common ground while clarifying differences, with the overall aim of making consensus recommendations on how data sharing could be progressed. Similar multi-stakeholder workshops held by the EFGCP in the past around the Clinical Trials Directive and the Roadmap Initiative seem to have been productive, said its Chairperson, Ingrid Klingmann. “Many suggestions have been taken up by the Commission,” she said. “It seems to be a mechanism that works.”

A total of 45 people attended, ranging from patient representatives and patients to academics, ethics committees, medical journals, industry and regulators. The workshop began with six presentations outlining the prime considerations of patients, ethics committees, researchers and academia, industry, regulatory authorities, and medical journals. This was followed by a brief roundtable discussion, and then the workshop split into three break-out groups examining three issues around achieving the intended level of transparency: public understanding of and trust in clinical research; public health and the requirements of high-quality secondary data analysis; and public understanding of and trust in the regulatory process. A roundtable discussion followed reports back from the break-out groups, and the meeting was then summarised by Ingrid Klingmann.

2. Key messages

Among the key messages – and somewhat of a surprise – is that no one said that everybody needs to have access to all data. Yes, patients have a fundamental right to information, but the way the information is structured needs to be handled in a useful way.

While there were many differences of approach and emphasis from the various stakeholders, there was consensus that any process needs to be transparent, scientifically sound and ethically acceptable, with information being provided to bona fide competent researchers in a structured way. That will inevitably involve a step-by-step approach, requiring dialogue between those who hold the information and those who seek to access it, as this will also ensure that the information is useful for the requestor.

Such detailed technical issues are probably best dealt with by including high-level principles in the Regulation, with the operational details left to guidelines, rather than written in legislative stone, concluded Ingrid Klingmann.

One – perhaps unexpected – outcome was a focus on the participants in clinical trials. “We have to do a lot more to get back to individual patients involved in clinical trials,” said Ingrid Klingmann. “We owe that to patients for their willingness to contribute to the trial. At present that concept is not embedded in the proposed Regulation – but as a fundamental right it should be.”

3. Setting the scene: stakeholder considerations

Session Chairs: Françoise Meunier, European Organisation for Research and Treatment of Cancer (EORTC), Belgium & Angelika Joos, Merck Sharp & Dohme, Belgium

PATIENTS: Laurène Souchet, European Patients' Forum, Belgium

Sharing data on clinical trials is a “moral imperative” that demonstrates respect for patients, including trial participants, said Laurène Souchet, Policy Officer of the European Patients' Forum (EPF). Patients take part for the benefit of wider society, and their data are “not to be owned by anybody”. Sharing clinical trial data means less duplication in research, she said, and also better research. Likewise, more transparency means quicker progress and more rational use of limited resources. And for a patient organisation such as the EPF, transparency is also relevant because it has an important role in peer support. “We need to be able to respond [to requests for support] based on the best relevant information,” she said.

We need to recognise the “fundamental right” of patients to have access to high quality information so that they can make informed decisions, she said. That means targeted, concrete and reliable information in a lay summary, along with free access to medical journals. She called for: mandatory publication of all results of all clinical trials in a timely manner, regardless of the outcomes; clear guidelines on content and format of lay summaries; and controlled access to raw data for researchers.

One “good solution” for such a scheme, she said, would be to agree the criteria for data sharing with patients. There need to be formal independent structures for this, and to achieve transparency and good governance. Such structures should be independent of companies but include patients. Laurène Souchet also called for guidelines for informed consent that include telling participants about secondary use of their data. Finally, she said, patients should be involved in the ethical review of all clinical trials.

ETHICS COMMITTEES: Robert Rubens, University Hospital Ghent, Belgium

Professor Rubens said that in reaching their decisions ethics committees would not just benefit from having before them “full information” about a trial in the form of a synthesis and the full protocol, but that access to raw data from earlier trials would be helpful for checking.

He also insisted that ethics committees have to be given the results of the trials that they approve, whether those results are positive or negative. That goes for the public and society at large as well, he said, dismissing industry arguments for confidentiality as “not evident”.

Medical journals also came in for criticism. Professor Rubens said that editors will not accept papers which give no new information, leading to a situation where many trial results are neither submitted for publication by industry nor published by journals. “Editors need to check their own conscience to see whether they continue like this,” he said.

The solution, said Professor Rubens, is a “publication agreement” whereby the results of every human experiment – and these “always involve some financial support from society at large” – are available to humankind. So every result has to be communicated, raw data has to be kept for the future, and sponsors should never block the publication of results. These results should be, “in some way or another”, available to the public at large. They will not always be in lay language, but the basic facts need to be available for scientists to check, with something more general for the public to read.

RESEARCHERS AND ACADEMIA: Anastassia Negrouk, European Organisation for Research and Treatment of Cancer (EORTC), Belgium

The EORTC submits all its trial results for publication, including negative results, said Anastassia Negrouk, Head of International Regulatory and Intergroup Office at the organisation – but “whether or not they are published is another question”. Its data sharing policy, in operation since 2001, works on the principle that data are made available on request after “appropriate scientific review”. In total, it has received 224 requests for data, of which 168 were accepted, 46 not, and 10 are still under evaluation. Reasons for rejecting requests for data include “inappropriate research”, and the data not actually existing.

Making trial data available enables researchers to re-evaluate pivotal clinical trials (“or any other clinical trial needing it”). It also means that researchers can ask new questions of the data without exposing new patients to the risks of a trial.

The results of clinical research should be available to the public, patients and scientists through the EU Clinical Trials Register, but in practice there are problems. The register has not yet been upgraded to enable results to be shown, the display format needs improvement, and the search is “not easy for a lay person to find their way around”. These results – of positive, negative, inconclusive and incomplete trials – are essential background information to foster the next generation of clinical trials, she said.

Anastassia Negrouk noted that the proposed Regulation calls for a summary report with some lay language. Such a summary, she said, should meet the requirement to make the public aware of trial results. However, many do not even know that the Register exists.

While the Regulation should guarantee the principle of data sharing, Anastassia Negrouk said that it should not define “the specific modalities”. The appropriate format or amount of data will depend on factors such as the nature of the research and the stakeholder requesting the data.

Of the data options currently under consideration, the industry proposal (from the US and European bodies PhRMA and EFPIA) is limited, she said: it covers only trials that have reached Phase III, and does not give any detail on the scientific boards that would review applications for data. She also criticised the draft policy from the European Medicines Agency: it lacks a process of independent scientific review to assess the science and methodology of the research for which the data are being requested; and it is unclear, she said, on the relative responsibilities of the EMA, the data requester and the sponsor. “We need to ensure that whenever [data] are requested for the right reasons they are indeed shared, and that the evaluation is independent and fair,” she concluded.

INDUSTRY: Sue Forda, Eli Lilly & European Federation of Pharmaceutical Industries and Association (EFPIA), United Kingdom

Industry is in favour of responsible data sharing, said Sue Forda, Vice President Global Regulatory Affairs – International at Eli Lilly, speaking for EFPIA. “We very much want to protect patient privacy, trust in the regulatory system, and incentives for research,” she said.

Dr Forda pointed to the industry’s progress in addressing expectations of transparency, and its plans for the future. At present, all clinical trials are notified to the regulator when started, and summary results are posted when trials are completed. Dr Forda also noted an enhanced commitment to open innovation, especially through the Innovative Medicines Initiative (IMI). From 2015, EFPIA companies will also be disclosing all financial relationships. And, of course, there will be enhanced sharing of data from clinical trials.

Areas for improvement include access to analysable patient-level and study-level data for “legitimate research” (though Dr Forda said it was “frustrating” to get repeated requests for health technology assessments on data just seen by the regulator). Like others, she wanted to improve the accessibility of trial results to lay audiences. And giving access to documents from the regulatory process will help in understanding how regulators make their decisions. . She also suggested that patients participating in a trial should receive the results of that trial on the personal and overall levels.

What does EFPIA mean by “responsible data sharing”? It’s summed up in the EFPIA/PhRMA Principles for Responsible Clinical Data Sharing¹ – five key points. First, there is a commitment to sharing patient-level data and protocols relating to medicines and indications approved in Europe and the US “upon request from qualified researchers”. Second, and at a minimum, companies will make available synopses of Clinical Study Reports where the trials have been approved by regulators in the US or Europe. Third, companies wish to work with regulators – and with patient organisations – to develop factual summaries of clinical trial results that can be made available to research participants. Fourth, public certification and declaration of these policies by sponsor companies, so that the system ensures that all research is published as promised. And finally, they reaffirm that they want journals to consider for publication the results of all company-sponsored trials, positive and negative as well as discontinued programmes.

To show what all this means in practice, Dr Forda explained the new steps being taken at Eli Lilly, including the creation of a new Office of Medical Transparency, with a broadly based steering committee and implementation team. It will be “an enormous step forward” for Eli Lilly, she said. Meanwhile, the industry plans to address issues such as accountability, the scope for technical alignment, and procedural simplification (as things stand, some smaller companies may not have the resources to set up their own boards to review data-sharing requests).

REGULATORY AUTHORITIES: Francesco Pignatti, European Medicines Agency; Birka Lehmann, Federal Institute for Drugs and Medical Devices (BfArM), Germany

Transparency matters, said Francesco Pignatti, head of oncology and haematology at the EMA. He cited four main reasons why. The first is to build trust in the regulatory system by enabling not just public scrutiny but also the possibility of verifying and challenging regulators’ decisions – “you need to be transparent to be accountable”. Second, transparency is an ethical responsibility to the patients taking part in trials. Third, independent re-analysis can benefit public health. And finally, the sharing of complex data can open up new scientific horizons.

At present, all that is available is what is published at the end of the process in the EMA’s Assessment Reports – which as Dr Pignatti said do not reach even the level of detail found in scientific publications. In theory, any member of the public can request access to the EMA’s documents, but in practice this is not easy. Much of the data the EMA receives are not suitable for public release; individual patients have to be de-identified, and the agency needs to protect commercially sensitive information. “We have to go through every page,” said Dr Pignatti, deleting dates of birth, initials and so on. The result is “maximum deletion of information”.

That is why the agency is proposing that in future companies seeking marketing authorisation should submit data that is either in a suitable format for publication or sharing, or that commercially sensitive data are “clearly identified and separated. Once a final decision is reached – either acceptance or rejection – data will then be made available. Aggregate data with little or no risk of patient privacy could be made available to everyone. De-identified patient-level data could be made available under a data-sharing agreement.

Of course, said Dr Pignatti, this would apply only to trials submitted to the EMA for marketing authorisation. And it does not deal with data generated by academic researchers or held outside the agency, nor with data relating to trials on products already approved.

The agency has set up advisory groups on a number of data-sharing issues, including protecting personal data. A draft policy on this was recently out for public consultation, and there have been “thousands of comments”. Publication of the EMA’s final policy is imminent – by the end of November 2013. He expected that at least that part of the policy relating to Clinical Study Reports would be implemented in 2014, with the sharing of raw data starting in 2015.

Commenting on Dr Pignatti’s presentation, Birka Lehmann from German regulator BfArM expressed the concern that competent national authorities may not receive from the companies all the clinical documents available. Applicants for marketing authorisation should guarantee that the regulator receives *all* available

¹ <http://transparency.efpia.eu/uploads/Modules/Documents/data-sharing-prin-final.pdf>

data, including negative and inconclusive data, she said (though she added that most companies do live up to their legal responsibilities). She also said that discussions with clinical colleagues indicate that publication of raw data might not be helpful and that an “unbiased synthesis” might be preferable. It is not feasible for everyone to review raw data, she said.

MEDICAL JOURNALS: Fiona Godlee, British Medical Journal (BMJ), United Kingdom

“We have a real problem,” began Fiona Godlee, editor in chief of the *British Medical Journal*. “We want to practise evidence-based medicine, but we know from a number of studies that the evidence on which we base decisions is fundamentally flawed.” She pointed to “substantial loss of trust”, and a quantity of examples of bad practice and bad faith over 30 years “amounting to malpractice”.

A review in 2010 by Germany’s IQWiG, which assesses the quality and efficiency of medicines, found misreporting and under-reporting of trials (industry- and academic-sponsored) across the whole of medicine on a substantial scale, said Dr Godlee. Benefits become overstated, harms understated. Industry has been reluctant to make data available. As the biggest funder of trials, it has an irreducible conflict of interest, she said.

“I am not complacent about journals, but we know that the main cause of publication bias is not with editors,” she said. Authors are less likely to write up their trials if the results are negative or inconclusive. But open access publishing has lowered barriers to publication, so there is no excuse for not publishing.

The end result is that – according to a study in 2010 – only half of clinical trials end up being published, while the “limited” US legislation is ignored and Europe has no regulatory framework for access to the results of clinical trials. There is progress, but solutions are “partial”: “The risk is that people think the problem is solved, and it’s not.”

Her solution: twelve points.

1. “Though it may seem extreme” – independent evaluation of all trials with drugs and devices to avoid that “irreducible conflict of interest”.
2. Proper scrutiny of trial protocols before ethical approval.
3. Public awareness and engagement of trial participants and patients, with an informed consent form that explicitly states that participants take part on condition open publication.
4. Prospective registration of all clinical trials, with better and internationally aligned mechanisms for this.
5. Summary results to be reported with a year of trial completion, and ethics committees should not give approval for studies to sponsors that have failed to publish results in the past.
6. Public access to Clinical Study Reports (and their equivalents) with “minimal redaction” – the EMA should be supported in this, not sued, and those supporting AbbVie’s legal challenge to the agency on data sharing “should be ashamed”.
7. Access to individual patient data for independent scrutiny by competent third parties who provide an adequate analysis protocol, commit to making their results public and give full credit to the researchers responsible for the original data.
8. Encouragement for companies to “step up to the plate” by a transparency score so that the public and investors can see what companies are doing.
9. A “transparency weighting” by journals and guideline developers.
10. Open access to the medical research literature.
11. Proper systems of post-publication peer review and comment (such as the *BMJ*’s “rapid responses”).
12. And finally, all this must be backed up by a regulatory framework that ensures transparency in clinical trials.

An initial synthesis: Laura Batchelor, Finsbury International Policy & Regulatory Advisers (FIPRA), Belgium

"The key word today is trust," said Laura Batchelor from global public affairs and regulatory consultancy FIPRA. "Transparency without trust doesn't lead us very far." The context is a suboptimal legacy, which inevitably frames part of the discussion.

Data sharing is an issue of "really key public interest", she said, and all the stakeholders are looking to define the optimal regulatory framework. Many of them are clearly dissatisfied, but there is a willingness to find the best solution.

Different stakeholders had identified a need for more comprehensible information, she said. The EFPIA's data-sharing principles might prove a good starting point, perhaps. Meanwhile, there seems to be agreement on the need to publish both positive and negative results. Other key principles enunciated are respect for patients and personal data, and the broad need to establish a level playing field, with same rules for industry and academics.

Some areas to work on: the consent form for patients needs to include consent to data sharing; the stakeholders need to agree on how to prevent the inappropriate use of secondary data; a robust technical and legal infrastructure.

The stakeholders appear to be aligned on the basic principle of sharing data, including with patients. The question is, in what form and to whom? It is important to develop a tailored system fit for all needs, with accountability and responsibility, and one that is both simple and affordable.

Yet there are also clear differences: on one side the call for regulation and on the other for self-regulation. "That's not new in this town," added Laura Batchelor. One suggestion is to focus on principles in the Regulation and work out the modalities later; certainly, once something is in a Regulation it is hard to change.

Discussion

In the relatively short period for discussion before participants went into the break-out sessions, four topics dominated the discourse: informed consent for secondary use of information and the role of ethics committees in this; whether raw data were really needed (rather than readable summaries); and where – and how – the data should be stored.

Informed consent and ethics committee review

Sabine Atzor from F. Hoffmann-La Roche noted that the EMA's draft policy foresees that the original ethics committee will review requests for secondary use of trial data if this is provided for at national level and asked what the focus would be of such reviews. There is currently no legal requirement for this. But, suggested Ingrid Klingmann, there should be, and the Regulation is an opportunity to do this in the interests of patients and of trust in the scientific process. Anastassia Negrouk disagreed: all secondary analysis is done under data protection controls, she said, and we don't want to add to these – even now, the costs of ensuring privacy are leading to some trials not being performed.

It is not clear whether consent forms could easily incorporate the principle of broad consent to (at the time unknown) secondary use. Stephan Dressler from the European Aids Treatment Group, which has been reviewing informed consent forms for twenty years, said it would be "immensely difficult", as for legal reasons the forms are not harmonised to begin with.

Robert Rubens suggested that it is "not so difficult to anonymise data" and make data readable. But he also said that an ethics committee should judge whether requests for information are relevant to the same type of person as in the study. "If you ask me, yes or no, whether you could use breast cancer data for a study of cardiovascular effects, we would say no," he said.

But even that simple example was controversial. Professor Françoise Meunier, Director-General of the EORTC, said that women with breast cancer treated with irradiation typically develop cardiac insufficiency in

later life. So, she said, when a woman gives her consent to be in a clinical trial for breast cancer, she wants to know about breast cancer management generally, including the cardiac implications.

Matthias Freund, President of the German Society of Haematology and Medical Oncology, agreed: patients in these studies want the long-term side effects to be looked at, he said, and such issues can be covered in consent forms.

Raw data

It's not surprising that much attention was devoted to the question of access to raw data, combining as it does the core issues of patient privacy, commercial interests, standardisation (or lack of it), and who should store the data.

It's not just about raw data, said Ingrid Klingmann. We are also talking about how and in what form we provide summary information to, for example, patient organisations, ethics committees and others. "We need a reliable way of summarising results that is useable and can be made available to those who need access – including those who may not know about their existence." Brendan Barnes, Director of EFPIA, agreed, adding, "But it's a bit more than format. We have to think about how this is communicated to people."

All the same, it was raw data rather than summaries that occupied most participants at this stage. Certainly, researchers and others want to have access to raw data from clinical trials, and not just for meta-analysis. "You need the raw data to test different hypotheses around the data," said Ann Martin, from the IMI, herself a statistician. Transparency is an issue, too, said Martin Posch, professor of statistics at the Medical University of Vienna – because it is an essential condition for re-doing the analysis and enhancing the level of scrutiny. This is particularly important in Europe, where in general, and unlike the FDA in the US, regulators do not independently re-analyse raw data.

Professor Posch was supported in this by Fiona Godlee. "Regulators do an amazing job but they do get things wrong and it is foolish to think no one else need look at it," she said, pointing to examples of independent researchers uncovering things regulators have missed.

Matthias Freund advanced the public interest view. "Most implicit in this discussion is that patients say they want to contribute to the community and mankind. This provides a strong basis not to see these data as private property," he said, concluding, "We need a public archive of these data."

"We cannot rely on the published reports in clinical journals to provide an accurate report of a clinical trial," said Fiona Godlee. "Even if only one person looks at the full data, they might find something."

And while Ann Martin was concerned about the "huge investment" needed to make the data interoperable, Dr Freund was not. "I don't believe that standardisation is achievable. Just collect the data and make them publicly available for later analysis." Accordingly, the Regulation should assure the legal principle of data exchange, but make no further detailed stipulations.

The key point here is to build a structure which ensures that independent scientific bodies can re-analyse the data. And that should go for data from academic as well as industry trials, said Holger Maria Rohde from MerckSerono. Ann Martin also raised the need for DOIs (digital object identifiers) to trace back where information is, adding, "But [the information] has to be there, and be persistent."

Others were not so sure about public archives. Anastassia Negrouk referred to the "huge effort" of lodging data elsewhere, and the fact that data are often live – so at what point do you deposit the data? "It's better for people to get raw data directly from us," she said.

And if the data are in a public archive, which one? Could EudraCT be involved, asked Gerald Van Roey from the European Centre for Clinical Research Training? That, said Francesco Pignatti, would be a matter for the Regulation, rather than the EMA. Matthias Freund was "sceptical" about establishing a central repository from the start; he suggested a networked system of repositories, with the proviso that data from one trial should be held in one repository, rather than split into the countries they come from.

Whatever the outcome, standardisation will remain an issue, with little belief that – as Matthias Freund put it – researchers will be able to “just press a button and get a meta-analysis”. But that might not be the full story. Mark Lambrecht from software company SAS, which among other things is helping GSK to host a data transparency repository, said that standards do exist: “I believe they can be used,” he said.

4. Reports from break-out groups

Session Chairs: Sabine Atzor, F. Hoffmann-La Roche, Switzerland & Fergal Donnelly, DG Research, European Commission

The trust issue: What is needed to educate the public and enhance trust in clinical research and collection of primary data?

Chair: Pim De Boer, Leiden University Medical Center/Lung Foundation Netherlands

Rapporteur: Tsveta Schyns, European Network for Research on Alternating Hemiplegia (ENRAH), Patients Network for Medical Research and Health (EGAN), Belgium.

Tsveta Schyns reported on a “very vivid” discussion, mainly among people involved in patient organisations and presenting a patient view, but there were also representatives from academia and industry. They focused on four issues: what patients and the public really want to see; what is “must have”; what would help; and what would either confuse or create mistrust.

What would patient/public really want to see? Here the group had in mind the altruistic patient, including the healthy volunteer, and came up with three points.

The first point was transparency throughout the whole process.

The second was open access to the information coming out of the clinical trials. This access should be at several levels – a lay summary of information from clinical trials is “a must”, but patients also want to see open access to the full results of clinical trials.

And lastly, patients want greater access for themselves to clinical trial data: above all to their own data as a clinical trial participant but also to the whole (aggregated, de-identified) data set. “We have to find mechanisms to do this, and also to ensure that we increase access to secondary usage of clinical trial data.”

Magda Gunn, from the IMI, expanded on this: the group thought raw data should be accessible and controlled by independent governance – but that access should be encouraged. So too did Holger Maria Rohde: raw data from clinical trials have become “part of the medical health record data which you might carry around on a chip”, he said. The patient, as owner of the data, has the right to access it.

Anastassia Negrouk was uneasy about the sponsor being required to provide this information. The EORTC is comfortable with the idea of the patient being informed by the investigator, but not happy with directly communicating itself. “We’re not qualified to do this,” she said.

What is “must have”? The group identified three equally important kinds of information to which patients require access: to information on clinical trial results; to the CT Registers, so that they know what trials are going on; and, for individuals, to the raw data on themselves – access that must be ensured by multistakeholder governance and independent review boards.

What would help? Given the need for mechanisms in Europe to allow appropriately controlled access, what would really help would be a harmonisation, in the form of a Regulation that would knock down “all barriers currently existing across countries”. And there needs to be change in the administration of informed consent: “We want informed consent that is not just legally binding but properly informing,” said Tsveta Schyns.

What would create more mistrust? Here the group’s answer was clear: divergent access requirements and information coming from different stakeholders; and continuation of the “artificial obstacles” currently in Europe.

Finally, Tsveta Schyns called on everyone to stop doing research “in” patients and start doing research “with” patients, involving patients as stakeholders at all levels of clinical trials.

The public health issue: What is needed to perform high-quality secondary data analysis for new research ideas?

Chair: Anastassia Negrouk, European Organisation for Research and Treatment of Cancer (EORTC), Belgium
Rapporteur: William Malbecq, Biostatistics and Research Decision Sciences, MSD Europe, Belgium

The group (which regrettably included no patient representatives) aimed to come up with recommendations for what should be in the Regulation and what should remain outside the Regulation as guidance.

William Malbecq was able to report consensus on many points: data sharing should be mandatory; information provided with Clinical Trial Reports should enable requesters to understand which data are available; all research organisations should have criteria-based data sharing and transparency policies, including patient involvement; data-sharing policies and details of applications should be publicly available and transparently approved or rejected; data requesters should make the results of their own subsequent analysis publicly available, and the rules above should also apply to them.

But there were also many areas of disagreement, and although many felt that a central repository for clinical trials data would be of benefit the concept was seen as premature and in need of further assessment.

The group discussed four points: aspects of data; science and methodology; legal and ethical framework; and accountability.

Aspects of data: secondary analysis. William Malbecq was able to report consensus on what is useful before secondary analysis is even considered. First, some data: the protocol, the Statistical Analysis Plan, summary results, and metadata – “so everyone can understand what kind of data we are talking about”. The group suggested that a guideline about metadata would be helpful to balance the need and the workload. Second, information about data quality: an idea about data management, dictionaries used, standards and so on. And finally, there must be controlled access to patient-level data (“it is very clear that we have consensus [on this]”).

Aspects of data: anonymisation. Is it clear, the group asked, what “really anonymised data” means? In the context of the on-going legislative review, it has been accepted that pseudonymised data should not be treated as anonymised. It concluded that there are no uniform rules: we need to go case by case, with a risk analysis. So a “proportionate approach” is proposed.

Aspects of data: when to make data available, and when to update. Stages at which data are to be made available should probably be defined in long studies with long follow-ups; and committees reviewing requests in a controlled manner might be able to agree timelines with data requesters.

Science and methodology: qualified researchers, pre-specified analyses. May only “qualified researchers” request access to trial data? There was no agreement on this, nor on the EMA’s policy that requestors would not need to submit their planned study proposals for scientific scrutiny before accessing data for secondary analysis (the EMA says that clinicians should be free to explore patterns).

Science and methodology, risks. With increasingly sophisticated data mining tools, uncontrolled access carries the risk of personal information being released to the public. Does that also imply, in the case of a potentially scientifically flawed secondary analysis a high risk of false information reaching the public? A majority of participants thought there were risks in presenting results from analyses that do not follow a good methodological plan (false alarms, for example). There were, however, divergent views.

Science and methodology, quality and suitability. Secondary analysis should have at least the same level of quality as primary analysis, thought some. But an area without consensus was how to weigh the pertinence of the proposed research question and the appropriateness of the methodology. Three options were identified: no review at all; review with different organisations involved; or review by the organisation receiving the request. The vast majority were in favour of a review process, but there was no consensus on the composition

of the review body. Everyone agreed, though, on full transparency in decision making, with the possibility of an appeals procedure in the case of rejection.

Legal and ethical framework: who can ask? Should anyone be allowed to request access to trial data? Views diverged sharply: the division was between allowing everyone, or just qualified researchers (those with a Cochrane certificate, perhaps) and statisticians. One question identified but left unanswered: Should the cost and resource implications of requests for the data provider be taken into account?

Legal and ethical framework: consent. When it comes to secondary use of data, should informed consent forms ask for broad or specific consent, or not ask for consent at all? The group felt that secondary research should be allowed without patients re-consenting if the data are adequately de-identified (itself not necessarily a clear-cut issue). Broad consent in advance can be a good solution, though that should not be seen as a “blank cheque” – requests for data will need discussion about what would be an appropriate level of data access, as this would have implications for data privacy. This is by no means straightforward, though. (As Robert Rubens made clear in reference to the controversial mention of alcoholism in the secondary analysis of a diabetes study carried out on Native Americans.)

Legal and ethical framework: accountability of secondary research. The consensus was clear: all results should be made public, and data requestors should be identified. Any damages caused by requestors after the granting of access to the data are probably the responsibility of the requester, the group concluded.

Legal and ethical framework: who holds the data. There were more questions than answers here. Unresolved questions included whether information should be passed from stakeholder to stakeholder, or held centralised in a library – and if a centralised repository, who would fund it?

The trust issue: What is needed to enhance public understanding of and trust in the regulatory process?

Chair: Birka Lehmann, Federal Institute for Drugs and Medical Devices (BfArM), Germany
Rapporteur: Fiona Godlee, British Medical Journal (BMJ), United Kingdom

The group clearly had a wide-ranging session, and Fiona Godlee’s report covered a number of issues discussed by the other two break-out groups. “I don’t think you can say we reached consensus,” she said, although there was agreement on the key issue of access to raw data.

Who should have access to raw data? Not the public in general, the group agreed. But the hurdles for access to raw data should not be set too high. The group’s suggested rule is that raw data should be granted on request, for a legitimate study purpose and stated study protocol, with a commitment to publish any results.

Timing of data release. A long discussion about this failed to produce consensus. Industry prefers raw data to be released once they have marketing authorisation in Europe, the US and Japan. But there is also a view that it is not feasible to wait for all the regulators to decide, and that data should be released in Europe following a decision by the EMA.

Failed and discontinued drugs. The proposed Regulation provides for Clinical Study Reports to be released once a decision is reached on marketing authorisation, whether approved or rejected. But what if a drug is not put forward for marketing approval? One view was that those data are useful and should be reported; the fact that they may be commercially sensitive means they are important to the public.

Where to get raw data. The view in the room was that the best place to get raw data from is the sponsor, with recourse to the EMA if the sponsor does not respond to a request.

Independent decision-making. Requests should be judged by independent decision-making bodies. The public would feel much more confident if the decision did not rest with the company. The group also seemed to confirm that companies themselves would be happier with an independent process.

How to incentivise pharma to invest. There were a number of suggestions here, including value-based pricing and, perhaps, longer patent terms or longer periods of exclusivity. But no consensus emerged.

How to engage the public. Some of the deliberations should take place in public (as happens with some US FDA advisory committees). Other suggestions included patient panels and public juries. National competent authorities could also engage in discussion with patient organisations.

Legacy trials. Most treatments relate to drugs trialled before 2004. While there have been some measures to bring trials since 2004 into the public domain, what about even earlier? We could do better, said Fiona Godlee. Why not begin with the trials that were submitted for authorisation? Legacy cropped up again in the view (not a consensus view) that data must be a central repository otherwise companies in future might not be able to find them; or at least a network of repositories, with one for each country and data being deposited in the country where the sponsor is located. (The issue has tremendous potential practical and financial implications, and no consensus was reached on it.)

Public trust and the question of access to Clinical Study Reports. There are three clear positions on access to Clinical Study Reports: the EMA's, the European Parliament's, and EFPIA's. The feeling, reported the *BMJ* editor in chief, was that the positions of the EMA and the European Parliament are based on a number of high-level principles "which seem to be ones that will increase trust in the future", but that the EFPIA policy allows companies to retain control, and "that seems to be a recipe to decrease public trust".

5. Roundtable discussion, conclusions and recommendations

Session Chairs: Sabine Atzor, F. Hoffmann-La Roche, Switzerland & Fergal Donnelly, DG Research, European Commission

As Director of meeting co-sponsor EFPIA, Brendan Barnes said he was very pleased with the quality of the discussion – "even if some of it makes uncomfortable reading or hearing". EFPIA recognises the positive response to its commitments, he said, but also notes concerns about whether they will be implemented in an accountable way. Is that for companies or someone else to do? "The underlying thought when we put the principles together is that researchers want access to raw data and that we thought companies best placed to be the interlocutors, if we can get the transparency of that interaction between researcher and company right," he said.

Anastassia Negrouk, speaking from the EORTC's dual perspective as both a data producer and data requester, said the organisation was "relatively comfortable" with the EFPIA principles, adding, "We tend to get more data from industry than from academia." She worried that if data release were completely out of the organisation's control, it might face issues such as a poor analysis of its data that damages its reputation. "So we want at least to be able to adapt or find out what will be done to the data," she said. "We can even help the data requester by providing the right data in the right format." Another concern is that the EORTC might have already planned research with its data that is exactly the same as that planned outside. "If we have invested huge time and money in gathering these data it is questionable whether someone can come straight in from outside," she said.

Sabine Atzor added that industry would not like to see this as an "on/off" discussion. "We are all in a learning process on the industry side, and it seems the third-party researchers are in a similar situation," she said. "We have to accept that it is evolving, and take a step-by-step approach."

Summary: Ingrid Klingmann, Pharmaplex, European Forum for Good Clinical Practice (EFGCP), Belgium

"The discussion has shown that this is a more complex topic than I thought," said Ingrid Klingmann. "The more we discuss it the more we become aware how many facets it has."

Among the key outcomes was the surprising fact that no one was saying that everybody needs to have access to all data. Patients certainly have a fundamental right to information, but the way the information is structured

needs to be handled in a respectful way. That means providing different types of useful information for different purposes.

Another area of consensus is that we have to improve greatly how we get back to individual trial participants about what kind of treatment they had and what the results – the individual data points – were. “We owe that to patients for their willingness to contribute to the trial,” she said. “At present that concept is not embedded in the proposed Regulation – but as a fundamental right it should be.”

The next level is that of general feedback to the patients and public at large – and other stakeholders – about the results of the trials, in the form of the summary of the Clinical Study Report, as proposed in the draft Regulation. No one is disputing that. The thorny question is when to provide that information to the public: at the time of the marketing authorisation decision or earlier? Here there is no consensus. Nor is there agreement on when results from early-terminated trials and trials from discontinued programmes should be published and what happens with the data relating to historical trials. EudraCT is supposed to be a repository for results, and will go back to 2004, she said, but can we go back earlier? That is something to be worked on for the future.

And then there are requests to provide the full report, which includes the data listing – “a huge amount of data”. How and when can these be made available to the public? The debate about who is the owner of the information and who should best handle it continues. Since the sponsor knows best what information is there, it makes sense for there to be a dialogue between sponsor and requester.

One proposal from the workshop is also to define the rules about what would be acceptable for a requestor to ask for, with the requester providing the sponsor with advance information about results of a secondary analysis and the opportunity to comment. “That is probably a polite way of collaborating,” she said, “but it would have to be defined in more detail in a guideline.” A mutually acceptable way of organising this analysis needs to be found, and the same rules should apply to commercial and academic sponsors.

Finally, we come to the big amounts of raw data and how we should handle them in the most efficient way. And there, said Ingrid Klingmann tactfully, “We have lots of room for a guideline to work out in detail how that might work.”

“One thing we have very clearly achieved is a true multi-stakeholder discussion,” she said. “All of us have a clearer view of the issues and attitudes.” The outcomes should be presented to the EMA, the European Parliament and the Council of Europe as quickly as possible, she said.

For any information:

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