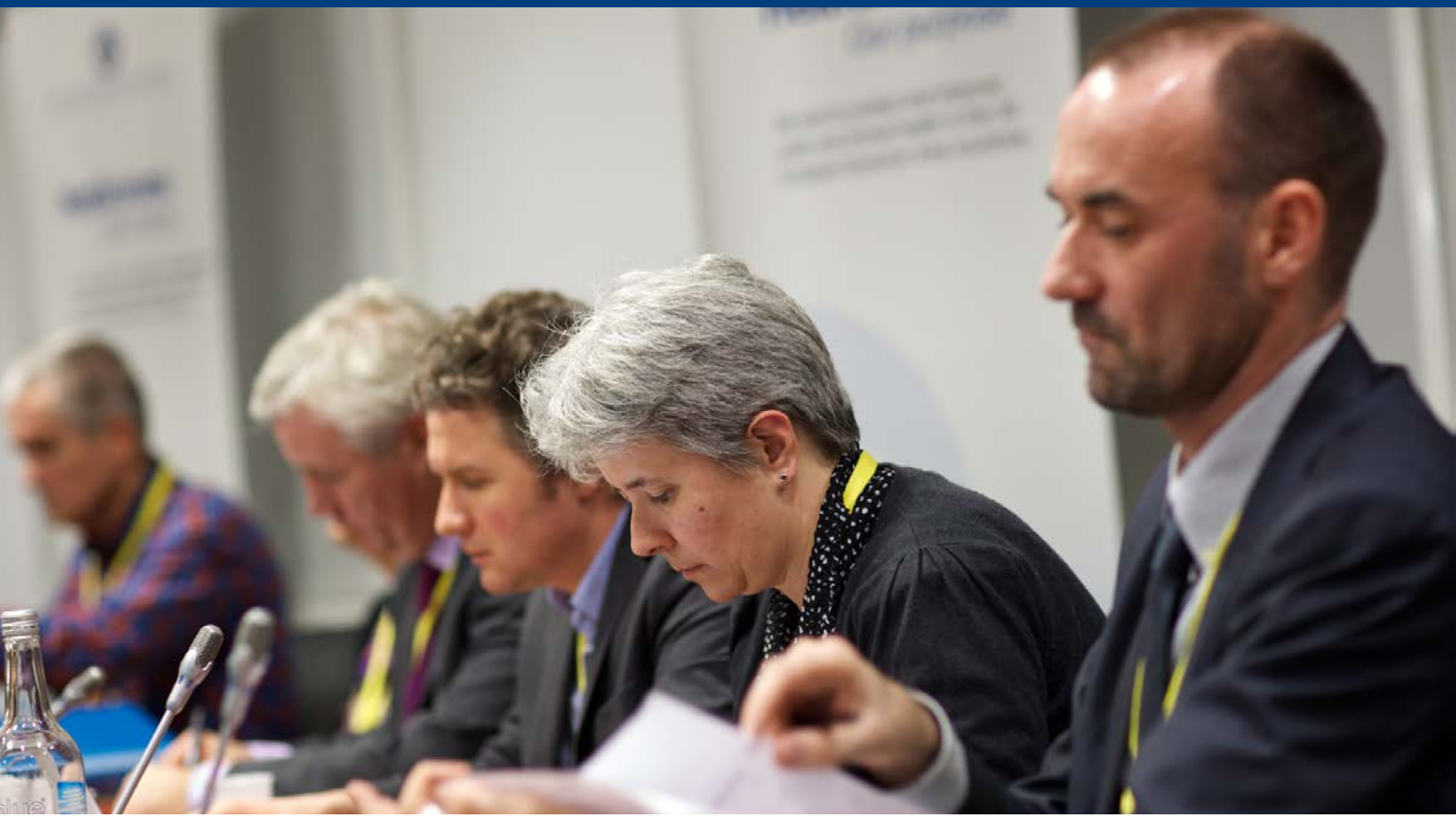
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Access to clinical-trial data and transparency

Workshop report

An agency of the European Union



Agency moves towards proactive publication of clinical-trial data

Across Europe, regulators and governments are turning their attention towards a key healthcare issue – the transparency of clinical trials, in particular the release and withholding of data.

The European Medicines Agency recognises the need to establish a way forward and convened a workshop on 22 November 2012, bringing together experts from across the European healthcare spectrum to debate the issues. With the Assistant European Data Protection Supervisor and a representative from the Office of the European Ombudsman in attendance, the event comprised an intense panel debate and a lively question-and-answer session, after which the Agency presented its plan of action.

The Agency's Executive Director, Guido Rasi, stated in his welcome address the Agency's commitment to publishing clinical-trial data once the marketing-authorisation process has ended. "Today represents the first step in delivering our vision. We are not here to decide *if* we will publish clinical-trial data, only *how*. We need to do this in order to rebuild trust and confidence in the whole system," he said. "Patients make their bodies available to us, so we have responsibility towards them. In the long run, the scientific process will also benefit as new horizons open up. Science will only improve if data is shared."

An expert panel of representatives from industry, academia, patient groups and the media kicked off the meeting by setting out their positions, their views sparking a dynamic panel debate.

The event was oversubscribed, underscoring the importance of the issue of data transparency. The conference was broadcast live on the internet and was watched by viewers in 27 different. It was also closely followed on Twitter.

At the end of the afternoon, all eyes turned towards potential outcomes, when the Agency presented its plan of action, which had been updated continually throughout the session. The plan called for volunteers to form five advisory groups, each to deliver firm proposals by the end of April 2013. Building on these outputs, the Agency committed to issue its policy on proactive publication of clinical-trial data in January 2014.

The debate

At the heart of the clinical-trial transparency event was the debate, comprising an illustrious expert panel drawn together to ensure that every angle and every opinion was covered. Such a divergent group needs a strong moderator and the Agency provided one in the form of Sir Mark Walport, Director of the Wellcome Trust.

Academia

First to speak was Peter Gøtzsche, Director of the Nordic Cochrane Centre, which is part of the Cochrane Collaboration. He immediately expressed his concern that the current system allows the industry to be its own judge. "Companies design and carry out trials, they analyse them and interpret the data, often introducing bias. If that is not enough, data from some trials may not even be published," he said.

He questioned if it was acceptable to use a method that has so many conflicts of interests, especially when a single data analysis can be worth billions of dollars on the world market. "Patients take part in clinical trials to benefit science and future patients; they do not take part to benefit the shareholders of pharmaceutical companies," he reminded attendees.

In response to a comment that companies do need to protect their intellectual property rights, Gøtzsche was quick to declare that if commercial success depends on withholding data that doctors need to make informed prescribing decisions, there is something wrong with healthcare priorities. He suggested an alternative scenario where the development of drugs would be publicly funded. This would be logical given that most medical breakthroughs are made by publicly funded research and development, he said.

The potential for poor analysis of data, when published, was a cause for alarm for many attendees and the entire panel agreed that a strict procedure was needed to remove weaker proposals. "By requiring people to register a protocol, we can look at the hypotheses and tests, and guard against too many fishing expeditions," said Gøtzsche.

"Data must be more easily accessible and in a format we can work with. We should go further and make the data available to everybody. After all, often it is those without qualifications that reveal the most interesting things, such as investigative journalists," he added.

Gøtzsche said he finds the argument that making the data available will result in bad analyses amusing, pointing out that the situation could not be worse than it is now. "Currently, the only people who see all the data for a new medicine are those inside the company – the company that stands to earn a lot of money from the product. The more eyes that look at the data, the better. The days of secrecy must end."

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The media

"Before I came today, I asked for input from several colleagues and the consensus was that journal editors and publishers want the research we publish to be reliable and reproducible," said Virginia Barbour, Medicine Editorial Director, Chief Editor, PLoS Medicine. "Releasing data in a timely and efficient way will help further that goal," she added.

> Any move towards better transparency must be a global initiative. There are many practical issues but they are not insurmountable if we work together.

Barbour was delighted to see the range of organisations represented at the event because she believes the drive to make clinical-trial data available must come from all the interested parties. "Today is an opportunity to debate the terms of engagement, for funders, regulators, editors, trialists, industry and academia to make a commitment to move the process forward, whether these assurances are practical, political or financial," she said.

"Ten years ago," she added, "such a conversation could never have taken place, but now there are tools, technologies and legal frameworks in place to make it happen. However, to move on, attendees need to take three key issues into consideration: transparency, reproducibility and practicality."

"In terms of transparency, the short-term objective should be that all data used to support an application be made publicly available at the time of licensing. In the longer term, data from unsuccessful applications should also be made available. If we establish a vetting procedure for requests for data, then it should be a transparent one, where all requests are logged," she said.

Barbour suggested that there should also be a mechanism to enforce the release of data, an independent verification that all the data are released and a process in place to follow up the outcomes of that data release.

The main issue in terms of reproducibility concerns the need for the analyses of the data to be made available in such a way that others can reproduce them. "However," she added, "the biggest hurdles will be practical ones, and the format in which the data is supplied will be critical. A 10-metre high pile of paper is useless; data should be available in an easily shared format."

Alongside adopting anonymisation standards and deciding where the data will be kept, Barbour proposed that data sets should be identified in such a way that they can be linked to protocols, publications, trial registries and patients.

"Any move towards better transparency must be a global initiative. There are many practical issues but they are not insurmountable if we work together," she concluded.

Industry

Representing the industry was Susan Forda, Chair of EFPIA's Scientific, Regulatory and Manufacturing Policy Committee, and Vice President, International Regulatory Affairs at Eli Lilly and Company. She told delegates that EFPIA wants to see "appropriate access to clinical data, especially for legitimate scientific researchers," concluding that it is a very sensitive issue.

She said that industry would like to see data access reviewed on a case-by-case basis and with decision makers taking a range of factors into account, including the nature of the product, the data being presented, its place in its lifecycle and the method of release. "We also ask that the protection of intellectual property rights be fully considered," she said.

"I would be terribly worried about making all data freely available. For example, if inappropriate data analyses were picked up by the media early in a product's lifecycle, it could confuse doctors and prevent patients from receiving effective medicines. Analyses should also be defined and reviewed, allowing interested parties to comment," she added.

"EFPIA is not in favour of releasing information from withdrawn products or those that received a negative opinion. This could damage the future interest of the product if it is resubmitted at a later date with additional data or submitted outside the EU."

Forda ended by confirming that pharmaceutical companies are committed to working with the Agency and other stakeholders to develop an approach to foster transparency that is appropriate and balanced.

The media

Although he is a Wellcome Research Fellow in epidemiology at London School of Hygiene and Tropical Medicine, Ben Goldacre is better known as a healthcare commentator in the UK. He believes that the public are both wise and can make an enormous contribution. "By sharing our ongoing problems, the public are likely to come up with valuable solutions," he said.

Goldacre was clear in stating that he thinks manufacturers should disclose the existence of all trials on all uses of all drugs in current use. "All protocols for clinical trials and planned analytic strategies should be published beforehand and any subsequent requests, objections and adjudications for data should be publicly recorded," he added.

"We must acknowledge that requests for data will come not just from independent academics but from competitors, and that is reasonable and good. We must also acknowledge that there are issues around patient confidentiality, but we must also be proportionate about the benefits and the risks of releasing clinical-trial data," he said.

He acknowledged that companies may be worried about the theoretical risk to their product of bad analyses but he was quick to point out that the current situation is full of bad analyses. The solution is very simple – if all protocols and data are made public, anyone can question them," he said.

Goldacre added that, while companies had the right to make money from the drugs they develop, they also have a duty to the public. "We are accustomed to the commercial balance, that's why we have patents. However, to anyone who says that industry can withhold risk/benefit information, I invite them to have that conversation with the public. I don't think they would receive a warm reception," he said.

Industry

Representing industry alongside Forda was Neil Weir. As well as sitting on EFPIA's Research Directors Group, Weir is Senior Vice President of Discovery at UCB Pharma.

He started by telling the room that industry does need to improve its ability to collaborate and communicate simply because this is how it will translate the great science being done in industry, academia and patient groups into the new treatments for the future.

"Through collaboration, we must find better ways to share data and new ways of working together. We must find a balance between when it is appropriate to share data and when it is not. After all, we will not be able to continue our work of bringing benefits to patients unless we are also able to derive suitable commercial return from our ideas," he said.

Weir suggested that an elegant solution might be to appoint an independent assessor to decide what data should be accessible. "In terms of the greater good, we must find a balance between fostering great science and an acceptable commercial environment," he added.

He agreed that there is great concern within the industry around the interpretation of the data. He revealed that, as a whole, industry wants to collect more data through collaborative studies and that the industry is moving towards studies that involve broader groups. "By involving more academic colleagues, many more people will be looking at our data. It is not the case that only people within a company have access to the data; most companies involve clinical experts in the field to help interpret clinical-trial data," he said.

When it came to debating who owns the patient data, Weir was clear. "Patient interests are important but it is important to recognise that a significant investment has been made to gather the data and if it is not owned by the funder this will lead to issues in the future."

Patients

Also speaking at the meeting was François Houÿez, Health Policy officer at EURORDIS, the European Rare Disease Organisation. The risks around data privacy vary depending on the disease area, he told the delegates. "When I started working in rare diseases, I was surprised by how many people were eager to share data if it might benefit others. Yet, at the other end of the scale, when it comes to diseases like HIV/AIDS, patients worry that if a certificate is signed by an infectious-disease department it could reveal their condition to others.

> Patients want to know that the trial they are taking part in has a specific purpose and that their samples will not be used elsewhere.

There is always a risk that data could identify individual patients, he conceded. "I spoke to a parent in Estonia about their child's metabolic disease.

As there are only nine patients with the condition and only one with an English-speaking parent, it would be a simple process to identify that patient. However, if we have to redact ethnicity, country of residence, age or medications, what is left to be analysed? The only way around this is to review what data can be released on a case-by-case basis," he said.

Houÿez said that when patients enter a clinical trial, they trust their clinical trial team. "Patients want to know that the trial they are taking part in has a specific purpose and that their samples will not be used elsewhere. They are not consenting to 'any use' and all consent forms should explain what will be done with the data and all samples."

In addition, making their data public afterwards creates an ethical problem. To address this, he suggested that, if data are to be shared with third parties, it should be clearly stated on the consent form for the trial – even if the third parties are not known at the time that consent is given.

"Data requests must contain information on its purpose, the proposed analytic method and the efforts taken to protect the data. Furthermore, requesters should also disclose any conflicts of interest and be able to demonstrate they have the necessary expertise to conduct the analysis."

European Ombudsman's representative

Gerhard Grill explained that the European Ombudsman has the mandate to examine complaints of maladministration by EU institutions, bodies, agencies and offices. "An important part of our work concerns transparency in general and access to documents in particular. When dealing with such matters we have to follow three main principles laid down in the regulations and case law of EU courts: the widest possible access should be given to documents; any exceptions to that right of access should be strictly interpreted; and any exception must be supported by adequate reasons.

"I would urge that any decisions made by the Agency are in conformity with all the relevant rules, ensuring the relevant documents or data are not covered by any of the applicable exceptions or identify when public interest outweighs the interest of those seeking exceptions."

Assistant European Data Protection Supervisor

Giovanni Buttarelli told attendees how his group foresees getting involved in the complexities of increased data transparency. "The EU Data Protection Supervisor welcomes the proactive approach to identifying key issues where transparency can be increased," said Buttarelli.

"We can help ensure that any steps taken are in compliance with the data-protection legislation. However, compliance will depend on the purposes behind publishing the data and it may be hard to ensure equal protection for all data subjects.

"For example, our position is that, as a rule, sensitive data about patients involved in trials cannot be disclosed, yet we recognise that identifying clinical investigators may be relevant in terms of conflict of interest. I would therefore encourage further discussion on modalities of publication," he said.

The way forward

After hearing from all interested parties, Hans-Georg Eichler, Senior Medical Officer of the European Medicines Agency, outlined the Agency's plans for taking action.

"This process is irreversible," he said. "It is no longer a question of if we start but only of how we achieve it. Many among you may have been wondering why the Agency has been so quiet this afternoon and the answer is simple – we have been listening and we have been adjusting our plan."

From the outset, explained Eichler, the Agency knew that the workshop may not end with a conclusion. "It was clear to us that we would have to cut one big problem into several smaller ones, each to be tackled by experts in that arena. That is where you come in."

The Agency has a clear, year-long plan that will bring the policy into force as early as January 2014, he said.

"I invite everyone present, as well as attendees joining the workshop remotely, to form advisory groups to propose policies that the Agency can adopt or politely refuse."

The advisory groups are:

- protecting patient confidentiality;
- clinical-trial-data formats;
- rules of engagement;
- good analysis practice;
- legal aspects.

All the information on the proposed advisory groups, including dates and application processes, will be available on the Agency's website from December.

Project timelines

- 5-21 December 2012 – Nominations for membership.
- January/February 2013 – Initial sessions to be convened for each advisory group.
- By 30 April 2013 – Final advice from each advisory group.
- By 30 June 2013 – Draft Agency policy to be completed and posted on website for public consultation.
- 30 September 2013 – End of public consultation phase.
- 30 November 2013 – Publication of Agency's final policy, including comments received.
- 1 January 2014 – Policy to come into force.

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