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A ROADMAP FOR SHARING CLINICAL TRIAL DATA

Report of a workshop held at Vlerick Business School, Manhattan Centre, Brussels, 27 August 2013







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On 27 August 2013, Vital Transformation organised a workshop at which key public health stakeholders met to consider the practical implications and examine how data transparency should work in practice. This report outlines the main discussion and sets out some of the recommendations made.

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This event was made possible with the support of:

Vlerick Business School

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INTRODUCTION

The pharmaceutical industry is entering a new era of clinical trials data transparency.

After setting out principles under which the industry is prepared to open up clinical study reports, the European Federation of Pharmaceutical Industries and Associations (EFPIA) is trying to reach a consensus with transparency campaigners, patients' groups, research funders and regulators, on how the principles should be applied in practice.

The sharing of this class of data must be handled in a sensitive and measured way that both protects patient privacy and respects commercial confidentiality. The issues involved in achieving such a balance have been thrown into sharp relief, with the debate polarising academic researchers who want all information to be made available, and companies that have invested large amounts of time and resources in clinical development, seeking to protect their commercial rights.

Under the commitments made in July, EFPIA has pledged to "dramatically increase" the amount of information that is available. But it insists this cannot be a free-for-all: It is necessary to ensure data is shared in a way that protects individual patient privacy whilst maximising public health.

The industry wants to establish a consensus for a system of self-regulation, and head off the European Medicines Agency (EMA) plan to bring in an open data transparency regime in January 2014, under which the Agency is proposing to systematically release the clinical study reports relating all drugs given a marketing authorisation.

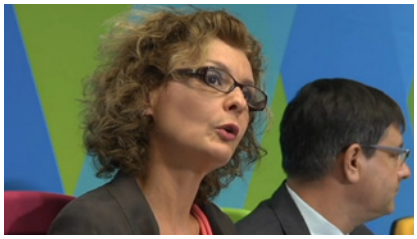
The EMA is due to publish its final policy on 30 November. However, the Agency has already made clear that in its view none of the information in a clinical study report (CSR) can be considered to be commercially confidential once a product is approved.

Meanwhile, EFPIA has said it will begin implementing its data sharing principles on 1 January 2014. The objective is that any researcher who asks a legitimate question should be able to get the data on request, but that appropriate and agreed controls are in place to maintain incentives to invest in clinical research.

On 27 August 2013, Vital Transformation staged a workshop at which key public health stakeholders met to consider the practical implications and examine how data transparency should work in practice. This report outlines the main discussion and sets out some of the recommendations made.

CONTENTS

ANNEXES



Clockwise from top left: Susanna Palkonen, Vice President of the European Patients' Forum; Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency; Duane Schulthess, Managing Director, Vital Transformation; Gisèle Roesems, Deputy Head of Unit - Health and Well-being, DG Connect, European Commission; Ruxandra Draghia-Akli, Director, Health Directorate, DG Research, European Commission and John Crawford, Healthcare Industry Leader Europe, IBM

MAIN OUTCOMES

EXECUTIVE SUMMARY, RECOMMENDATIONS AND SUGGESTED ACTION POINTS

Participants of the workshop at Vlerick Business School in Brussels

While there is general agreement on the need for increased clinical trials data transparency, and some common ground on how this should be delivered in practice, there are areas of contention, most notably over commercial confidentiality and the publication of retrospective data.

Putting these areas of disagreement to one side, it is necessary to draw up rules and standards for how data disclosure is managed at a practical level so that genuine research and the public interest are promoted, whilst ensuring a workable system . Here is a summary of the main points raised in the workshop.

1 Review Panels

EFPIA proposes each company sets up its own system to register and review applications, raising several issues:

a. Is there a need to establish technical standards for doing this to avoid duplication of effort?
b. How will review panels be audited to ensure transparency over who makes requests and monitor how many are turned down and if so, why and by whom?
c. Should there be some form of centralised access, to cut down on bureaucracy by allowing one application to cover requests for access to data owned by more than one company?
d. Once there is an agreement to share data, how will it be accessed? Different models exist, ranging from sending information by email to requiring researchers to access information at the data owner's premises.
e. Is an independent broker needed to supervise the setting up of a research review system and provide oversight of its operation?
f. Tiered access could be considered: if there is no possibility of patients being identified, lighter controls are needed.

Nicola Perrin, Head of Policy, Wellcome Trust

2 Retrospective data

While the industry's data sharing proposals do not cover retrospective data, EFPIA notes that much data is already published routinely. Transparency campaigners meanwhile, are calling for all retrospective studies relating to all currently marketed drugs to be published.

One source of tension is that estimates of how many studies are published vary widely. New research to assess the true picture would be helpful in informing the debate.
Products frequently change hands and it is often the case that

the current owners cannot provide data, particularly relating to early-stage studies, because they did not conduct them. Research to assess the extent of such missing data would reduce suspicion that studies are being deliberately withheld.

Consent forms signed by patients may preclude data disclosure, as may commercial agreements with drug development partners.

Academics need to meet the same standards for disclosure as industry – there should be no differentiation in terms of who is the sponsor.

3 Patient confidentiality and sharing study results with patients

Patients have an interest in the outputs of trials in which they participate being disseminated as widely as possible. But they are also concerned about maintaining confidentiality in the age of big data when it is possible to triangulate different data to identify trial participants.

Patients' groups must be involved in the process of formulating procedures for increasing transparency.

Consent forms vary considerably across Europe, raising the question of if there should be moves to create standards in this area.

There is support for EFPIA's proposal to publish lay language summaries of trials for patients, but there must be independent oversight to ensure the language is understandable and the information is complete.

4 Commercial confidential information

EFPIA and the EMA are at loggerheads over the issue of commercial confidentiality, with EMA saying there is no commercial confidential information in clinical study reports of approved drugs, while the industry says that even if the products are patented, information on know-how and trade secrets in CSRs will allow competitors to cut development times.

The EMA wants the industry to provide "concrete examples" of how publication of CSRs could undermine commercial confidentiality and damage the future of drug research.

From the industry's point of view it is difficult to move the debate forward if EMA does not accept that CSRs may contain confidential information, over which companies should be able to maintain control.

It should not be possible for competitors in parts of the world where patent protection cannot be enforced to access CSRs.

5 Trust

The issue underpinning much of the discussion was trust – or rather lack of trust – between stakeholders.

If trust in the regulatory system is undermined new treatments will not get to patients; trust is needed to keep the wheels of innovation turning.

In fact, there is much common ground and this should be the basis for building trust and coming up with a workable system for data sharing.

Johanna Gibson (left), Director, Queen Mary Intellectual Property Research Institute and Jacqueline Bowman-Busato, Executive Director of the multi-stakeholder health & innovation think tank Epposi

THE PROPOSAL

A PRESENTATION OF THE EFPIA AND PHARMA CLINICAL TRIAL DATA SHARING PROPOSAL

Nicola Perrin, Head of Policy, Wellcome Trust and Beat Widler, Managing Partner, Widler & Schiemann

The industry is "stepping up to the plate" in the debate about data sharing, said Richard Bergström, Director General of EFPIA, outlining the principles for allowing access to clinical trial information that have been agreed by EFPIA and its US counterpart PhRMA (the Pharmaceutical Research and Manufacturers of America).

The 'Principles for Responsible Clinical Trial Data Sharing' call for access to be consistent with the need to safeguard the privacy of patients, to respect the integrity of national regulatory systems and to maintain incentives for investment in biomedical research.

The industry's position should be viewed in the wider context of the extent to which data are shared currently, both in the interests of patient safety and cost-benefit analyses, and to advance scientific research and healthcare. This is best exemplified in the Innovative Medicines Initiative (IMI), the €2 billion public-private partnership set up under the EU's Framework Programme 7, which is due to enter a second €3.4 billion phase in the upcoming Horizon 2020 R&D programme starting in January 2014.

Within IMI 1, EFPIA members have shared information with each other and with SMEs and academic partners, demonstrating that pharma companies "are already committed to open innovation," Bergström said. IMI projects have reported positive results that highlight the benefits of pooling and sharing data.

It should also be noted that the industry has a "history of transparency" having committed to register trials and post results on registries some ten years ago; undertaking to disclose all financial relationships from 2015 onwards; and setting out the principles for sharing clinical trial data in July 2013.

These principles are the foundationof a commitment to further open up access to data from January 2014. Member companies are now making preparations to comply, setting up systems to receive and review research proposals, Bergström told the workshop. This will include the formation of scientific panels to review applications for data. EFPIA has pledged this will be a transparent process, with the names of reviewers and details of requests made public.

The aim is to strike a balance between satisfying legitimate requests for data and the need to protect patient confidentiality and intellectual property. "A framework run by industry is more

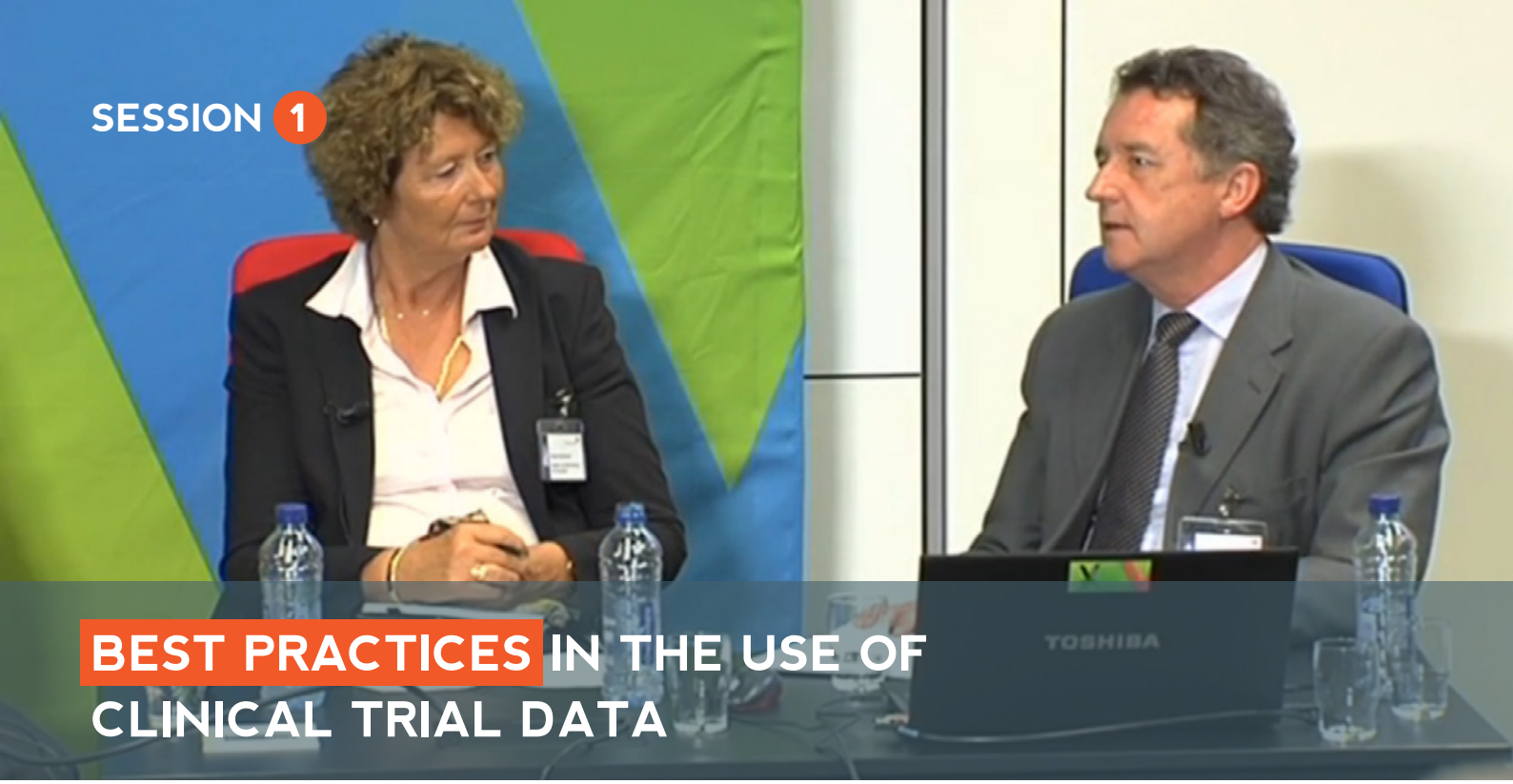
Richard Bergström, Director General, EFPIA

likely to reflect this balance," Bergström said. While the European Medicines Agency as regulator says it needs to be in control of data disclosure, "We as the industry think we should do it ourselves".

Self-regulation will provide an in-built quality control mechanism. While there will be a dramatic increase in the availability of data, the review boards will examine research proposals and "make sure it's not bad science," said Bergström. It will also allow companies – with their understanding of the competitive landscape – to maintain control of commercial confidential information, with accredited researchers required to not give information to competitors.

EFPIA is also committing that "as a minimum" from January 2014 onwards synopses of clinical study reports will be published when a product receives regulatory approval. In addition, patients will be informed about the results of trials in which they participate, in a lay language summary. Bergström acknowledged that publishing the data sharing proposal is not the end of the story. A lot of practical details on how the system is implemented remain to be agreed. "I'm here with open ears. I want to hear from stakeholders about how to make it work," Bergström told delegates.

The event took place at Vlerick Business School's new Brussels Campus



SESSION 1

BEST PRACTICES IN THE USE OF CLINICAL TRIAL DATA

Gisèle Roesems, Deputy Head of Unit - Health and Well-being, DG Connect, European Commission and John Crawford, Healthcare Industry Leader Europe, IBM

There are risks and benefits of the EMA's proposed policy, which plans tosystematically publish the clinical study report when a drug is approved, starting from January 2014. However, the industry will be a major beneficiary, according to Hans-Georg Eichler, Senior Medical Officer, EMA. "It will make the industry more efficient," he told the workshop.

The open trials policy will spawn new avenues of research, enable profiling and open the way for the use of biomarkers to stratify patient populations, and make it possible to carry out comparative effectiveness studies without the need for head-to-head trials.

At the same time, the EMA will face public scrutiny, with its decisions open to examination by third parties. EFPIA and others have cited a consequent risk to the integrity of regulatory systems as a reason to give the industry control over the release of data. But while admitting there may be an uptick in false analyses and health scares, Eichler said, "This is something that has always happened ….. we can live with it."

The risk that the EMA's plan to publish clinical study reports will undermine the investment pharma companies make in product development is the source of the greatest dispute between the regulator and the industry. While the EMA says it respects commercial confidentiality "Where we disagree is over what in a clinical study report is commercial confidential information," Eichler said. "We are of the view that [nothing in a clinical study report] is commercially confidential."

Against the benefits, the most obvious risk is the violation of patient confidentiality. However, the question of how to attenuate this risk is a "technical debate", which the EMA will lead over the next year. Having made the commitment to open data, the EMA is in the thick of working out how to implement it. The draft policy is available for comment until the end of September. EMA's aim in framing its policy has been to "maximise benefits and minimise risks," Eichler concluded.

EMA's intention to publish clinical study reports of drugs approved from January 2014 onwards leaves the question of access to studies relating to currently marketed drugs hanging. It's clear that "all trials of all drugs" are needed to make the best judgements on what are the best treatments, said Ben Goldacre, Wellcome Trust Research Fellow in Epidemiology at the London School of Hygiene and Tropical Medicine, and co-founder of the AllTrials transparency campaign.

AllTrials has three core demands: that all trials are registered, that a summary of results is published and that clinical study reports are available to enable third party researchers "to see the meat and drink" and "spot the methodological shortcomings," Goldacre said.

At present, none of these requirements is satisfied: between one third to one half of all trials are not registered, and

of those that are, estimates on how many summaries are published vary from 22 per cent recorded by independent academic researchers, to 50 per cent according to the US National Institutes of Health, and the claim of 66 per cent made by the industry. “This discussion shows the legislation has failed; you must have continuous audit,” said Goldacre.

In terms of the third requirement, for access to clinical study reports, the EFPIA/PhRMA data sharing proposal does not go far enough to meet the demands of campaigners, with no reference to off-label use and no mention of retrospective trials. “This promise gets us nothing from the past,” Goldacre said.

A further issue is degree of independence of the proposed review panels and the public audit of requests for access. “We need to see who tried to get access, and if rejected, why and by whom,” Goldacre told delegates.

Patients are increasingly participating in their own care and to make this involvement meaningful it is “vital” clinicians and patients have access to all the information needed to make decisions,” believes Susanna Palkonen, Vice President of the patients’ group European Patients’ Forum (EPF). However, positive trials are two times more likely to be published than negative ones. “EPF wants all trials published in a timely manner, regardless of if they are successful or not,” Palkonen said.

While the EFPIA/PhRMA commitment to publish summaries for patients is welcome these summaries should be reviewed to make sure they are complete and that the language is understandable. However, raw data is needed also, to enable a study to be re-visited. “This can be of use to patients’ associations,” said Palkonen.

For Palkonen, another element that is missing from the EFPIA/PhRMA proposal is the moral imperative – of recognition of respect for trial participants. “It can be considered the data belong to the participants, and by extension to the wider society; it can’t be owned by commercial entities or academics.”

There are complex issues to be dealt with in coming up with a system for sharing clinical trials data. EPF wants to contribute and currently is discussing with its members – which include 55 disease-specific groups and national patients’ groups – on how best to share data. Over and above the publication of clinical study reports, tools are needed to access and use the data.

EPF is particularly concerned about the question of who gets access to individual patient data, and Palkonen said patients’ organisations must be involved in formulating procedures to ensure confidentiality is protected, whilst at the same time allowing data to be shared in a way that potentiates research.

Beat Widler, Managing Partner, Widler & Schiemann

SESSION 2

BUILDING A DATA SHARING HEALTH INFRASTRUCTURE

From left: Richard Bergström, Director General, EFPIA; Ben Goldacre, Wellcome Research Fellow in Epidemiology, London School of Hygiene and Tropical Medicine; Alastair Kent, Director, Genetic Alliance UK; Susanna Palkonen, Vice President of the European Patients' Forum and Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency

Whatever the points of difference over specific aspects of transparency, there is a general push and willingness to increase access. The second session 'Building a data sharing health infrastructure' considered the contribution that such a new era of transparency can make to advancing science and healthcare. Practical measures and best practices for data sharing to realise this potential were discussed.

One small but powerful example of how increased processing power, new data analytics and patient-level data can lead to advances in health care is the EUResist database, set up to reduce antiretroviral drug resistance and help clinicians in selecting which of the huge number of options for treating HIV is the best for each patient at different time points in the natural history of the infection.

The system factors 60,000 previous treatment histories against 70,000 examples of different viral loads and 150,000 possible combinations of drugs. "It is better than all but one in ten doctors we pitted the system against; whilst it only gets it right 75 per cent of the time, this is better than the experts, so you begin to see the potential," John Crawford, Healthcare Industry Leader Europe at IBM, told delegates. EUResist illustrates how it is possible to take advantage of the huge pools of data that are available to improve first-line decision making, resulting in patients getting the most appropriate treatment at the outset, with cost-savings for healthcare systems.

In another example, IBM's Watson supercomputer is used by the US health insurer WellPoint to authorise requests from physicians to administer particular treatments. The system makes decisions in three seconds, with only ten per cent of cases needing to be referred for a more in-depth assessment by clinical experts. Similarly, in a project with researchers at Memorial Sloan Kettering Cancer Center in New York, Watson has been shown to be better than oncologists at making a correct diagnosis, with the number of cancers diagnosed correctly on the basis of first opinion increasing from 50 per cent to 90 per cent. Watson does not understand human biology. Rather it uses information tied up in patient records and medical journals to weigh all available evidence and list evidence-based treatment options and the confidence limits for each, within seconds. "This is driving a fundamental change in the way doctors think," Crawford said.

These are profound illustrations of how third generation cognitive computing – or big data as it is familiarly known – can make sense of repositories of patient-level data. These insights can be used to deliver remarkable improvements in healthcare, both in terms of treatment and administration, highlighting the need to rethink and reform how information is managed going forward.

"Data sharing is essential across the whole piece to get the most value,"

Nicola Perrin, Head of Policy at the UK medical research charity, the Wellcome Trust, told delegates. Different scientific and clinical disciplines are in different positions vis-à-vis the amount of data that is shared and the speed with which it is made available. Genomics has led the way, but other researchers in public health and epidemiology may be less inclined to share information, if they have spent years recruiting subjects to cohort studies.

Similarly, electronic health records and clinical trials data represent an important and as yet underutilised resource. The way in which the opening up of access to clinical trials is managed is particularly delicate. "There's a real obligation to participants to make sure we get this right," said Perrin.

Although there may not be full compliance, the mechanisms are in place for handling the first two levels of transparency – of registering clinical trials and recording the main summary findings on registries such as clinicaltrials.gov. Now a system is needed for opening up patient-level data under some form of controlled access. There are a number of models for doing this and Wellcome currently is carrying out a study to pull together best practices. This is considering not only how review panels assessing requests are organised and what level of external scrutiny there is, but also how data is accessed once permission is given.

As more data repositories become available, the Wellcome Trust anticipates a need to consolidate the review process to avoid duplication and ensure the system is workable. The Trust is currently making moves to establish a single panel to handle access requests across its multiple genomics databases, for example.

Whilst there are existing models for providing controlled access, many issues remain to be resolved to ensure the maximum value can be extracted from this information source. This raises questions of whether standards – both at a technical and administrative level – are needed; if it should be possible for researchers to make a single request and have a single point of access to clinical trials data from two or more companies; and how industry and academic trials should be linked.

The Wellcome Trust is now involved promoting the formation of a global consortium to coordinate moves to provide access to patient-level data, and Perrin said the Trust is prepared to act as broker in helping the pharma industry set up and run a controlled access system. "We are interested in a joined-up model, and helping to get there, if there is agreement," she said.

In August the Association of the British Pharmaceutical Industry launched a clinical trials disclosure toolkit to assist members in complying with the transparency provisions in its code of conduct. The toolkit was developed by Beat Widler, Managing Partner at Widler & Schiemann, based on his experience in implementing a disclosure compliance system at Roche.

The toolkit is "a starting point" showing companies how to go about ensuring compliance and how to deal with the practical issues. It provides a single generic approach to managing the process of clinical trial data disclosure, to avoid each company re-inventing the wheel and allowing the industry to share best practice going forward, Widler told delegates. It is hoped the toolkit will provide a framework for changing attitudes towards disclosure from it being a routine (and often neglected) task, to being a key deliverable.

However, no toolkit can equip the industry to meet transparency campaigners' demands for all data on all prescription drugs currently on the market to be released. "It's hard to go back 20 years," Widler said. "Often big companies don't have the information because they didn't do the study."

As Gisèle Roesems, Deputy Head of Unit – Health and Well-being, DG Connect told the workshop, DG Connect initiatives to provide the framework for sharing health data will be continued when the new €70 billion Horizon 2020 research and development programme begins in January 2014. This includes such measures as building data repositories, promoting standards for interoperability in ehealth and telemedicine; funding research projects in ehealth and personalised medicine; and calling for the installation of the information and communications networks that are needed to underpin data sharing..

In addition, there will be moves to foster development of the emerging mobile health (mhealth) market, Roesems said. "mhealth apps are becoming widely available and we think we need to create a framework where citizens can build up trust – after all, anyone can develop an app," she said, noting that mhealth could bring benefits for Europe's hard-pressed healthcare systems by empowering patients and helping them to manage their own medical conditions.

One specific project in Horizon 2020 will look at the technical issues behind integrating data from mhealth apps with electronic health records.

SESSION 3

BALANCING PUBLIC HEALTH AND COMMERCIAL CONFIDENTIALITY

Ruxandra Draghia-Akli, Director, Health Directorate, DG Research, European Commission

For the European Commission, striking the correct balance in allowing access to patient-level data goes to the heart of the disclosure process. "We do have to increase the transparency of clinical trial data" and "use the data to generate new knowledge" in order to promote faster development of better treatments, said Ruxandra Draghia-Akli, Director of the Health Directorate, DG Research of the European Commission.

But on the other hand, the Commission also emphasises growth, competition and the protection of intellectual property in the global and the trade context. Experience from the Commission's own research programmes, in partnerships with member states and in collaborations with the pharma industry in the Innovative Medicines Initiative, has shown that sharing information can be balanced in a way that protects both patient and commercial interests, to the benefit of science.

"The devil is in the detail," Draghia-Akli said. It is necessary to work with various stakeholders to foster the development of science and bring new treatments to patients faster and without compromising patient confidentiality.

Johanna Gibson, Director, Queen Mary Intellectual Property Research Institute also thinks that a balanced approach is important, but she said the problem is that different stakeholders are balancing different factors. For Gibson, intellectual property is an enabler of data sharing, rather than – as portrayed currently – the barrier to sharing. "IP's fundamental value is to provide an incentive to share what you are doing," she said. "While the focus is on how data is used, the risk is that it isn't."

So rather than setting down and enforcing a prescriptive set of rules governing data disclosure there should be moves to build a culture that embraces transparency. One of the key elements of this is public engagement, to stress co-ownership, in a popular rather than a legal sense. "That's where the momentum comes from [for participating] in biobanks, for example," Gibson said.

Jacqueline Bowman-Busato, Executive Director of the multi-stakeholder health & innovation think tank Epposi, agreed intellectual property is not the problem. Rather she said, "Trust is the problem."

Although at first glance it appears there is some distance between EMA and EFPIA in terms of the definition of commercial confidential information, Bowman-Busato said, "In fact [the two] are reasonably aligned; agreeing is down to trust." To inform this discussion, Epposi is currently carrying out an assessment of what factors should be considered when decisions about releasing data are taken.

Public health and commercial confidentiality can be reconciled, but the context for this is the recognition that there is a public health interest in maintaining commercial confidential

information to drive the pharma industry forward, said Neal Parker, Section Head Legal – Biologics Strategic Development, Abbvie.

Much of the information that is contained in marketing applications is made public currently. In addition, scientists involved in industry-sponsored trials regularly present results at conferences. “In other words, a vast amount of data is released without any controversy,” Parker said.

The question of how to decide what of the remaining data is shared depends on a product-by-product analysis of the competitive landscape and will differ company-by-company. For this reason data release “has to be in the control of companies” said Parker. Information on study design, protocols, subject-level and study-level results could be used by other companies to speed up development of competing products.

Controversially, Parker suggested that the level of control needed to protect commercial confidential information could include withholding details of adverse events; an opinion that has gone viral via twitter feeds and been featured in a recent article by the BMJ.

Parker said Abbvie is committed to give access to clinical study reports to allow others to duplicate results and “prove or disprove what the label says.” But third party researchers do not need access to the internal judgements or rationales for routing a product through a particular development pathway to get approval, as articulated in clinical study reports, to be able to test the robustness of the outputs. “Information released without prohibition undermines the public interest in the release of data in the first place,” Parker said. However, he added, “That’s not saying it wouldn’t be released if we get a promise not to share it with competitors.”

Bergström said most EFPIA members are “quite relaxed” about the clinical study reports for most products being released. But there can be issues about data going to a company developing a competitor product, or in the case of a biologic drug, information about expensive bridging studies. Another example involves the re-purposing of existing drugs where the compound itself is generic. In all, Bergström estimates such sensitivities apply to about 10 per cent of products.

The question of data release is also sensitive at a global level because it could allow copying in locations where intellectual property rights cannot be enforced.

Information will be made available for legitimate research, providing commercial confidentiality and patient confidentiality are respected. “But we don’t want all data out there for everyone,” Bergström said.

ANNEX I

Principles for Responsible Clinical Trial Data Sharing

Our Commitment to Patients and Researchers

Biopharmaceutical companies are committed to enhancing public health through responsible sharing of clinical trial data in a manner that is consistent with the following Principles:

- **Safeguarding the privacy of patients**
- **Respecting the integrity of national regulatory systems**
- **Maintaining incentives for investment in biomedical research**

Companies routinely publish their clinical research, collaborate with academic researchers, and share clinical trial information on public web sites at the time of patient recruitment, after new drug approval, and when investigational research programs have been discontinued.

Biopharmaceutical companies will apply these Principles for Responsible Clinical Trial Data Sharing as a common baseline on a voluntary basis, and we encourage all medical researchers, including those in academia and in the government, to promote medical and scientific advancement by adopting and implementing the following commitments:

1. Enhancing Data Sharing with Researchers

Biopharmaceutical companies commit to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and the European Union (EU) as necessary for conducting legitimate research. Companies will implement a system to receive and review research proposals and provide applicable data and protocols to help facilitate such scientific and medical research.

Each company will establish a scientific review board that will include scientists and/or healthcare professionals who are not employees of the company. Members of the scientific review boards will participate in the review of data requests to determine whether they meet the criteria described below regarding the qualifications of the requestor and the legitimacy of the research purpose, unless a company makes an initial determination on its own to share applicable clinical trial data. Companies will publicly post their data request review process and the identity of the external scientists and healthcare professionals who participate in the scientific review board, including any existing relationships with external board members.

Companies will provide access to patient-level data and other clinical trial information consistent with the principle of safeguarding patient privacy; patients' informed consent provided in relation to their participation in the clinical trial will be respected. Any patient-level data that is shared will be anonymized to protect personally identifiable information. Companies will not be required to provide access to patient-level data, if there is a reasonable likelihood that individual patients could be re-identified. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions

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may preclude granting access under these Principles. Where co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

Data requestors will be required to submit a research proposal to document the legitimacy of the research question and the qualifications of the requestor. Research proposals should include, and will be evaluated against the following: a description of the data being requested, including the hypothesis to be tested; the rationale for the proposed research; the analysis plan; a publication and posting plan; qualifications and experience of the proposed research team; a description of any potential conflicts of interest, including potential competitive use of the data; and the source of any research funding.

Researchers who are provided access to company data will be encouraged and expected to publish the results of their analysis. Researchers must agree not to transfer the shared data or information to parties not identified in the research proposal, use the data for purposes not contained in the research proposal, or seek to re-identify research participants.

2. Enhancing Public Access to Clinical Study Information

In order to help patients and healthcare professionals understand the results of clinical trials and the evidence used to approve a new medicine, following approval of a new medicine or new indication for an approved medicine in the US and EU, biopharmaceutical companies will make publicly available, at a minimum, the synopses of clinical study reports (CSRs) for clinical trials in patients submitted to the Food and Drug Administration (FDA), European Medicines Agency (EMA), or national competent authorities of EU Member States. Companies will make this information available consistent with the need to protect patient privacy, publication rights, and confidential commercial information through appropriate redaction. In addition, companies will evaluate requests for full CSRs, including patient-level and study-level data, and share them under the terms of commitment 1 above. Companies will make available CSR synopses filed with regulators on or after January 1, 2014; such CSR synopses will be made available within a reasonable period of time after approval of the product and indication.

3. Sharing Results with Patients Who Participate in Clinical Trials

In order to help inform and educate patients about the clinical trials in which they participate, biopharmaceutical companies will work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants.

4. Certifying Procedures for Sharing Clinical Trial Information

Companies following these Principles for Responsible Clinical Trial Data Sharing will certify on a publicly available web site that they have established policies and procedures to implement these data sharing commitments.

5. Reaffirming Commitments to Publish Clinical Trial Results

All company-sponsored clinical trials should be considered for publication in the scientific literature irrespective of whether the results of the sponsors' clinical trials are positive or negative. At a minimum, results from all phase 3 clinical trials and any clinical trial results of significant medical importance should be submitted for publication. This commitment also pertains to investigational medicines whose development programs have been discontinued.

Implementation of these commitments will begin on January 1, 2014.

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Questions & Answers

Q What type of information are biopharmaceutical companies prepared to share with qualified medical and scientific researchers under commitment 1?

A The biopharmaceutical industry is committing to sharing with qualified medical and scientific researchers patient-level data, study level data, and clinical study designs and protocols.

Patient-level data refer to information on individual patients collected during a clinical study, including: demographic data, lab results, baseline characteristics, drug concentration, biomarker and pharmacogenetic data, and adverse events experienced. Such information has been gathered and recorded on case report forms (CRFs), or captured electronically and inputted into electronic databases, where it can be readily organized into patient-level listings and datasets. This information is created through what the Institute of Medicine (IOM) has described as a process by which data in a clinical study originate with CRFs, either handwritten or electronic, then go through several stages of auditing, queries, and refinement by original investigators and study staff to resolve ambiguities, and then ultimately yield "individual participant data."[1]

Study-level data consist of patient-level data that have been amalgamated, compiled and tabulated, manipulated, stratified, or otherwise organized into study-level data sets, to be used in interpreting the outcome of a clinical study. Study-level data present clinical trial data in an objective manner, without subjective analysis or interpretation, usually in tabular, graphic, or statistical form showing, for example, averaged, stratified, or patterned presentations of study data gathered. Examples would include a table that presents cross-patient data on baseline patient characteristics (demographic and disease-related), patient disposition (i.e., numbers/percentages of patients who completed or discontinued the trial), endpoints (primary, secondary, and other), study drug exposure, adverse events, vital signs, and laboratory and other safety measures provided for the overall study population, and by subgroups.

Clinical study design information and protocols direct investigators how to run a particular study. Protocols give instructions to the investigators on, for example, what drug to give and when, what study measurements to take and when and how to record them, and how to treat and record adverse events.

Q What is the rationale for providing the synopsis of CSRs in commitment 2?

A Given the volume of data contained in regulatory submissions – often running to millions of pages – companies commit to publishing a synopsis after marketing approval in the US, EU, or member states. The synopsis will provide patients and their physicians with enhanced information about the results of clinical trials and the evidence used to approve a new medicine. The synopsis is a part of the CSR and is reviewed by the FDA and EMA as part of their approval. In order to accelerate research and advance scientific understanding, companies will also evaluate requests for full CSRs, including patient-level and study-level data, and share them under the terms of commitment 1.

In addition to providing the synopsis, some companies may choose voluntarily to provide to the public additional parts of CSRs redacted to protect patient privacy and confidential commercial information.

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Q Why may it be necessary to limit the availability of patient-level data for clinical trials conducted involving patients whose data are likely to be re-identified?

A Protecting the privacy of patients who participate in clinical trials is a critical obligation of biopharmaceutical companies that sponsor and conduct medical research. It may be possible even for "anonymized" patient-level data to be re-identified using modern data mining techniques.[2] For this reason, companies generally withhold patient-level information from disclosure when there is a reasonable possibility that patient privacy could be jeopardized. The risk of "re-identification" is significantly higher when the number of patients is small, such as is typically the case for trials involving patients with rare diseases, which may include as few as 25 or fewer patients.

Q Under commitment 1, are companies committing to share patient-level data and other proprietary information with competitors?

A No. Discovering and developing new medicines is a long, complex, and costly process. For every 5,000 to 10,000 experimental compounds considered, typically only one will gain FDA approval, after 10 to 15 years of research and development costing an average of $1.2 billion, based on a 2007 study. The few successes must make up for the many failures. In fact, only two out of every 10 medicines will recoup the money spent on their development.

Biopharmaceutical companies are dedicated to fostering a sustainable research ecosystem that protects the ability of companies to make extremely costly investments to discover and develop new medicines. One of the risks to innovation is disclosure to competitors of companies' trade secrets and proprietary information that could allow others to "free ride" off of the substantial investments of innovators. Such an environment will not foster the ability of companies to make decades-long investments in new medical technology. Therefore, in a sustainable research ecosystem, companies must be certain that their proprietary information will remain secure from disclosure to competitors. That is why commitment 1 calls for a company to share patient-level data and other confidential commercial information — which could be used to help gain approval of a competing medicine — only for legitimate scientific and medical research. Commitment 1 reflects these concerns by allowing companies to consider requests for release of clinical information in light of potential conflicts of interest, including any potential competitive use of the data.

Under commitment 1, companies will evaluate, among other things, whether the research proposed has a legitimate scientific or medical purpose, including whether there is any potential conflict of interest between the data requestor and the company or competitive use of the data. In the latter case, it may be assumed that the data requestor may intend to use the company's patient-level data or other information to help gain approval of a potentially competing medicine. While companies may enter into agreements to co-develop medical products, these data sharing Principles are not intended to allow free-riding or degradation of incentives for companies to invest in biomedical research. Accordingly, it would be appropriate under commitment 1 for companies to refuse to share proprietary information with their competitors.

Q How will companies determine who can receive patient level data or other proprietary information?

A Each company will implement a system for reviewing research proposals and the credentials of requesting researchers to determine that the proposed research is bona fide. Companies may choose to implement these systems individually or with centralized scientific review boards. Among the considerations for protecting patient privacy are the research participants' informed consent and other legal permissions, such as privacy authorizations (e.g., HIPAA in the United States) and/or data use agreements. With respect to these commitments to patients, any patient-level data that can be shared will, therefore, be "anonymized" in accordance with applicable legal requirements to protect personally identifiable information. Companies will not provide access to patient-level data when there is a reasonable likelihood that individual patients could be re-identified. In addition, where co-development

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agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information if feasible.

Q Will there be any other restrictions on use of data provided under commitment 1?

A Each company will determine the best method for safeguarding the privacy of patients and ensuring that access to patient-level data does not jeopardize incentives for future investment in biomedical research. Commitment 1 requires that data requestors must agree not to transfer shared data to parties not identified in the research proposal, use the data for purposes not contained in the research proposal, or seek to re-identify research participants. Companies may also require that the data are only used for non-commercial purposes. Additional conditions may include granting access to the data only on a company's information system and/or requiring that data requestors notify the company of any safety finding that may be reportable to regulatory authorities or of other significant results.

Q Other than patient privacy information, what type of information could be withheld from CSR information provided to the public under commitment 2?

A In order to maintain incentives for future investment in biomedical research, individual companies may choose at their discretion to withhold from public access to CSRs various business and analytical methods; manufacturing and pre-clinical information or other confidential commercial information; any information not directly related to the conduct of the study or that could jeopardize intellectual property rights; or information that the company has no legal right to share (e.g., due to an existing co-development agreement).

Information withheld from public access to CSRs may nevertheless be available to qualified researchers under the terms of commitment 1.

Q If a company chooses, may it share more clinical trial information than is described in these commitments?

A Yes. Companies will make their own determinations regarding how to implement these commitments and whether to exceed these common commitments to responsible data sharing. For example, companies may choose to provide voluntarily to members of the public the main body of CSRs redacted to protect patient privacy or confidential commercial information.

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[1] Institute of Medicine, Sharing Clinical Research Data: A Workshop Summary 10 (2013).

[2] See Melissa Gymrek et al., Identifying Personal Genomes by Surname Inference, 339 SCIENCE 6117 321-324 (2013).

JULY 18, 2013

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ANNEX II

ABPI TOOLKIT WILL HELP MEMBERS MANAGE CLINICAL TRIALS DISCLOSURE PROCESS

Research by the ABPI indicates current statistics on the state of play in transparency are not accurate. A toolkit will guide members in complying with disclosure requirements and generate more reliable information on compliance

Bina Rawal, Director of Research, Medical and Innovation, ABPI

The debate of the past year – and the initiatives of some individual pharmas – illustrates that while the industry in increasingly committed to transparency there is no prescribed route for companies making moves to open up clinical trials data stores.

In the UK, the Association of the British Pharmaceutical Industry (ABPI) made a pledge to increase transparency in February this year, by putting in place measures to monitor compliance to the clinical trial transparency provisions contained in its Code of Practice. At the same time the ABPI said it would provide a clinical trial disclosure toolkit to assist members with compliance.

The toolkit, launched in August, is intended to guide companies through the different steps of the disclosure process. "Expectations about transparency are definitely changing, and that's a good thing. Our members vary enormously from small biotechs to large international pharmaceutical companies and we wanted to set out a single generic approach to managing the process of clinical trial disclosure," says Bina Rawal, Director of Research, Medical and Innovation at ABPI, who has spearheaded preparation of the toolkit. "It's ready to take off the shelf and modify and embed within the clinical research process."

Transparency is not something that can be retrofitted, but needs to be threaded through clinical development. This should ensure disclosure is handled in an appropriate and balanced way, and create an audit trail that can be used to demonstrate compliance. Rawal believes this will help address one of the main sources of dispute between campaigners and the industry, which is that there is no reliable information on the current state of play in clinical trials transparency. "It's become an accepted figure in the public debate that half of all trials go missing; based on my experience of working in the industry that just doesn't resonate with me," Rawal said. After joining the ABPI in October last year, Rawal commissioned research to test this statistic. The work involved checking to see how many of the trials that fed into the files of the 53 new drugs approved by the European Medicines Agency in the three years from the beginning of 2009 to the end of 2011 had been published.

The research is currently awaiting publication in a peer review journal, so Rawal does not want to give figures at this point, but said, "It's clear the situation is not as bad as it is painted, and is a lot better than in the past." Some of the early studies of the drug approved from 2009 – 2011 were done more than ten years previously, and it is these that are more likely to be missing from the record, rather than later stage trials.

Rawal also pointed to the complications of ascertaining what trials have been published and where. "This is a difficult area to get a handle on the evidence, there's no single registry system, or single type of trial, data could be published in a wide range of places," she said. One significant and widespread issue that has emerged from the research is that products frequently change ownership during development and current rights owners do not have access to data from earlier trials. Rawal said this underlines the need to embed transparency measures so that when a drug changes hands, the data goes with it. "You have to involve the legal function and ensure clauses are written into deals ensuring access to data," she said.

In the case of the ABPI research all the trials listed in the EPARs (European public assessment reports) of the 53 drugs were tracked down to see if the data was in the public domain. For studies that were not disclosed, the researchers then referred back to the companies concerned to find out why not. "For any that were not disclosed we have a statement from the medical director explaining why," said Rawal.

Overall, says Rawal, "There's a very different picture from that painted in the public debate."

GLOBAL CONSORTIUM IS NEEDED TO MANAGE ACCESS TO PATIENT-LEVEL DATA

Providing controlled access to identified patient-level information is an essential element of realising the full potential of clinical data stores. A global agreement is required to put in place formal mechanisms and ensure appropriate access, says Nicola Perrin, Head of Policy at the Wellcome Trust.

Nicola Perrin, Head of Policy, Wellcome Trust

All researchers funded by Wellcome are required to maximise access to their data and clinical trials – including ones where the results are negative – are no exception. Specifically, this means all studies must be registered, and the summary results reported, on public registries such as clinicaltrials.gov.

The debate around clinical trials transparency has provided a spur for the Trust to step up its monitoring process to check the researchers it funds are complying with these requirements, says Nicola Perrin, Head of Policy. Overall, she believes it is now generally acknowledged both by academics and industry that there is a duty to register and report trials.

This represents important progress in terms of transparency, but it still leaves much of the potential of clinical trials data under-exploited. There is now a need to put in place formal mechanisms for allowing access to patient-level data. “At present there are some ad hoc approaches. If we could get it right, this would reduce duplication, answer new research questions and stimulate innovation,” Perrin said.

Whilst the Wellcome Trust wants to encourage access to identified patient data, patient confidentiality remains the overriding concern. “This type of data should not be openly published; there should not be a free-for-all,” said Perrin. Some form of review process is needed, both to check the bona fides of researchers applying for access, and the scientific value of their proposed research. There are models here, such as the procedures for accessing a named individual’s samples and data from biobanks, which could form the basis of such a system.

The initial opening up of pharma industry clinical trial data stores, for example by GlaxoSmithKline and Roche, is happening at the level of individual companies, with each setting up its own panels to review research requests. A coordinated approach is required. “What won’t work is if everyone has their own system,” Perrin said.

Such coordination would allow research to be carried out linking separate industry sponsored clinical studies, and enable access to the relevant data sets via a single portal.
Over the past 12 months, the argument over clinical trials data transparency has moved in a positive direction. There is now agreement not only about listing and reporting trials on registries, but also on the value to be extracted from balanced and controlled access to patient-level data. “There is agreement transparency is right. The question is how do we do it, how do you get best practice?” Perrin said.

The Wellcome Trust is now involved in moves to promote the formation of a consortium to steer a system into place. This would apply to future trials. “There needs to be appropriate consent by patients, so the idea is to have something in place so we can get it right from now onwards,” said Perrin. “The consortium has to be global, it has to involve academics and industry, and has to cover the whole spectrum of clinical research.”

IT'S TIME FOR RAPPROCHEMENT BETWEEN ACADEMIC CAMPAIGNERS AND PHARMA COMPANIES OVER CLINICAL TRIALS DATA TRANSPARENCY

The current polarised debate is not helpful to anyone, least of all patients, says Alastair Kent of Genetic Alliance UK

Alastair Kent, Director, Genetic Alliance UK

"There's absolutely no point in having a polarised debate where people are standing on soap boxes and shouting at each other," says Alastair Kent, Director of Genetic Alliance UK, a body representing more than 160 rare diseases patients' groups, commenting on the current impasse in Europe over opening up access to clinical trials data.

"You are going to end up in a situation where patients lose rather than gain because the pace of development slows and undue attention is given to any problems with a drug, rather than the benefits."

The way forward is to recognise that both patient confidentiality and commercial confidentiality must be factored in to any equitable and practicable clinical trials data transparency system, but that one cannot trump the other, that neither is absolute, and – in particular – that the industry cannot use patient confidentiality as a "magic shield" to avoid answering awkward questions, Kent says.

"Fundamentally, I, and I think most patients' groups are in favour of transparency. But that does not mean putting everything in the public domain for anyone who wants to look at it."

The approach taken in rare diseases provides a model for how to move forward, and will be increasingly useful as the advance of personalised medicine leads clinical trials of drugs for treating common, complex, chronic diseases to be stratified into small subsets of patients.

Patients with rare diseases want the maximum value possible to be extracted from any samples and data they contribute to clinical studies. They are also keen to be on rare disease registries set up to promote research, increase understanding of the natural history of a rare disease, and for identifying patients who could participate in a clinical study.

"When setting up a registry, all sorts of things need to be taken into account and incorporated into the original consent document. By participating in a registry you know data and samples will be available for research purposes, and you also get the benefits of visibility," said Kent.

As Kent noted, those allowed access to registries could be public sector academics, but given rising commercial interest in rare diseases, they could equally be pharma companies, highlighting the fact that a proportionate data transparency regime should not exclude competitors from getting access to data.

Methods for providing access without compromising an individual's privacy already work in practice. Kent pointed to researchers who get grants from the UK Economic and Social Research Council being required to place their raw data in secure archives. Similarly, resources such as the UK Biobank and the 1000 Genomes Project, which relate to named individuals, will be open for public and private researchers who demonstrate appropriate credentials.

"There are models for allowing data transparency, while protecting individual and commercial interests. It's fair enough to share non-identified, pooled data in the public domain, alongside secure data archives that are accessed by approved researchers," said Kent.

Overall, "You can't allow one side or the other of this argument to win," Kent believes. "If the rules are too draconian you will prevent discoveries from happening. If things are too laissez-faire, with no respect for commercial confidentiality there's less incentive to invest and a risk the regulatory system gets undermined," he said.

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