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New Clinical Trial Regulation in Europe—A Move to Greater Transparency

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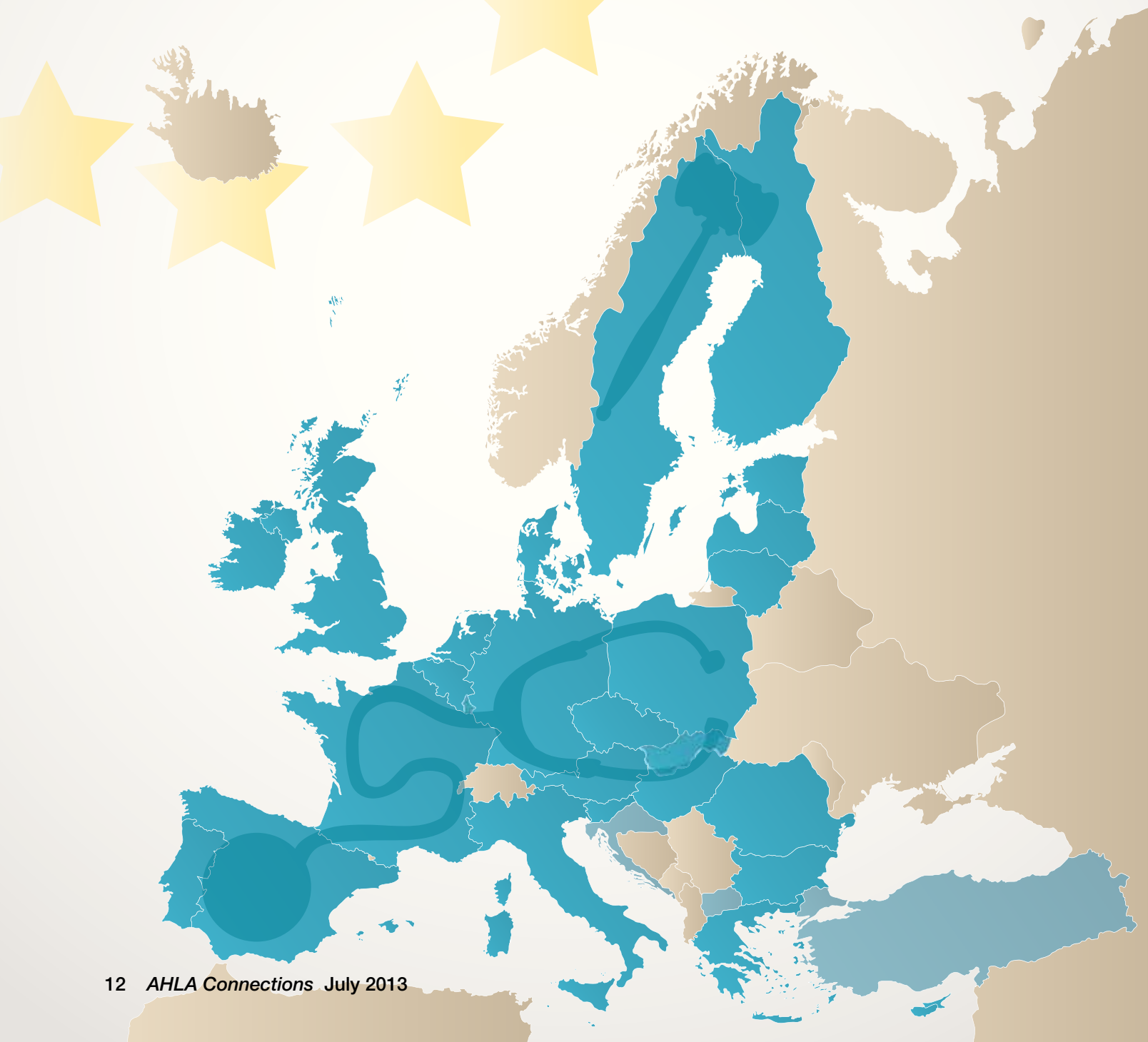

Current Situation in Europe

A draft report by the European Parliament (EP) on January 31, 2013 stated that one of the major problems at the moment with the regulation and performance of clinical trials in Europe is the lack of transparency of clinical trial results.

The report concluded that this lack of transparency has reduced public trust in trials and their findings, stating:

> *Independent academics often find it difficult to get the data they need to verify the results of trials and carry out systematic reviews, and a lot of data is withheld. It is also known that when trials are unsuccessful the results are often never published or made available at all. Trials can be carried out repeatedly before it becomes public knowledge that they are ineffective or even dangerous.*[1]

Current Regulation in Europe

Directive 2001/20/EC on the approximation of laws, regulations, and administrative provisions of member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the Directive) was implemented to (1) standardize research activity in clinical trials (2) harmonize the regulation and framework of clinical trials among member states of the European Union (EU) and (3) provide greater protection for clinical trial subjects.

Since its implementation, the Directive has been heavily criticized by numerous stakeholders, particularly because a result of the Directive has been greater administrative burdens with a consequential increase in costs.[2] The European Commission (EC) has even commented that the Directive is arguably the most heavily criticized piece of EU legislation in the pharmaceutical area.[3]

The EC assess that this is due to the following reasons:[4]

- The Directive may have contributed to a significant decline in the attractiveness of patient-oriented research and related studies in the EU (as between 2007 and 2011, the number of applications for clinical trials in the EU fell by 25%);
- Post implementation, costs for conducting clinical trials have increased, particularly due to the increase in administrative requirements for non-commercial sponsors and because the clinical trial authorization process under the Directive can be cumbersome;
- Insurance fees have increased by 800% for sponsors of clinical trials, to a certain extent as a result of the Directive; and
- Post implementation, the average delay for launching a clinical trial has increased by 90% to 152 days across Europe.

The EC's Proposal for Change

The Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (the Proposal) was adopted by the EC on July 17, 2012 and aims to repeal the Directive and replace it with a regulation that addresses the shortfalls of the Directive. The scope of the Proposal is essentially identical to that of the Directive, focusing on the rights, safety, and well-being of subjects and the generation of reliable and robust data in clinical trials on medicinal products for human use.

Why a Regulation?

The Proposal takes the form of a regulation rather than a directive to ensure consistency in its application by member states, as the transposition of the previous Directive into national law led to varied legal regulations of clinical trials across Europe.[5]

The Proposal seeks to make the following key changes to encourage transparency of medical data in clinical trials:

- The introduction of a new authorization procedure for clinical trials that will involve a harmonized authorization dossier and a 'single portal' for submitting an application for conducting a clinical trial. This will be linked to an EU database holding information on all trials, whether successful or not. The aim is to achieve greater collaboration on approval by authorities throughout the EU;
- Making a clear distinction between 'scientific advice' (which establishes which clinical data are desirable in order to possibly grant or uphold a marketing authorization at a later stage) and 'clinical trial authorization' (which establishes if a clinical trial is acceptable in view of patient rights and safety on the one hand and data reliability and robustness on the other hand);
- Trial sponsors will have to (a) ensure that the group of subjects participating in the trial reflect the target population groups (including an age and gender balance) to ensure that the safety and efficacy of the drugs are evaluated accurately for the population that will ultimately be treated, and (b) provide a systematic review of the existing data on the investigational medicinal products;

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- Including rules for clinical trials conducted outside the EU but referred to in a clinical trial application within the EU (these clinical trials must comply with regulatory requirements at least equivalent to those in the EU);
- Leaving the decision to member states as how to best organize, internally, the attribution of tasks to different bodies to approve or reject clinical trials;
- Does not regulate or harmonize the precise functioning of local ethics committees;
- Remains focused on the importance of establishing a clear distinction between aspects where member states should coordinate with each other in the assessment of the application for authorization of a clinical trial and those aspects where member states should construct their assessment individually; and
- Ensuring that no personal data of subjects participating in a clinical trial will be collected in the EU database.[6]

The Draft Report

An amended draft report by Glenis Willmott, a member of the EP, on the Proposal (the Draft Report) seeks to advance the amendments made by the Proposal, in particular by:

- Adding a requirement for prior approvals of ethics committees composed of lay persons, patients, and healthcare professionals;
- Trial sponsors will be required to state the reason for the withdrawal of any clinical trial application via the EU portal and for any new application to contain an explanation of any previous withdrawals of old applications;
- All data submitted in support of a clinical trial application will have to be recorded in publicly accessible databases and, if based on clinical trials conducted before the date of the application of the proposed regulation, be registered in a public register that is a primary or partnered registry of the international clinical trials registry platform of the World Health Organization;
- Older trials not present in databases will have to be registered before being referred to in applications;
- All clinical trials will have to be registered in the EU database before they are started. Incomplete or early terminated trials also will need to be published on the EU database, within 12 months of the suspension of the trial;
- In most circumstances, publication of a summary of trial results will need to be made within a year of the end of the trial;
- The introduction of a clinical study report, the aim of which will be (1) greater transparency with more data becoming available to patients and independent researchers and (2) harmonization of all of the information provided. Each clinical study report would include full results and a full account of the trial undertaken, with penalties being imposed on member states for noncompliance; and
- That data generated during a clinical trial must not be treated as commercially confidential once a marketing authorization has been obtained.[7]

Application to United States

The Proposal suggests that the sponsor's obligations are independent from where the sponsor is established, whether in the EU or in a third country. However, if the sponsor is established in a third country, to ensure an effective supervision of a clinical trial, an EU contact person must be provided. Communication with that contact person will be considered as communication with the sponsor.[8]

Further Developments

European Medicines Agency 2012 Workshop

On November 22, 2012, the European Medicines Agency (EMA) held a workshop with key members of the European healthcare sector, including the Assistant European Data Protection Supervisor and a representative from the Office of the European Ombudsman, to discuss the transparency of clinical trials, in particular the release and withholding of data. The session focused on 'how' rather than 'if' clinical trial data should be published. The outcome of the meeting was a plan in which volunteers formed five advisory groups, with each tasked to deliver firm proposals by the end of April 2013 covering the following areas: protecting patient confidentiality; clinical trial data formats; rules of engagement; good analysis practice; and legal aspects. The EMA will then build on these outputs and is expected to issue its policy on proactive publication of clinical trial data in January 2014.[9]

The Debate

The various issues discussed included the potential for sponsors to introduce bias into their data analysis if there is no potential for public scrutiny, the need to protect personal data and patient confidentiality, the protection of intellectual property rights and research and development investment, the

format in which data should be made available, and the need to guard against poor analysis. In the case of products where the outcome of the marketing authorization assessment is a withdrawal of the application or a negative opinion, industry representatives presented the position that release of data in such cases could damage the future of the product if it was resubmitted at a later data with additional data, or submitted outside the EU.[10]

Commentary

The following comments were made from various interested sectors:

Support for Trial Data Transparency

The workshop report from the EMA workshop on November 22, 2012 noted support for trial data transparency from both the Nordic Cochrane Centre (part of the Cochrane Collaboration) and the Chief Editor of the Public Library of Science both in terms of monitoring bias in trials and results, and the benefits of ensuring timely and efficient methods of publishing clinical data publically.[11] Support for the proposals also has been reported from the Medical Research Council's Clinical Trials Unit and Sense About Science (part of the AllTrials campaign for data transparency).[12]

Further, the Draft Report noted that patients decide to take part in a trial to help advance medicine for themselves and other patients in their situation, not to help a particular company, and that sharing more knowledge about trial results may not only increase trust in medicines, but accelerate the development of live-saving treatments.[13]

Concerns for Trial Data Transparency

Commentators have noted apprehension amongst the pharmaceutical industry in the wake of the proposed changes, with the Vice President of International Regulatory Affairs at Eli Lilly and Company and the Senior Vice President of Discovery at UCB Pharma both expressing concerns at the EMA workshop on November 22, 2012. Both parties emphasized a balance between fostering good science and an acceptable commercial environment. They noted that patient interests are important but that it is also important to recognize that a significant investment has been made to gather data and that if data is not owned by the funder this may lead to issues in the future.[14] The overarching industry position favored the review of data access on a case-by-case basis 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. The protection of intellectual property rights was also important to many pharmaceutical industry members.[15]

The UK Bioindustry Association chief executive Steve Bates expressed concerns that overly stringent requirements for the publication of clinical trial data in the EU could put investment in early stage research at risk, as funding may be harder to find, leaving a potential shortfall of money for such purposes in the future.[16]

Conclusion

Commentators have concluded that the current proposals represent a dramatic expansion in the transparency of data in clinical trials in Europe, and are similar in nature to proposals made by the AllTrials.net initiative[17] calling for all trials to be registered and all results reported. This initiative is supported by a number of prominent groups, including GlaxoSmith-Kline. On a national level, the UK Government is pursuing an open access policy[18] and other influential bodies such as the British Medical Journal and The Wellcome Trust have become involved in support of open access.

For example, commenting on the open access to data policy, the Wellcome Trust said: "The Trust encourages all its researchers to maximise access to research data with as few restrictions as possible, and clinical trials should not be seen as an exception. Researchers are encouraged to explore opportunities to make anonymised patient-level data available where appropriate. However, further discussion is needed about the best model to facilitate access to research data and a controlled access model might be the most appropriate way to achieve greater scrutiny of trial data."[19]

There also has been a notable recent shift towards more collaborative pharmaceutical research, involving individual or groups of companies and academic or publicly funded institutions sharing data and research outcomes, which is an encouraging step towards greater transparency and collaboration.[20]

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Although the majority of the healthcare sector is aligned in its appreciation of the benefits of greater transparency of clinical trial data, it is hard to see how the proposed changes will dramatically increase the attractiveness of conducting clinical studies in the EU for the commercial entities responsible for funding clinical trials.

It will be interesting to see how the EP's final legislation balances the commercial interests and indeed the rights of the owners of clinical data with the apparent need for greater public access to data. Although the majority of the healthcare sector is aligned in its appreciation of the benefits of greater transparency of clinical trial data, it is hard to see how the proposed changes will dramatically increase the attractiveness of conducting clinical studies in the EU for the commercial entities responsible for funding clinical trials.

Next Steps

The Proposal has been submitted to the Council and the EP for adoption. The EC expects it to come into effect in 2016. In order to allow a smooth transition, both sets of rules may apply in parallel for three years after the date of application of the new regulation. C

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Endnotes

1 G. Willmott, Draft Report on the Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, at 51 (Jan. 31, 2013).
2 European Commission, Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, at 2 (July 17, 2012).
3 *Id.*
4 *Id.* (Explanatory Memorandum).
5 *Supra* note 1, at 49.
6 *Supra* note 2, at 4.
7 *Id.* (summary of document).
8 *Id.* at 9.
9 European Medicines Agency, Access to clinical-trial data and transparency workshop report (Nov. 22, 2012).
10 *Id.*
11 *Id.*
12 *Id.*
13 *Supra* note 1.
14 *Id.*
15 *Supra* note 8.
16 Peter Mansell, *Transparency demands could threaten early trial investment*, Clinical News, Feb. 26, 2013.
17 *See* www.alltrials.net/ (last visited May 2, 2013).
18 *See* https://www.gov.uk/government/news/government-to-open-up-publicly-funded-research (last visited May 2, 2013).
19 For more information about the Trust, *see* www.wellcome.ac.uk.
20 *See* www.euractiv.com/health/debate-clinical-trials-seen-shif-news-519212.

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