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Briefing paper

New European Clinical Trials Regulation: a major advance in transparency, to be confirmed

- **A new European Regulation on clinical trials was adopted in late May 2014, and will apply from late May 2016. Its main objective is to make it easier to conduct trials in several Member States of the European Union.**
- **Members of the European Parliament and Europe's health ministers greatly improved the European Commission's original proposals, particularly on the issue of access to the results of clinical trials.**
- **However, this advance is at risk of being neutralised by industry lobbies, which are now attempting to block clinical data transparency on the pretext of the protection of their intellectual property and of their trade secrets. The European Medicines Agency (EMA) is in a key position as regards access to clinical data.**

In July 2012, the European Commission released a proposal for a new European Regulation on clinical trials. The aim of the proposal was to deregulate research conducted on human subjects: all reference to ethics committees was expunged, and certain measures would have left Member States incapable of protecting participants in clinical trials conducted on their territory (impossibly short deadlines for evaluating applications for authorisation to conduct trials, the conclusions of one reporting Member State were to be binding on all Member States in which the trial was to be conducted, etc.) (1).

Thanks to the mobilisation of many organisations representing civil society, several measures to protect trial participants were reinstated, and the need for independent, critical analyses of the results of clinical trials emerged in the parliamentary debate (1).

The new Clinical Trials Regulation (Regulation (EU) No 536/2014 repealing Directive 2001/20/EC) was adopted in late May 2014. It will apply in late May 2016, two years after its publication (2).

MEPs recognised that access to clinical study reports is in the public interest. Clinical study reports (CSRs) present the results of clinical trials in a detailed manner. In late April 2013, the Members of the European Parliament (MEPs) of the Environment, Public Health and Food Safety (ENVI) Committee stipulated that the clinical data included in these reports "*should not be considered commercially confidential once (...) the decision-making process on an application for marketing authorisation has been completed*", in accordance with the policy on access to documents held by the European Medicines Agency (EMA), which has been in effect since 2010 (1,3).

EU health ministers also in favour of transparency. The position of European health ministers on the issue of access to clinical data was awaited with particular interest. In fact, at that time, two pharmaceutical companies were intimidating the EMA, having brought legal action against the Agency to prevent it from granting access to clinical study reports (1,4).

In late December 2013, health ministers adopted a common position by consensus that confirmed the political will to increase transparency regarding the results of clinical trials in Europe. They also stipulated that clinical study reports must be made publicly accessible within 30 days after marketing authorisation has been granted and asked for penalties to apply when this requirement is not met (5).

In a plenary session held on 2 April 2014, MEPs adopted the Clinical Trials Regulation as amended by the ENVI Committee and the Council of ministers by a huge majority (594 votes in favour, 17 votes against, 13 abstentions) (6). The Council then adopted the final version of the Regulation, which was published in the Official Journal of the European Union on 27 May 2014 (2).

A new Regulation that makes it easier to conduct clinical trials in several Member States. As foreseen by the European Commission, this Regulation will enable clinical trial sponsors to submit a single request, via a centralised portal, for all Member States in which they would like to conduct their clinical trial. The request will then undergo joint “scientific review” by the Member States concerned, coordinated by a “reporting Member State”. In parallel, each Member State will have to conduct an “ethical review” (2). In practice, this ethical review is limited to checking how informed consent is obtained, and authorisation to conduct the trial will be acquired automatically if the authorities do not respond within the stated deadlines (tacit authorisation) (1,2).

The Council of health ministers did however reinstate several measures that protect clinical trial participants. In particular, it added the stipulation that if a national ethics committee issues a negative opinion, the trial cannot be conducted on the territory of the Member State concerned (2). It also restored more reasonable timelines for the assessment of applications: 45 days in total, with the possibility of prolonging this deadline for certain categories of drugs (the Commission’s proposed timeline was between 10 and 30 days) (2,5).

A missed opportunity to improve the quality of the clinical evaluation of new drugs. Neither the MEPs nor the EU health ministers seized the opportunity offered by the adoption of a new regulation on clinical trials to demand that the evaluation of new drugs must include trials that compare them with standard treatments.

Worse still, this new regulation considers certain clinical trials in which a drug is used outside its authorised indications (off-label use) as “low-intervention” trials which, as such, are subject to less stringent regulation (2). It will now be in manufacturers’ interests to apply for marketing authorisation for a narrow therapeutic indication, which can be granted on the basis of small clinical trials since few patients are concerned, and then to promote the drug’s off-label use, enabling them subsequently to apply for additional indications based on “low-intervention” trials.

Transparency: an advance to be confirmed. Despite the adoption of the Clinical Trials Regulation in late May 2014, the pharmaceutical industry continues to oppose transparency (a). The industry lobby is now fighting to restrict public access to clinical data on the intellectual property front. With the support of the European Commission currently negotiating free-trade agreements with the US, the pharmaceutical industry lobby argues that clinical data are “trade secrets” and “commercially confidential information”, even if this means misinterpreting World Trade Organization agreements (b) (7).

And in mid-May 2014, the EMA announced a U-turn on its policy on access to clinical data, offering instead very limited access in order to protect “commercially confidential” data on behalf of the pharmaceutical industry (see inset on page 3) (8).

a- For example, as soon as the Clinical Trials Regulation was adopted, the European Federation of Pharmaceutical Industries and Associations (EFPIA) called in particular for “the Commission and EMA [to] interpret the Clinical Trial Regulation in a manner that respects (...) incentives for companies to make long-term investments in biomedical research” [Editor’s note: to protect what they consider commercially confidential information] (ref 9).

b- Article 39(3) of the international agreement on the protection of trade-related intellectual property rights (TRIPs agreement) aims to protect companies that have collected clinical data from unfair competition, by preventing rival companies from using these data to apply for marketing authorisation. This article does not prevent the disclosure of clinical data to the public: the protection of public health is rightly an exception to the principle of non-disclosure of data (ref 7).

Access to data: EMA in key position

• The European Medicines Agency must fulfil its transparency obligations and resist industry pressure.

In June 2013, the European Medicines Agency (EMA) released a draft policy on access to clinical data for public consultation (1). It included plans to proactively publish, on its website, almost all of the clinical data submitted in support of applications for marketing authorisation (in particular the data included in clinical study reports) (1).

Industry opposition. In late November 2013, the European Commission published a proposal for a European directive on trade secrets (2,3). To the delight of the association that represents the European pharmaceutical industry, the proposal covered aspects of the clinical development of drugs (3). And in early 2014, the association representing the US pharmaceutical industry expressed its opposition to the EMA's draft policy proposal. In particular, it asked the US government to take action as part of the free trade agreement under negotiation between the US and the EU (2).

The EMA's U-turn. In mid-May 2014, despite the support of the European Parliament and the Council of health ministers as part of the Clinical Trials Regulation, the EMA backtracked on its commitment to transparency (3). On the pretext of aligning its policy with "*the Commission's clear message that [the EMA] would also have to assure compliance with national and international obligations (...) including but not limited to the TRIPS Agreements and copyright laws*", the EMA proposed that anyone requesting access to clinical study reports would first have to sign a confidentiality agreement (3,4). It also proposed a procedure that would enable pharmaceutical companies to censor clinical study reports before their online publication, and various restrictions that would make it impossible to use clinical study reports for the purposes of analysis or research (the data could only be viewed on screen and could not be downloaded or saved) (3).

Transparency should not be sacrificed. Many civil society organisations as well as the European Ombudsman and the MEP appointed as the rapporteur for the Clinical Trials Regulation criticised the EMA's U-turn and urged it to fulfil its transparency obligations (3,5-9). In the face of this mobilisation, the EMA announced in mid-June 2014 that researchers, but not the public, would be allowed to download the files (10). And in early July 2014, the EMA agreed to postpone adoption of its policy on access to documents until early October 2014, in order to improve it further (11). We shall continue to monitor the situation.

1- AIM, HAI Europe, ISDB, MiEF "Transparency in the public interest: How the EMA policy on publication and access to clinical-trial data could help save lives" Joint Submission of comments on 'Policy 0070 on publication and access to clinical-trial data: 15 pages.

2- Cohen D "Trade talks between US and EU could increase cost of drugs, new report says" *BMJ* 2014; 348: 1 page.

3- AIM, Medicines in Europe Forum, HAI Europe, ISDB, Nordic Cochrane Centre "Backpedalling on EMA's "proactive publication of clinical-data" draft policy: Who or what is the EMA afraid of?" press release; 20 May 2014: 4 pages.

4- Rasi G "European Medicines Agency response to European Ombudsman letter regarding proactive publication of and access to clinical trial data" 22 May 2014: 2 pages.

5- European Ombudsman "Ombudsman concerned about change of policy at Medicines Agency as regards clinical trial data transparency" press release; 16 May 2014: 2 pages.

6- "Mrs Willmott's Open letter to Executive Director of the EMA on clinical trial transparency" 6 June 2014.

7- IQWiG "Just look, but don't touch: EMA terms of use for clinical study data are impracticable" press release; 27 May 2014: www.iqwig.de: 2 pages.

8- Jefferson T and Doshi P "EMA's double U-turn on its Peeping Tom policy for data release" 13 June 2014: 2 pages.

9- AIM, MiEF, HAI Europe, ISDB, Nordic Cochrane Centre "EMA's new policy on access to clinical data: About to privatise pharmaceutical knowledge? The proof will be in the pudding" joint press release; 23 June 2014: 4 pages.

10- EMA "European Medicines Agency agrees policy on publication of clinical trial data with more user-friendly amendments" press release; 12 June 2014: 1 page.

11- EMA "Management Board delays formal adoption of EMA publication of clinical trial data policy to October 2014" press release; 9 July 2014: 2 pages.

In summary. Although the opportunity to shift the emphasis of clinical research towards unmet health needs was not taken, the new European Clinical Trials Regulation (Regulation (EU) No 536/2014) could still constitute a major advance in terms of transparency. Provided that it is not neutralised through increased protection of intellectual property and that it is properly implemented by the European Commission and drug regulatory agencies (10).

Will the democratic process be respected despite the huge private financial interests at stake? The decision by the European Commission President, Jean-Claude Juncker, to transfer responsibility for health technology, pharmaceuticals, and the European Medicines Agency (EMA) away from the Commission's health directorate to the industry directorate does not augur well. Glenis Willmot, MEP rapporteur on the Clinical trials Regulation, explained that when she was negotiating the transparency laws for clinical trial results, "*it was DG Enterprise that wanted to water the rules down. Now they will be overseeing the European Medicines Agency as it implements the transparency regime, which is frankly concerning*" (11). On 16 September 2014, twenty-eight organisations co-signed a joint letter asking President Juncker to reconsider his decision (12).

References:

- 1- Prescrire Rédaction "Essais cliniques: un nouveau Règlement européen à améliorer" *Rev Prescrire* 2013; **33** (360): 781-783.
- 2- "Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC" *Official Journal of the European Union*, 27 May 2014: 76 pages.
- 3- ENVI Committee "Report on the proposal for a regulation on clinical trials on medicinal products for human use (COM(2012)0369 – C7-0194/2012 – 2012/0192(COD))" 7 June 2013: 266 pages.
- 4- Prescrire Rédaction "Débat mondial sur l'accès aux données cliniques: l'Agence européenne en position clé" *Rev Prescrire* 2014; **34** (367): 377-379.
- 5- Council of the European Union "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 - 2012/0192 (COD)" 20 December 2013: 152 pages.
- 6- European Parliament "Minutes of the sitting of Wednesday 2 April 2014": 44 pages.
- 7- Wadlow C "Regulatory data protection under TRIPs Article 39(3) and Article 10bis of the Paris Convention: Is there a doctor in the house?" *Intellectual Property Quarterly* 2008: 355-415.
- 8- AIM, MiEF, HAI Europe, ISDB, Nordic Cochrane Centre "Backpedalling on EMA's "proactive publication of clinical-data" draft policy: Was it all just a window-dressing exercise? Who or what is the EMA afraid of?" joint press release; 20 May 2014: 4 pages.
- 9- "EFPIA calls for collaboration in the implementation of clinical trials regulation following vote in the European Parliament" press release, 3 April 2014: 2 pages.
- 10- Goyens M, BEUC Director General "EMA transparency policy on clinical trial data should not be diluted" Letter sent to Prof. Guido Rasi, EMA Director General (ref.: 164/2014 – dated 22/05/2014): 3 pages.
- 11- Willmott G, MEP "Juncker should reverse decision on medicines shake up" 11 September 2014: 1 page.
- 12- "Medicinal products and health technology belong under the responsibility of the Commissioner for health" Joint open letter to President Juncker by 28 organisations (AGE, AIM, BEUC, CEO, CPME, EAHP, EATG, ECL, EFA, EHMA, EHN, ELPA, EMSA, EPF, EPHA, ESIP, HAI, HEAL, HOPE, IDF, IFMSA, ISDB, MiEF, NCC, PGEU, SFP, UAEM, UEMS) 16 September 2014 : 1 page.

List of signatory organisations

AIM. The Association Internationale de la Mutualité (AIM) is a grouping of autonomous health insurance and social protection bodies operating according to the principles of solidarity and non-profit-making orientation. Currently, AIM's membership consists of 41 national federations representing 29 countries. In Europe, they provide social coverage against sickness and other risks to more than 150 million people. AIM strives via its network to make an active contribution to the preservation and improvement of access to health care for everyone. More info: www.aim-mutual.org. Contact: corinna.hartrampf@aim-mutual.org

BEUC. BEUC, the European Consumer Organisation, acts as the umbrella group in Brussels for its members and our main task is to represent them at European stage and defend the interests of all Europe's consumers. BEUC investigates EU decisions and developments likely to affect consumers, with a special focus on eight areas identified as priorities by our members: Financial Services, Food, Digital Rights, Consumer Rights, Sustainability, Safety, Health and Energy. BEUC is acknowledged as a trustworthy representative by both decision-makers and opponents alike, thanks in particular to the collective skills, knowledge and expertise of our member organisations. More information: www.beuc.org. Contact: ipa@beuc.eu

ISDB. The International Society of Drug Bulletins (ISDB), founded in 1986, is a worldwide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently ISDB has around 80 members in 41 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org

MiEF. The Medicines in Europe Forum (MiEF) was launched in March 2002 and reaches 12 European Member States. It includes more than 70 member organizations representing the four key players on the health field, i.e. patients groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is unique in the history of the European Union and is testament of the importance of European medicines policy. More information: english.prescrire.org. Contact: pierrechirac@aol.com

NCC. The Nordic Cochrane Centre is part of the Cochrane Collaboration, an international not-for-profit international network of more than 28,000 dedicated people from over 100 countries preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care. More information: www.cochrane.org. Contact: Peter Gøtzsche (pcg@cochrane.dk)

TACD. The Transatlantic Consumer Dialogue (TACD) is a forum of US and EU consumer organisations which develops and agrees on joint consumer policy recommendations to the US government and European Union to promote the consumer interest in EU and US policy making. More information: www.tacd.org. Contact: tacd@consint.org or hammerstein.david3@gmail.com

Wemos. Wemos influences international policy in such a way that the right to health is respected, protected and promoted. In doing so, Wemos devotes special attention to vulnerable sections of society. Wemos advocates ethical conduct, coherent policy and equal access to care. Its lobbying work focuses on lasting improvements in Dutch, European and global policy. More information: www.wemos.nl. Contact: annelies.den.boer@wemos.nl