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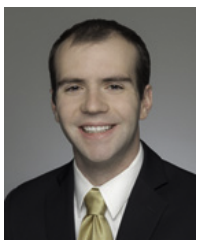
Data Management

New EU Clinical Trials Regulation and its Interaction With Proposed EU Privacy Regulation and Proposed EMA Policy on Clinical Trials Data Transparency


BY SHINE CHEN, DAVID PELOQUIN & MARK BARNES

On April 16, 2014, the European Union ("EU") adopted a new clinical trials regulation, titled "Regulation (EU) No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC" (the "Regulation").[1] The Regulation replaces the existing Clinical Trials Directive 2001/20/EC and will be incorporated into the national laws of all EU Member States on its effective date, which is expected to be sometime in the latter half of 2016.[2]

The authors are attorneys at Ropes & Gray LLP. Mr. Barnes is the Harvard faculty co-director of the Multi-Regional Clinical Trials Center (Harvard MRCT) and serves as co-chair of the Subcommittee on Harmonization of Research Regulations of the HHS Secretary's Advisory Committee on Human Research Protections (SACHRP).

[1] *See* Regulation (EU) No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 2014 O.J. (L 158) 1, 27.5.2014, *available at* http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN (hereinafter, *"Regulation"*).

[2] The precise effective date of the Regulation is uncertain at this point, as the Regulation provides that it will take effect six months after the web-based portal for submission of all clinical trials applications (the "EU Portal") and the database to house all clinical trial data and information submitted in accor-

One of the driving forces behind the Regulation has been to increase the transparency of clinical trial data in the EU. While the Regulation contains provisions that conceivably could increase the transparency of clinical trial data, the impact that the Regulation ultimately will have on clinical trial data transparency remains an open issue due to other proposed legislative changes currently taking shape in the EU. The first of these is the proposed replacement of the EU's current data protection legislation, Directive 95/46/EC (''1995 Directive''), with the draft General Data Protection Regulation (the ''Proposed GDPR''). The second of these proposed changes is publication by the European Medicines Agency (''EMA'') of the final version of its *Policy on Publication and Access to Clinical Trials Data* (the ''EMA Policy''), which currently is scheduled to be released in October 2014. Based on the currently available draft of the Proposed GDPR and recent discussion surrounding the EMA Policy, there appear to be several inconsistencies, if not outright contradictions, between the Regulation, the Proposed GDPR and the EMA Policy. Unless these inconsistencies are addressed prior to formal adoption of the Proposed GDPR and the EMA Policy, confusion may ensue during the implementation process for any one of them. In order to frame our discussion, we begin with an overview of some of the most important changes introduced by the Regulation and then address in some detail the potential inconsistencies regarding transparency.

Streamlined Application Platform

The Regulation streamlines the application process for those seeking to conduct clinical trials in the EU by creating a web-based portal (the ''EU Portal'') for submission of all applications to conduct a clinical trial in the EU, regardless of the number of Member States in which the clinical trial sponsor (''Sponsor'') intends to conduct the trial (each, a ''Concerned Member State,'' and collectively, the ''Concerned Member States'').[3] The EU Portal will be the main communication tool between the Sponsor and the Concerned Member States throughout the clinical trial application and review process until a final decision is made regarding whether the application will be allowed or denied.

Upon submission of the application to the EU Portal, the Sponsor will nominate one of the Concerned Member States to be its Reporting Member State (the ''Reporting Member''). The Reporting Member facilitates the progression of the application from submission to final decision.[4] Within 10 days following the application submission, the Reporting Member State will either confirm that the application is complete and in compliance with the Regulation, thereby validating the application, or request more information from the Sponsor.[5]

Once the application is validated, a two-part concurrent assessment process takes place—Part I is performed under the auspices of the Reporting Member State and must be completed within 45 days of the validation. Part I evaluates several components of the application, including its anticipated therapeutic and public health benefit and the risks and inconveniences for the subject, the characteristics of the intervention compared to normal clinical practice, the safety measures proposed, and compliance with requirements related to labelling and the completeness of the investigator's brochure.[6]

Part II is conducted concurrently by each of the Concerned Member States and must be completed within 45 days of the application's validation.[7] Part II evaluates the application for its compliance with the Regulation with respect to: informed consent, subject recruitment, subject compensation, qualification of investigators, suitability of research sites, the presence of a damage compensation system and applicable rules for the collection and storage and future use of biological samples of the subjects.[8]

In a recognition of the increasing importance of clinical trial registries, such as ClinicalTrials.gov in the U.S. and the European Clinical Trials Database (''EudraCT'') in the EU, the Regulation requires that all data supporting the application to commence a new clinical trial in the EU originate from clinical trials that have been registered and recorded on a publicly and freely accessible database.[9] All this information will be uploaded into the new EU Database, under the authority of the EMA.

If the application is approved, or approved with conditions for both Part I and Part II, the clinical trial may be conducted in all Concerned Member States.[10] If Part I concludes that the application is unacceptable, then the application is refused on behalf of all Concerned Member States. Conversely, if Part I concludes that the application is either acceptable or acceptable with conditions, a Concerned Member State still may refuse to authorize the application with respect to its own jurisdiction if: (a) it disagrees with the conclusion of Part I for one or more enumerated reasons (such as patient safety); or (b) it finds the application unacceptable under its Part II review. In such a case, the clinical trial would not be permitted within the Concerned Member States that rejected the application.[11]

Informed Consent

In addition to streamlining the clinical trials application process, the Regulation introduced two major changes that permit increased flexibility with regard to obtaining the informed consent of research subjects: a simplification of the consent requirements for randomized cluster trials and a provision for obtaining consent in emergency situations.

Randomized Cluster Trials

In the case of randomized cluster trials conducted exclusively in one Member State, the Member State may waive the general requirement that informed consent be obtained following a face-to-face discussion with a qualified member of the research team.[12] Such simpli-

dance with the Regulation (the ''EU Database''), both of which are currently under development by the European Medicines Agency, become fully functional. The Regulation requires that the EU Portal and EU Database be fully functional by May 28, 2016, at the latest.

[3] *Regulation,* Article 5(1).
[4] *Regulation*, Articles 5, 6.
[5] *Regulation*, Article 5.
[6] *Regulation*, Article 6.
[7] *Regulation*, Article 6.
[8] *Regulation*, Article 7.
[9] *Regulation*, Article 25(d)(6).
[10] *Regulation*, Article 8.
[11] *Regulation*, Article 8.
[12] *Regulation*, Articles 29, 30.

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fied informed consent may be obtained if all the following conditions are met:[13]

- national law does not contradict such simplified means for obtaining informed consent;
- the clinical trial methodology requires groups of subjects instead of individual subjects to receive different investigational medicine products;
- the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorization;
- no interventions exist other than the standard treatment of the subjects concerned; and
- the clinical trial protocol justifies obtaining simplified informed consent and describes the scope of information provided to the subjects, including the method of providing such information.

Emergency Consent

When a patient suffers a sudden life-threatening medical condition requiring immediate medical intervention, informed consent may be obtained after a subject is included in a clinical trial if the following conditions are met:[14]

- the subject is unable to provide prior informed consent and unable to receive prior information on the clinical trial due to a life-threatening or other sudden, serious medical condition;
- the subject and the subject's legal representative are incapable or unavailable to receive all the clinical trial information within the therapeutic window or to provide informed consent prior to the intervention;
- the clinical trial is directly related to the cause of the life-threatening or other serious medical condition, such that the intervention should have a direct clinically relevant benefit in a measurable health-related improvement for the subject and the clinical trial is of such nature that it may be conducted exclusively in emergency situations;
- the investigator certifies that he or she is unaware of the subject expressing any prior objections to participating in the clinical trial; and
- the clinical trial poses a minimum risk to, and imposes a minimal burden on, the subject, as compared to the standard treatment of the subject's condition.

Following the emergency intervention, informed consent to continue participation in the clinical trial must be obtained from the subject or the subject's legal representative without undue delay.[15] If the subject or the legal representative does not provide informed consent, he or she must be informed of the right to object to the use of data already obtained from the trial.[16]

[13] *Regulation*, Article 30.
[14] *Regulation*, Article 35.
[15] *Regulation*, Article 35.
[16] *Regulation*, Article 35.

Data Transparency and the Regulation

Providing greater clinical trials data transparency is one of the stated goals of the Regulation.[17]

In order to further this goal, the Regulation tasks the EMA with creating a database to store all the information submitted as part of the clinical trial application process, which also will include the summaries of results for all clinical trials conducted in the EU, regardless of outcome.[18]

Despite the fact that the Regulation focuses on the process of applying for and carrying out a clinical trial rather than the process of applying for a marketing authorization, the Regulation contains an EU Database upload requirement related to the marketing authorization process. Specifically, Article 37(4) of the Regulation states that for clinical trials intended to be used for obtaining a marketing authorization for the investigational medicinal product, the clinical study reports from the marketing authorization process subsequently should be uploaded into the EU Database within 30 days of the marketing authorization decision or 30 days after the applicant for marketing authorization has withdrawn the application. However, as further explained below, the public availability of clinical study reports used in support of a marketing authorization has been proposed as part of, and likely will be required by, the EMA Policy, meaning that the Regulation's requirements in this area may be redundant in regard to those of the EMA Policy and thus likely to create confusion.[19]

The EU Database will be publicly accessible, except in the following situations: cases involving personal data, commercially confidential information of a medicinal product going through market authorization (unless there is an overriding public interest) or protecting confidential information between Member States in relation to the assessment report.[20] In addition, the data within the application will not be publicly accessible before a decision on the clinical trial has been made. The data will be grouped by EU trial number and hyperlinks will be inserted to link to other EU databases such as EudraCT, which is a registry of clinical trials, akin to ClinicalTrials.gov in the U.S.[21] The Regulation states that the EU Database is meant to be separate from and not duplicative of the EudraCT and EudraVigilance databases.[22] However, given the text of the Regulation, it is unclear how the databases will not be in large part duplicative, except perhaps in their organization of information by investigational product (EU Database) versus by clinical trial (EudraCT).[23]

Anticipating that creation of the EU Database may lead to the release of commercially confidential information or personal data, the Regulation addresses the issue of commercially confidential and personal data in connection with the issue of which data may be made publicly available. Generally, the Regulation does not consider the data included in a clinical trial study report to be commercially confidential once the marketing authorization has been granted or if the application for

[17] *Regulation*, Preamble 25.
[18] *Regulation*, Article 37(4).
[19] *Regulation*, Article 37(4).
[20] *Regulation*, Article 81.
[21] *Regulation*, Article 81(2).
[22] *Regulation*, Article 81(1).
[23] *Regulation*, Article 81.

marketing authorization has been withdrawn.[24] Additionally, the protocol, the main characteristics of the clinical trial, the conclusion on Part I of the clinical trials application, the final decision on the clinical trials application and the clinical trial results, including reasons for early termination or for temporary halt (if applicable), are not considered confidential under the Regulation.[25]

In what is one of the most confusing aspects of the Regulation, the article creating the EU Database indicates explicitly that ''[n]o personal data of subjects shall be publicly accessible.''[26] However, this same article of the Regulation goes on to indicate that the data subject retains the right to have ''inaccurate or incomplete data corrected or erased.'' This begs the question of how the data subject would know of the existence of inaccurate or incomplete data concerning him- or herself since personal data, *i.e.*, data that relate to an identified or identifiable natural person, are not to be publicly accessible. Because, as noted at the beginning of this article, the EU Database currently is under construction, it is not yet clear how the EU Database will appear in practice, and whether this apparent contradiction will be worked out by the time the Database ''goes live.''

Inconsistencies Between the Regulation, the EMA Policy and the Proposed GDPR Regarding Data Transparency

Whether the Regulation will provide a practical increase in data transparency is unclear at present and will depend partially on: (1) finalization of the EMA Policy; and (2) the final text of the Proposed GDPR.

EMA Policy Whiplash

The EMA Policy was introduced to encourage data transparency by requiring the release of clinical trials data submitted in support of a marketing authorization with the EMA. The draft policy, released by the EMA in June 2013, provided for three tiers of data, each with different restrictions on release:

- data containing commercially confidential information, which are not to be made publicly available;
- data without ''protection of personal data'' concerns, *i.e.*, data that are not related to an identified or identifiable natural person, which are to be made publicly available; and
- data with protection of personal data concerns, which will be made available only upon researcher request through a process involving the entry of a data use agreement between the investigator and the EMA.[27]

While the final version of the EMA Policy was expected to be released and formally adopted in the fourth quarter of 2013, taking effect on Jan. 1, 2014, the release date has now been delayed several times, with the final EMA Policy now scheduled to be released in October 2014.[28]

While the EMA has not publicly released an updated draft of the EMA Policy since the release of the initial draft in June 2013, it has privately released revised drafts to certain stakeholders. Commentary by such stakeholders has indicated that the EMA has made dramatic changes in the proposed policy during the past year. Most prominently, the EU Ombudsman noted in May 2014 that drafts of the policy made available to her suggested that the EMA would permit only on-screen access to data via an interface provided by the EMA, meaning that it would be virtually impossible for those obtaining access to manipulate the data and conduct secondary analyses.[29] A few weeks later at the meeting during which the EMA was supposed to approve the final version of the EMA Policy, the EMA announced that it had made ''user-friendly amendments'' that would ''give the possibility to download, save and print the trial data for academic and noncommercial research purposes,'' and that a final version of the policy would be approved in July 2014.[30] However, in July 2014 the EMA announced that it was still ''not able to conclude on the final wording of the policy'' and that recent views expressed by board members and the Member States ''largely reproduce the complexity of the debate on both political and technical aspects which have emerged during the previous general and more targeted consultation phases.''[31] Given this language, which suggests continuing disagreement among certain EMA stakeholders on the final shape of the EMA Policy, it seems that those following the EMA process closely may be in for yet another surprise when the final version of the EMA Policy is released.

Despite the fact that the EMA Policy has yet to be finalized, given what we know from the draft policy, it seems likely that certain inconsistencies will appear between the Regulation and the EMA Policy. For example, while the Regulation takes an expansive view that clinical study reports are not commercially confidential and therefore should be publicly shared and registered, the EMA's draft policy indicated that certain parts of clinical study reports do indeed contain commercially confidential information that would be redacted prior to be-

[24] *Regulation*, Preamble 68.
[25] *Regulation*, Preamble 68.
[26] *Regulation*, Article 81(7).
[27] *See* EMA, *Publication and Access to Clinical-Trial Data: Draft for Public Consultation*, Policy/0070 (2013). For a concise discussion of the draft policy released in June 2013, *see* David Peloquin et al., *EMA Draft Policy on Publication and Access to Clinical Trials Data Provides Broad Researcher Access to Participant-Level Data*, Bloomberg BNA, Medical Research Law & Policy Report (2013) (12 MRLR 482, 7/17/13).
[28] European Medicines Agency, ''Management Board delays formal adoption of EMA publication of clinical trial data policy to October 2014,'' accessed on July 7, 2014, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/07/news_detail_002138.jsp&mid=WC0b01ac058004d5c1.
[29] *See* Letter to EMA Director, Guido Rasi, *EMA policy on publication of and access to clinical-trial data* (May 13, 2014), *available at* http://www.ombudsman.europa.eu/en/resources/otherdocument.faces/en/54347/html.bookmark.
[30] European Medicines Agency, *European Medicines Agency agrees policy on publication of clinical trial data with more user-friendly amendments* (June 12, 2014), *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002124.jsp&mid=WC0b01ac058004d5c1.
[31] European Medicines Agency, ''Management Board delays formal adoption of EMA publication of clinical trial data policy to October 2014,'' accessed on July 7, 2014, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/07/news_detail_002138.jsp&mid=WC0b01ac058004d5c1.

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ing made publicly available.[32] Accordingly, the EMA could theoretically be required to administer two clinical trials databases, one under the Regulation and one under the Policy, each with a different concept of commercially confidential information.

More fundamentally, while one of the goals of the Regulation, and the primary goal of the EMA Policy, is to increase the ability of researchers and the public at large to have access to data from clinical trials, it seems quite likely that the average person interested in such data would be confused by a multiplicity of portals through which data may be accessed. As it currently stands, it appears that there will be at least four databases of clinical trials data: the EU Database developed under the Regulation, EudraCT, EudraVigilance and whatever database may emerge from the EMA Policy. Understanding the differences between these resources likely will prove a challenge to the very researchers that the EU hopes to empower through its transparency initiatives. Furthermore, submitting the proper data to each database may become a large burden for clinical trial sponsors, thereby undermining the Regulation's goal of streamlining the clinical trials process in the EU.

Informed Consent Confusion

One aspect of the Regulation that appears particularly promising to the research community is that it permits sponsors to ask data subjects, as part of the informed consent process, to grant consent to use of their data for secondary research uses outside of the protocol.[33] The EMA Policy (at least the draft released in June 2013) also appears to take the position that broad consent for future research is permissible, as it notes that future uses of data released under the policy must respect the ''spirit'' of informed consent, noting that the advancement of science and public health may weigh in favor of a broader interpretation of such consent.[34] Nevertheless, the Regulation indicates that it must be interpreted in accordance with applicable data protection laws, *i.e.*, the 1995 Directive, which may soon be replaced by the Proposed GDPR.[35] The EMA Policy, once enacted, also presumably will be subject to data protection laws.

Yet, by contrast, the Proposed GDPR, if enacted, would complicate and limit the ability of sponsors to make secondary research uses of data from clinical trials, as the Proposed GDPR requires ''specific'' consent for processing of health data.[36] The term ''specific'' previously has been interpreted by EU governing bodies in the context of informed consent to prohibit consent to ''an open-ended set of processing activities'' or to ''future research.''[37] Such an interpretation of the requirements of informed consent is very much at odds with the concept of permitting data subjects to consent to secondary research uses of their data, since such secondary uses most often will not be known at the time informed consent is obtained from the subject; thus the informed consent document would need to be worded broadly in order to be useful. The requirement of ''specific'' consent also appears to be contrary to the ''spirit'' of the informed consent language that the EMA Policy emphasizes. Thus, there appear to be contradictory provisions and intentions between the Regulation, the 2013 GDPR and the EMA Policy, with the Regulation's original intent to allow a more flexible approach in obtaining informed consent for secondary research potentially being overridden by the Proposed GDPR.

The Proposed GDPR does not apply to ''anonymous data,'' which are defined as ''information that does not relate to an identified or identifiable natural person,''[38] and thus anonymization of data may allow researchers to make secondary uses of data without meeting the ''specific'' consent requirements of the Proposed GDPR. However, the Proposed GDPR indicates that ''an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, unique identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social or gender identity of that person.''[39] The Proposed GDPR also provides that both encrypted and pseudonymous data (*e.g.* key-coded data) are to be considered ''personal data.''[40] Accordingly, if the data for which a researcher proposes a secondary use include data elements that fit within the definition of ''personal data'' (*e.g.*, cultural or gender identity), or if such data are key-coded, it is likely that such data would not be considered ''anonymous'' for purposes of the Proposed GDPR and thus would remain subject to the ''specific'' consent requirement.

Right-to-Erasure Confusion

Further complicating matters, the Proposed GDPR includes a ''right to erasure'' that entitles the data subject to withdraw his or her consent for the processing of personal data, at which time the data controller must erase personal data concerning the subject, abstain from further dissemination of such data and obtain from third parties the erasure of any links to, or copy or

[32] *See* European Medicines Agency, *Publication and Access to Clinical-Trial Data: Draft for Public Consultation*, Policy/0070 (2013), at 4.

[33] *Regulation*, Article 28.

[34] *See* EMA, *Publication and Access to Clinical-Trial Data: Draft for Public Consultation*, Policy/0070 (2013), at 4.

[35] *Regulation*, Articles 28, 93.

[36] *See Proposed GDPR*, Article 2, paragraph 8. For a concise description of the potential impact of the Proposed GDPR on clinical research, see David Peloquin et al., *European Union's Proposed General Data Protection Regulation Promises Big Changes for Secondary Uses of Data from Clinical Trials*, Bloomberg BNA, Medical Research Law & Policy Report (2013) (12 MRLR 752, 11/20/13).

[37] *See* Article 29 Working Party Opinion 3/2013, at 52; Article 29 Working Party Opinion 15/2011, at 17.

[38] *See* Proposed GDPR, Recital 23.

[39] *See* Proposed GDPR, Article 4, paragraph 2.

[40] Note that the definition of ''anonymous data'' under the Proposed GDPR is both stricter and more subjective than the ''de-identification'' standard employed in the U.S. for health information under the Health Insurance Portability and Accountability Act of 1996 (''HIPAA''). The Proposed GDPR refers to general categories of information, such as genetic, mental, economic, cultural or social characteristics that may render a person identifiable, whereas under HIPAA data may be considered ''de-identified'' if 18 specific identifiers are removed and the data controller lacks ''actual knowledge'' that the data can be used to identify the individual who is the subject of the information. *See* 45 C.F.R. § 164.514(b)(2). Unlike the Proposed GDPR, HIPAA does not consider genetic, mental, economic, cultural or social characteristics to be ''identifiers.''

replication of, such data.[41] Accordingly, a data subject could request that his or her data be erased from any database created under the EU Policy and erased from any datasets released to researchers pursuant to the EU Policy. Importantly, because the Proposed GDPR considers key-coded and encrypted data to be ''personal data'' subject to the restrictions of the Proposed GDPR, if a data subject exercises his or her ''right to erasure,'' a data controller who has shared key-coded data with other researchers for secondary research purposes may need to contact such researchers and request that they expunge such data from their records. This is the case even if the secondary researchers lack the key to the coded data and thus could not easily re-identify such data. If a large number of data subjects take such action, it could undermine the goal of making clinical trials data available on a broad scale.

The Proposed GDPR does provide that an individual may not be able to exercise his or her ''right to erasure'' if retention of the data is needed for ''historical, statistical and scientific research purposes in accordance with Article 83'' or for ''reasons of public interest in the area of public health in accordance with Article 81.''[42] These provisions therefore may provide an avenue for researchers to argue that the ''right to erasure'' should not apply to their use of personal data. Nevertheless, the Proposed GDPR does not elaborate on the types of research that would qualify for these exceptions from the ''right to erasure,'' and thus it appears likely that there will be disputes between researchers and data subjects regarding whether specific data are subject to the ''right to erasure.''

Conclusion

The Regulation represents a step forward in streamlining the clinical trial application process, which should be appreciated by clinical trial sponsors and Member States alike. Nonetheless, research institutions and clinical trial sponsors will need to pay close attention to the finalization of the Proposed GDPR and the EMA Policy to examine how the provisions of these two pieces of legislation interact with those of the Regulation with respect to transparency of clinical trials data. Many changes are likely as these pieces of legislation are finalized over the next several months and years.

[41] *See* Proposed GDPR, Article 17, paragraph 1.

[42] *See* Proposed GDPR, Article 17, paragraph 3(b), (c).

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