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Recent Changes in French Law Affecting Clinical Research and Trials




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There have been several recent changes to French law that affect clinical research and trials. Several of the most noteworthy pieces of legislation from 2016 are discussed in detail below.

Decree No. 2016-1537 of 16 November 2016 on research involving the human being

Decree No. 2016-1537 (''Decree 1537''), which was made pursuant to *Law No. 2012-300 of 12 March 2012* (the ''Loi Jardé''), includes several new elements related to clinical research and trials involving human beings.

Decree 1537 expands the reach of the regulatory framework by replacing the concept of ''biomedical research'' with ''research concerning the human being,'' a term which now is defined to include both interventional research and non-interventional research.[1] Previously, non-interventional research was excluded from the ''biomedical research'' definition. Non-interventional research is defined as research in which all products are used in the usual way without additional or unusual diagnostic, treatment, or surveillance procedures.[2] Non-interventional research also would include records research and the administration of questionnaires.

Decree 1537 creates a National Commission for research involving the human being (the ''National Commission'') and sets forth its mission, mode of operation, and composition.[3] Among its duties, the National Commission will coordinate and harmonize the activities of the Comités de Protection des Personnes (CPPs), which serve a similar function to institutional review boards in the United States in reviewing research to ensure the protection of human subjects.[4] Notably, the National Commission will serve as the single initial point of contact for the sponsor and will randomly select the CPP that will review and generate an opinion on the spon-

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[1] *See* Decree No. 2016-1537, Article 1.
[2] *Id.*
[3] *See* Decree No. 2016-1537, Article 11.
[4] *Id.*

sor's application.[5] Decree 1537 requires that an information technology (IT) system be put into place to conduct the random selection of the cognizant CPP, and to facilitate exchanges between sponsors and the CPP and between the CPP and the Agence nationale de sécurité du medicament et des produits de santé (ANSM).[6] Until the IT system is established, the sponsor will be responsible for selecting the cognizant CPP.

Decree 1537 changes the authorization requirements for certain institutions performing Phase I clinical trials. The validity of the authorization of sites performing Phase I trials is extended from five years to seven years, except for clinical trials involving the first administration of a drug in humans, which is issued for three years.[7]

Decree 1537 strengthens surveillance and vigilance during clinical trials by adding several new reporting requirements. First, the sponsor must inform the National Commission and the ANSM without delay following the termination of an investigator because of a serious deviation or a deliberate pattern of deviation from the protocol, or because of a serious disregard for or ignorance of regulations or good clinical practices that could affect the safety and well-being of research subjects or the reliability and integrity of the research data.[8] Second, the sponsor must notify the competent authority: (1) immediately of any unexpected serious adverse event which led to a death or put lives at stake, and (2) within 15 days for other unexpected serious adverse events.[9] In both cases, additional information on the event must be provided to the ANSM within eight days of the notification. Third, in first-in-human trials involving healthy volunteers, the sponsor must notify the ANSM without delay upon the occurrence of any ''new event.''[10] In this case, the administration of the product must be suspended, appropriate urgent security measures must be taken, and the competent authority and the CPP must be informed.[11] This final provision likely is a response to the January 2016 tragic incident that occurred in a first-in-humans Phase I trial conducted in France, in which one person died and five others were hospitalized.[12]

Decree 1537 entered into force on Nov. 18, 2016, with the exception of provisions relating to the IT system described above, which will be effective when the system is fully operational as determined by the Minister of Health, and no later than December 31, 2017.[13] In the interim, exchanges between sponsors, CPPs, and the ANSM are to be made directly by post or electronically.[14]

[5] *See* Decree No. 2016-1537, Article 9.
[6] *See* Decree No. 2016-1537, Article 11.
[7] *See* Decree No. 2016-1537, Article 4.
[8] *See* Decree No. 2016-1537, Article 12.
[9] *See* Decree No. 2016-1537, Article 14.
[10] *See* Decree No. 2016-1537, Article 15.
[11] *Id.*
[12] *See* Scientists in the Dark after French Clinical Trial Proves Fatal, *Nature*, 18 January 2016, available at: http://www.nature.com/news/scientists-in-the-dark-after-french-clinical-trial-proves-fatal-1.19189.
[13] *See* Decree No. 2016-1537, Article 24.
[14] *Id.*

Decree No. 2016-1538 of 16 November 2016 on the Unique Agreement for the implementation of commercial clinical trials involving human beings in health care institutions

Promulgated under section 155 of *Law No. 2016-41 of 26 January 2016 for the modernization of our health system*, *Decree No. 2016-1538* (''Decree 1538'') requires that sponsors use a clinical trial agreement template, entitled ''convention unique,'' to conduct clinical trials with French public and private health care institutions.[15] The purpose of this agreement template (the ''Unique Agreement'') is to strengthen the competitiveness of French health-care institutions for clinical trials by simplifying the internal review procedure and speeding the negotiation process.

The Unique Agreement governs the relationship between the sponsor, the principal health-care institution (the ''coordinating institution''), and the investigator. However, only the sponsor and the coordinating institution are required to sign the agreement; the investigator need not sign the agreement, but must attest that he/she is aware of and has seen the agreement.[16] As such, the historical French practice by which the sponsor has an agreement with the investigator and not the institution has been modified by this Unique Agreement template, thereby bringing French law in line with the common United States practice in which the clinical trial agreement typically is between the sponsor and the institution at which the trial takes place, with the principal investigator signing as having ''read and acknowledged'' the agreement.

According to Decree 1538, the Unique Agreement can provide for compensation for the expected quality of clinical trials data, thereby permitting the inclusion of incentive payments for this purpose.[17] The Unique Agreement also allows for all or part of the compensation to be paid to a third party entity participating in the clinical trial upon satisfaction of three conditions: (i) the third party entity is designated by the legal representative of the coordinating institution according to public procurement law (if applicable); (ii) the third party entity's governance is able to prevent certain risks associated with the third party's or its executives' receipt of such compensation, including conflicts of interest or breach of the main principles and rules protecting clinical trial subjects; and (iii) the third party entity uses the funds received from the sponsor for investigation purposes.[18] This provision accommodates the frequent French practice of including an association or a foundation as a responsible party for the conduct of a clinical trial.

The Unique Agreement must be signed no later than 45 days following the coordinating institution's receipt of the sponsor's proposal, which is intended to take into account processing time by the coordinating institution.[19] For a trial involving many research sites, the signature timeframe is reduced to 15 days for the associ-

[15] *See* Decree No. 2016-1538, Article 1.
[16] *Id.*
[17] *Id.*
[18] *Id.*
[19] *Id.*

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ated sites, as the agreements signed with the associated sites are duplicates of the agreement with the coordinating institution.[20] Once the agreement has been signed, the sponsor immediately must send the Unique Agreement to the National Council of the Medical Association.[21]

The Unique Agreement template applies to all commercial research studies launched since publication of Decree 1538 on Nov. 17, 2016, that are carried out in either public or private institutions.[22] However, at present, Decree 1538 does not contemplate sanctions in the event that another type of clinical trial agreement is used.

Order No. 2016-800 of 16 June 2016 on research involving the human being

Order No. 2016-800 (the ''Order'') was taken pursuant to Article 216 of the *French Public Health Law No. 2016-641 of 26 January 2016* (the ''Health Reform Law''), which gives the government authority to adapt national law to European Union (EU) law through governmental orders. The Order aims to align French legislation on clinical trials of medicinal products with the provisions of the *EU Clinical Trials Regulation* (536/2014/EU) (the ''EU Clinical Trials Regulation''). The EU Clinical Trials Regulation will come into force no earlier than 2018, subject to an opinion by the European Commission.

The EU Clinical Trials Regulation requires that to be granted authorization prior to implementation, clinical trials be subject to ethical and scientific review, the details of which must be provided by each member state. The Order provides further detail on the respective roles of French authorities responsible for the review of clinical trials of pharmaceutical products.[23] According to the Order, responsibility for review of the scientific and technical portion lies with the ANSM, while the ethical review is conducted by the CPPs.[24]

One innovation of the EU Clinical Trials Regulation is the creation of an EU database through which data and information related to clinical trials are to be shared. The EU Clinical Trials Regulation provides that failure to share clinical data meant to be made available to the public in the EU database must be sanctioned at the member-state level. The Order updates the French Public Health Law to harmonize French criminal law provisions to the EU Clinical Trials Regulation by specifying that the penalty for failure to share such data is one year imprisonment and a fine of up to 15,000 Euros.[25]

The Order also contains several provisions regarding informed consent. First, the Order clarifies that, in the event a trial subject withdraws his/her informed consent, researchers have the right to continue using, in the context of the then-current study, data obtained from a trial subject before such consent was revoked.[26] Second, researchers may request that subjects agree to future research uses of data, exclusively for scientific purposes, at the time informed consent is given. The subject, however, must be able to withdraw his/her consent for, and/or exercise his/her right to object to, the research (including future uses) at any time thereafter.[27]

Most provisions of the Order become effective following the publication of a decree and no later than Dec. 16, 2016, with a few provisions becoming effective with the entry into force of the EU Clinical Trials Regulation.[28]

Health Reform Law No. 2016-641 of 26 January 2016 (the ''Health Reform Law'')

Among many reforms made to the French health-care system, the Health Reform Law enhances transparency and strengthens the existing regulatory framework by expanding Sunshine rules. Article L1453-1 of the French Public Health Code has been amended to increase the scope of disclosure and reporting obligations for financial relationships with health-care professionals and health-care organizations.[29] Under the amended Article L1453-1, companies must disclose on a single public website the exact purpose, the date, the final beneficiary, and the amount of any agreements concluded with health-care professionals and health-care organizations above a certain threshold to be set by decree.[30] Companies that produce, market, or provide services relating to non-corrective lenses, cosmetics, and tattooing products also must disclose publicly on the website any safety assessment agreements and biomedical research agreements with health-care professionals and health-care institutions.[31] The same disclosure obligation exists for all benefits in kind or in cash given to health-care professionals or health-care organizations above a certain threshold to be set by decree.[32] Under the amended Article L1453-1, the information disclosed on the single public website may be accessed and used by a third party, free of charge, if used for purposes related to transparency.[33]

Conclusion

France recently has adopted, and is in the process of implementing, several changes to its laws governing clinical research. These changes will affect U.S. companies, academic medical centers, and other similar entities that sponsor research in France or otherwise collaborate with French research institutions. Fortunately, many of these reforms, including the Unique Agreement and the Health Reform Law, appear designed to streamline the process of carrying out clinical research in France. The research community should stay alert to similar changes in the laws and regulations of other EU member states in the coming years, as each of the EU states prepares for the upcoming effective date of the EU Clinical Trials Regulation.

[20] *Id.*
[21] *Id.*
[22] *See* Decree No. 2016-1538, Article 2.
[23] *See* Order No. 2016-800, Article 4.
[24] *Id.*
[25] *See* Order No. 2016-800, Article 6.
[26] *See* Order No. 2016-800, Article 2.
[27] *Id.*
[28] *See* Order No. 2016-800, Article 8.
[29] *See* Law No. 2016-641 of 26 January 2016, Article 178.
[30] *Id.*
[31] *Id.*
[32] *Id.*
[33] *Id.*