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Clinical Trials: Overview (France)

by Eveline Van Keymeulen and Alexandra Lauré, Latham & Watkins.

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A Practice Note providing an overview of the regulation of clinical trials of medicinal products in France.

This Note provides an overview of the regulation of clinical trials of investigational medicinal products (IMPs) in France, including the legislation and regulatory framework governing the conduct of clinical trials and the relevant regulatory authority. It also outlines the process for applying for clinical trial authorisation in France, including any pre-trial considerations, and explains the procedural requirements during and after the end of the clinical trial, including requirements for reporting safety information.

The Note also contains a high-level discussion on regulation of decentralised clinical trials in France and other important considerations.

Legislation and Regulatory Framework

In the EU, until 31 January 2022, clinical trials of medicinal products were governed by the Clinical Trials Directive (2001/20/EC). Relevant provisions of the Clinical Trials Directive were transposed and complemented in the French Public Health Code (*Code de la santé publique*) (FPHC), which sets out the legislative and regulatory framework applicable to all studies involving human subjects (*recherches impliquant la personne humaine*), defined as "studies organised and carried out on [healthy or sick] humans with a view to developing biological or medical knowledge," to evaluate the mechanisms of the human organism, or the effectiveness and safety of procedures or products intended to diagnose, treat, or prevent pathologies (Articles L. 1121-1 and R. 1121-1 al. 1, FPHC).

Studies fall into one of the following three categories:

- **Category 1:** interventional studies which involve an intervention on a study subject not justified by their usual care.
- **Category 2:** interventional studies which only involve minor risks and constraints for the study subject, and do not involve a medicinal product (Article 2, Order of 12 April 2018).
- **Category 3:** non-interventional (or observational) studies, which do not involve any risk or constraint on study subjects, and where all procedures are performed, and products are used in the usual way.

(Article L. 1121-1, FPHC.)

Any clinical trial on a medicinal product therefore fell within the scope of studies involving human subjects as defined above. Until 31 January 2022, these clinical trials were regulated, along with the other types of studies, by the relevant provisions of the FPHC.

On 31 January 2022, the Clinical Trials Regulation ((EU) 536/2014) started to apply in the EU. The Clinical Trials Regulation is directly applicable in France and now governs interventional clinical trials on medicinal products, which are defined as clinical studies in which one of the following conditions is met:

- The assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the member state concerned.
- The decision to prescribe the IMP is taken together with the decision to include the subject in the clinical study.
- Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

(Article 2(2), Clinical Trials Regulation.)

Certain provisions of the FPHC, for example, insurance obligations and applicable sanctions remain applicable.

Transitional provisions of the Clinical Trials Regulation allow for the application of the Clinical Trials Directive (and therefore relevant FPHC provisions) until 31 January 2025 in the following cases:

- Clinical trials for which an application was submitted before the Clinical Trials Regulation became applicable.

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- Clinical trials for which an application was submitted between 31 January 2022 and 31 January 2023, if the trial's sponsor chose to submit the application in conformity with the Clinical Trials Directive.

Therefore, ongoing clinical trials which were approved under the Clinical Trials Directive must comply with the Clinical Trials Regulation by 31 January 2025 at the latest.

The Clinical Trials Regulation does not apply to studies on medical devices. Although they were previously governed by the framework applicable to studies involving human subjects in France, since 26 May 2021, all clinical studies intended to assess either the safety or performance of a medical device (clinical investigations) are now governed by the Medical Devices Regulation ((EU) 2017/745) (MDR). Since 26 May 2022, clinical studies carried out on an in-vitro diagnostic medical device (IVD) to establish or confirm its analytical or clinical performance (performance studies) are governed by relevant provisions of the In Vitro Diagnostics Regulation ((EU) 2017/746) (IVDR). In both cases, as with clinical trials on medicinal products, some provisions of the FPHC, such as those on insurance and applicable sanctions, remain applicable. However, clinical investigations and performance studies are outside of the scope of this Note.

Non-interventional studies fall outside the scope of the Clinical Trials Regulation (Article 1, Clinical Trials Regulation) and remain governed in France by relevant provisions of the FPHC on studies involving human subjects. They are considered Category 3 studies involving human subjects (Article L. 1121-1, FPHC).

Specific provisions apply regarding the participation of certain vulnerable populations in clinical trials, such as:

- Pregnant or breastfeeding women (Article L. 1121-5, FPHC; Article 33, Clinical Trials Regulation).
- Incapacitated adults (Articles L. 1121-8, L. 1121-11, L. 1122-2, L. 1125-10, and L. 1126-9, FPHC; Article 31, Clinical Trials Regulation).
- Minors (Articles L. 1121-7, L. 1121-11, L. 1122-2, L. 1125-10, and L. 1126-9, FPHC; Article 32, Clinical Trials Regulation and Pediatric Regulation ((EU) 1901/2006)).
- In an emergency situation (Article L. 1122-13, FPHC; Article 35, Clinical Trials Regulation).

Regulatory Authority

Under both the Clinical Trials Directive and Clinical Trials Regulation frameworks, oversight of clinical trials lies with the EU member state authorities. Although clinical trials are regulated at European level under the Clinical Trials Regulation, they are authorised by member states' competent authorities following a favourable opinion by national ethics committees.

In France, the French National Agency for the Safety of Medicinal and Healthcare Products (*Agence Nationale de Sécurité du Médicament*) (ANSM) is responsible for granting authorisations under both frameworks, and for ensuring that all clinical trials taking place in France are carried out in compliance with the applicable legal and regulatory framework. A favourable opinion from a French ethics committee (*comité de protection des personnes*) (CPP)) is also required before initiating a clinical trial in France (Article L. 1121-4, FPHC; Article 4, Clinical Trials Regulation).

While responsibility for the oversight of clinical trials under the Clinical Trials Regulation remains with the EU member states, the European Commission oversees its general implementation, and has issued guidance in Volume 10 of the rules governing medicinal products in the European Union (see European Commission: EudraLex: Volume 10: Clinical trials guidelines). The European Medicines Agency (EMA) also publishes guidance, often in co-operation with the Heads of Medicines Agencies (HMA), or to the extent the guidance relates to the Clinical Trial Information System (CTIS), for which it is responsible. At a local level, the ANSM also provides guidance and recommendations, available at its website.

Register of Clinical Trials

Under the **Clinical Trials Directive** framework, any clinical trial which involved at least one investigational site located in a member state had to be registered on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), managed by the EMA. Some of the information provided on EudraCT is made publicly accessible on the EU Clinical Trials Register, such as protocol-related information and the summary results of the trial once it is completed.

Under the **Clinical Trials Regulation**, registration of the clinical trial takes place on the Clinical Trials Information System (CTIS), maintained by the EMA, through the filing of a single clinical trial application (see Application Process), even when the trial takes place across several EU member states.

Most of the information submitted through CTIS is made publicly available at CTIS once a decision on the clinical trial application is issued, or later in specific cases, depending on the classification of the clinical trial and the type of data. For more information, see Table 1 of the Appendix on disclosure rules to the "Functional specifications for the EU portal and EU database to be audited (EMA/42176/2014)" (EMA: Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited" (EMA/228383/2015) (2 October 2015)).

At national level, three registers have been set up for specific pathologies (cancer, infectious diseases, and

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rare diseases) by specialised institutions in collaboration with the ANSM. The ANSM maintains a list of available registers (in French) at its website (see ANSM: Registers of clinical trials on medicinal products (*Répertoires des essais cliniques de medicaments*)).

Applying for Clinical Trial Authorisation

When Is Clinical Trial Authorisation Needed?

Under both the Clinical Trials Directive and the Clinical Trials Regulation, an authorisation from the EU member state competent authority and a favourable opinion from the relevant ethics committee must be obtained prior to initiating any clinical trial of a medicinal product (Article 9, Clinical Trials Directive; Article 4, Clinical Trials Regulation).

Under the Clinical Trials Directive framework, as under the Clinical Trials Regulation, the authorisation is delivered in France by the ANSM. However, under the Clinical Trials Regulation and in multi-centre trials taking place in more than one country (including France), this authorisation can be delivered by either the ANSM or another member state competent authority, depending on which member state is designated as responsible for assessing the application. The Clinical Trials Regulation now allows for a co-ordinated evaluation of applications in these cases (Article 5, Clinical Trials Regulation), whereas under the Clinical Trials Directive, the applicant was required to submit a request for authorisation in each relevant member state.

Different rules apply to non-interventional studies, which can be carried out without the ANSM having to authorise them. However, a favourable opinion from the competent ethics committee remains necessary for a non-interventional study to be initiated (Article L. 1121-4 al. 3, FPHC).

Application Process

Under the Clinical Trials Directive as transposed under the FPHC, the application for authorisation of a clinical trial previously had to be submitted to the ANSM by email (see ANSM: [Former] Notice to Applicants for Clinical Trials on Medicinal Products: Part I (Version 4, 1 June 2018) (*Avis Aux Promoteurs d'Essais Cliniques de Medicaments, y Compris les Essais Cliniques Portant sur les Medicaments de Therapie Innovante (MTI): Tome I*)).

Since the application of the **Clinical Trials Regulation**, any sponsor wishing to obtain an authorisation to carry out a clinical trial with at least one investigational site located in a member state must submit a request for authorisation at CTIS (Article 5, Clinical Trials Regulation) (see Register of Clinical Trials). This is especially useful for multi-centre clinical trials taking place in several member states, as it allows a sponsor to submit a single request for authorisation for all relevant member states. A reporting member state is designated among them, in charge of co-ordinating the scientific assessment of the application (Articles 5 and 6, Clinical Trials Regulation).

Any request for authorisation submitted under the Clinical Trials Regulation must contain all the relevant elements listed in Annex I to the Clinical Trials Regulation.

The following documents must be included in the application:

- Cover letter.
- Duly completed application form.
- Protocol and a summary of the protocol.
- Investigator's brochure.
- Good Manufacturing Practice (GMP) compliance documents.
- IMP dossier.
- Auxiliary medicinal product dossier.
- Content of the labelling of IMPs.
- Recruitment arrangements.
- Subject information, informed consent form, and informed consent procedure.
- Proof of insurance coverage or indemnity.
- Financial aspects.
- Proof of payment of fee.
- A statement by the sponsor that the data will be collected and processed in accordance with EU legislation, including a declaration of compliance with the data processing regulations; see Annex I(R), Clinical Trials Regulation.

(Annex I, Clinical Trials Regulation.)

The ANSM has specified that, although most of the documents listed above can be provided in English, the protocol summary and the labelling of the IMP must also be provided in the French language for the ANSM to review the application (see ANSM: Notice to Applicants for Clinical Trials on Medicinal Products: Part II (2022) (*Avis aux promoteurs: Essais Cliniques de Medicaments Relevant du Reglement Europeen N°536/2014 (REC): Partie II*)).

For clinical trials still governed by the **Clinical Trials Directive**, the ANSM must issue a decision

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on the authorisation of the trial within 60 days of acknowledgement of receipt of a complete application. If the ANSM does not issue a decision within that timeframe, the request is deemed granted. The ANSM can request any additional information it considers necessary from the sponsor and provides a timeline for the sponsor to provide the requested information. There is no clock-stop mechanism; any request for information has no impact on the 60-day assessment period. However, if the sponsor does not provide the requested information within the timeframe set by the ANSM, its application is deemed withdrawn (Article R. 1123-38, FPHC).

A decision on the application must be issued within 45 days of acknowledgment of receipt of a complete request (Article 6, Clinical Trials Regulation). However, if the ANSM submits a request for information to the sponsor as part of its assessment, this timeline increases to a maximum of 76 days (Articles 6 and 7, Clinical Trials Regulation). Additional time may be added when the trial involves specific medicinal products, such as advanced therapy medicinal products (ATMPs) (Article 6(7), Clinical Trials Regulation). The authorisation delivered by member states can be subject to conditions, if those conditions cannot be fulfilled at the time of authorisation (Article 8, Clinical Trials Regulation).

Specific fast-track procedures have been introduced in France, for example, for:

- Clinical trials on ATMPs which meet set requirements.
- New trials on a medicinal product already evaluated by the ANSM.

(See ANSM: Clinical trial on medicinal products submitted to the ANSM as part of the Fast-Track procedure; Practical Information Guide for Applicants (18 February 2019)).

Fast-track procedures can also apply to clinical trials of medicinal products relating to COVID-19 which have received the "national priority research" label (see ANSM: Covid-19: Ongoing clinical trials (*Soumission des essais cliniques COVID-19*)).

Trial Preconditions That Must Be Met

Trial Sponsor and Legal Representative

Any study involving human subjects taking place at least in part in France, including clinical trials, must have a sponsor, who is a natural person or legal entity "responsible for the study ... who handles its management and ensures its financing is provided for" (Article L. 1121-1 al. 3, FPHC). The definition of sponsor provided in the Clinical Trials Regulation is quite similar to that of the FPHC, and is defined as "an individual, company, institution, or organisation which takes responsibility for the initiation, for the management, and for setting up the financing of the clinical trial" (Article 2(14), Clinical Trials Regulation).

The FPHC further provides that "when several persons initiate the same study involving human subjects, they designate a natural or legal person who will have the status of promoter and will assume the corresponding obligations" (Article L. 1121-1 al. 3, FPHC).

Under the French legal framework, therefore, co-sponsorship is not prohibited *per se*, but an official sponsor must be designated to fulfil the role and obligations attached to the role, rather than allowing a sharing of those obligations among several persons or entities.

In contrast, the Clinical Trials Regulation expressly provides for potential co-sponsorship. All sponsors can choose to split the responsibilities attached to the role in a written contract among themselves. In the absence of a contract, each sponsor carries all the obligations associated with the role of sponsor (Article 72, Clinical Trials Regulation). In any event, co-sponsors remain jointly responsible for designating the following responsibilities among themselves:

- A sponsor assuming all responsibilities relating to the clinical trial authorisation procedure, as well as the authorisation procedure applicable to substantial modification of that trial.
- A sponsor acting as contact point for subjects, investigators, or any national competent authority.
- A sponsor in charge of implementing corrective measures taken by any competent national authority regarding the clinical trial they are sponsoring.

(Article 72, Clinical Trials Regulation.)

If the sponsor is located outside the EU, it must designate a legal representative established in the EU, in charge of compliance with the sponsor's obligations, who will be the contact point for all communications with the sponsor. This applies to both clinical trials governed by the Clinical Trials Regulation and those still governed by the Clinical Trials Directive, as transposed under French law (Article 74, Clinical Trials Regulation; Article L. 1121-1 al. 3, FPHC).

Insurance

The Clinical Trials Regulation provides that a system for "compensation for any damage suffered by a subject resulting from participation in a clinical trial" must be implemented by member states, for any clinical trial conducted on their territory (Article 76, Clinical Trials Regulation).

Under French law, this system comprises the obligation for the clinical trial sponsor to compensate participants for any harmful consequence arising out of their

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participation in the trial, to the extent that the sponsor does not prove that the harm is not attributable to its misconduct or that of another party involved (Article L. 1121-10, FPHC). Consequently, sponsors must hold appropriate insurance, under which guarantees must be no less than:

- EUR one million per victim.
- EUR6 million per protocol.
- EUR10 million for all claims made during one insurance year under several protocols.

(Articles L. 1121-10, R. 1121-4 to R. 1121-9, FPHC.)

When a sponsor is found not liable for damages suffered by participants, compensation can still be obtained by a participant from the French National Office for the Compensation of Medical Accidents, Iatrogenic Disorders and Nosocomial Infections (*Office National d'Indemnisation des Accidents Médicaux, des Affections Iatrogènes et des Infections Nosocomiales*) (ONIAM)) (Article L. 1142-3 al. 2, FPHC).

The above insurance requirements apply to clinical trials governed by the Clinical Trials Directive and by the Clinical Trials Regulation. Failure to comply with these insurance requirements exposes sponsors to the following criminal sanctions:

- A one-year prison sentence and a EUR15,000 fine for individuals.
- A EUR75,000 fine for legal entities, which can be accompanied by criminal penalties.

(Article L. 1128-2 and Article L. 1128-6, FPHC.)

Trial Site or Facilities

Clinical trials, whether governed by the Clinical Trials Regulation or the Clinical Trials Directive, can only take place in France in locations which "have the human, material, and technical resources appropriate to the research and are compatible with the safety requirements of the persons involved" (Article L. 1121-13, FPHC).

In principle, an authorisation must be obtained for a site to be able to carry out clinical research within its premises. When the site is a standard place of care, such as a hospital or other healthcare institution, this authorisation is only required to the extent that the clinical trial requires the performance of acts which either:

- Are not usually carried out as part of the institution's activities.
- Are carried out on persons who present a clinical condition distinct from that for which the relevant service is competent.

(Article L. 1121-13, FPHC.)

Any site on which IMPs are administered on humans for the first time must have this authorisation.

The authorisation is delivered by the competent Regional Health Agency (*Agence Régionale de Santé*) (ARS)) for a period of seven years, or three years when the clinical trials to be carried out onsite include the first administration of IMPs on humans (Articles R. 1121-10 to R. 1121-15, FPHC).

Ethics Committee, Institutional Review Board, or Equivalent Approval

A favourable opinion from a French CPP must be obtained before any clinical trial (whether governed by the Clinical Trials Regulation or the Clinical Trials Directive) can be conducted in France (Article L. 1121-4, FPHC; Article 4, Clinical Trials Regulation) (see When Is Clinical Trial Authorisation Needed?).

The designated CPP will be responsible for evaluating the following aspects, among others:

- The level of protection of persons involved in the trial, including participants.
- The adequacy, completeness, and comprehensibility of the information provided to participants, as well as the procedure used to obtain their informed consent and sufficient time for the participant to reflect before giving their informed consent.
- The necessity to include in the protocol a prohibition on participation in other trials.
- The relevance of the trial, the satisfactory nature of the risk/benefit analysis, and the soundness of its results.
- The balance between the objective pursued and the means implemented.
- Investigator(s) qualifications.
- The amount and methods of compensating participants.
- Methods of recruitment.
- The scientific and ethical relevance of any project to collect biological samples during the trial.
- The trial methodology, considering:
  - applicable legislation on the protection of personal data;
  - the need to collect and process personal data; and
  - the relevance of data collected regarding the objective of the trial.

(Article L. 1123-7, FPHC.)

The application to the CPP can be either submitted alongside that to the ANSM (see Application Process),

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or separately. A CPP is then designated randomly within the pool of 39 French CPPs (Article L. 1123-9, FPHC). For a list of CPPs, see CPP Directory).

Once a CPP is designated, it must issue an opinion within 45 days of the acknowledgment of receipt of a complete application, which is sent out within ten days of the complete application being submitted. However, longer timelines apply if the application is deemed incomplete by the CPP, or if the CPP requests additional information during their review, in which case clock-stop mechanisms apply and the review timeline extends from 45 days to 60 days (Article R. 1123-23, FPHC).

Informed Consent

For clinical trials governed by the Clinical Trials Directive, the type of consent to be obtained from patients differs depending on the category of research involving human subjects the trial fits into (Article L. 1122-1-1, FPHC) (see Legislation and Regulatory Framework). As clinical trials on medicinal products fit into the first category of research involving human subjects, the consent sought must be "free and informed, obtained in writing," after having delivered all required information on the trial to the patient, particularly through the "patient information sheet," which must be provided in writing to the patient (Article L. 1122-1-1, FPHC).

This patient information sheet must contain at least the following information:

- The objective, methodology, and duration of the trial.
- Expected benefits and foreseeable constraints and risks, including when the trial is interrupted before it reaches completion.
- Possible medical alternatives.
- Medical care arrangements planned at the end of the trial where necessary, in the event of premature termination, or exclusion from the trial.
- The opinion delivered by the CPP and the authorisation delivered by the ANSM (see Ethics Committee, Institutional Review Board, or Equivalent Approval).
- Where applicable, the prohibition from participating simultaneously in another research project or the exclusion period provided for in the protocol, and the registration of the trial in the relevant register (see Register of Clinical Trials).
- Where the trial has a commercial purpose, the methods used to pay compensation in addition to reimbursement of expenses incurred.
- Where applicable, the need to process personal data in accordance with applicable data privacy laws and regulations.
- The rights of the participant to:
  - have access, during or at the end of the trial, to information held by the investigator pertaining to their health; and
  - refuse to participate and to withdraw their consent, without incurring any liability or prejudice as a result.

(Article L. 1122-1, FPHC.)

For clinical trials governed by the Clinical Trials Regulation (see Legislation and Regulatory Framework), the participants' informed consent must be "written, dated, and signed" by both the participant (or their representative) and the member of the investigating team performing the interview with the participant (Article 29 (1), Clinical Trials Regulation). Similar to the French regulatory framework applicable under the Clinical Trials Directive, a patient information sheet must be provided to the patient in a manner understandable by a layperson, containing information on:

- The nature, objectives, benefits, implications, risks, and inconveniences of the clinical trial, including its EU trial number.
- The subject's rights and guarantees regarding their protection, in particular their right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification.
- The conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial.
- Possible treatment alternatives, including follow-up measures, if the participation of the subject in the clinical trial is discontinued.
- The applicable damage compensation system.
- Availability of the clinical trial results.

(Article 29(2), Clinical Trials Regulation.)

Risk Assessment

Under French law, clinical trials governed by the Clinical Trials Directive can only be carried out if the foreseeable risk for participants is proportionate with the anticipated benefits for those participants or the interest of the trial (Article L. 1121-2, FPHC). There is a risk-based approach to clinical trials and, as part of their evaluations, both the CPP and the ANSM will assess whether the relevant risks and benefits have been properly evaluated and remain proportionate to one another, prior to giving a favourable opinion or delivering an authorisation for a specific trial (Articles L. 1123-7 and L. 1123-12, III, 2°, FPHC).

A similar approach applies to clinical trials governed by the Clinical Trials Regulation (Article 28(1)(a), Clinical

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Trials Regulation), under which sponsors must identify and evaluate the potential risks and benefits of the trial before it can be authorised and initiated. Regardless of the applicable regulatory framework, this risk-benefit assessment must be described in the clinical trial protocol, as well as in the investigator brochure (ANSM: Notice to Applicants for Clinical Trials on Medicinal Products: Part II (January 2020) (*Avis aux Promoteurs D' Essais Cliniques de Medicaments y Compris les Medicaments de Therapie Innovante: Tome II*); Annex I, Clinical Trials Regulation).

Outcome of Assessment

Whether under French law or the Clinical Trials Regulation, a sponsor can request a re-examination of its application:

- When the relevant CPP issues an unfavourable opinion, in which case a new CPP is designated for the re-examination procedure (Articles L. 1123-6 and R. 1123-25, FPHC; Article 8, Clinical Trials Regulation).
- When the ANSM refuses to issue an authorisation for the trial. If the trial takes place in several member states and is governed by the Clinical Trials Regulation, this request for a re-examination can only take place if the initial application has been withdrawn or rejected. The application for re-examination is considered a new application for authorisation and the standard procedure described applies (Article 13, Clinical Trials Regulation).

Under both frameworks, the applicant can withdraw its application at any time during the application process until a decision is reached (Article R. 1123-23, FPHC; Article 12, Clinical Trials Regulation).

Conducting and Managing a Clinical Trial

Ethical Guidelines and GCP

Under both the clinical trials directive and clinical trials regulation, good clinical practice (GCP) is set out at European level and applies to all clinical trials taking place at least in part in the EU. GCP is set out under the EMA Guideline for good clinical practice (see EMA: Guideline for good clinical practice E6(R2): Step 5 (EMA/CHMP/ICH/135/1995) (1 December 2016)), which is based on the version of GCP issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The Clinical Trials Regulation directly refers to such ICH guidelines (Article 47, Clinical Trials Regulation). However, these guidelines and the related EMA guidance were issued prior to the entry into application of the Clinical Trials Regulation and therefore also apply to clinical trials governed by the Clinical Trials Directive. For clinical trials governed by the Clinical Trials Directive, principles of GCP as well as requirements applicable to IMPs more specifically (particularly their manufacturing and importation) are set out under the Good Clinical Practice Directive (2005/28/EC).

Specific guidelines apply when the IMP is an ATMP (European Commission: Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products (C(2019) 7140 final) (10 October 2019)).

All clinical trials taking place in the EU must be conducted "in accordance with the ethical principles that have their origin in the Declaration of Helsinki [available on the website of the World Medical Association], and that are consistent with GCP and the applicable regulatory requirement(s)" (EMA, Guideline for good clinical practice E6(R2) (1 December 2016), section 2.1).

It is the CPP's responsibility to ensure that clinical trial documents address any ethical concerns.

Reporting Safety Information

Under both the Clinical Trials Directive framework and the Clinical Trials Regulation, the investigator's brochure must include a "Reference Safety Information" section, which provides "product information on the IMP and on how to determine which adverse reactions are to be considered as expected adverse reactions, and on the frequency and nature of those adverse reactions" (ANSM: Notice to Applicants for Clinical Trials on Medicinal Products: Part II, Annex I (E)(30); Clinical Trials Regulation). This section must be updated yearly, in accordance with relevant guidance from the HMA (HMA: Clinical Trial Facilitation Group (CTFG): Q&A document: Reference Safety Information (November 2017)). For IMPs for which a marketing authorisation has been granted, this information can be found in section 4.8 of the relevant summary of product characteristics.

Throughout the clinical trial, and regardless of the applicable regulatory framework, the investigator must:

- Record and document all adverse events or laboratory abnormalities which are identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the timelines set out in the protocol.
- Record and document all adverse events and report all serious adverse events to the sponsor (unless specified otherwise in the protocol), without undue delay and at the latest within 24 hours of obtaining knowledge of the event. A follow-up report may be necessary to assess whether the serious adverse event affects the benefit-risk balance of the trial.

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- After the end of the trial, report any serious adverse event with a suspected causal relationship to the IMP to the trial sponsor without undue delay.

(Article L. 1123-10, FPHC; Article 41, Clinical Trials Regulation.)

The sponsor must report the following information on suspected unexpected serious adverse reactions (SUSARs) at the EudraVigilance database (European database of suspected adverse drug reaction reports) (see EMA: EudraVigilance):

- All SUSARs to IMPs (regardless of the location where the SUSAR has taken place), during and after the trial.
- All SUSARs related to the same active substance (regardless of the pharmaceutical form or dosage) in IMPs used in the clinical trial occurring in a clinical trial performed exclusively in a third country, if that clinical trial is sponsored by:
  - the same sponsor; or
  - another sponsor from the same parent company or who co-develops a medicinal product jointly with the sponsor of the clinical trial at hand (based on a formal agreement).

(Article 42(1), Clinical Trials Regulation.)

The period for reporting depends on the seriousness of the reaction, as follows:

- Fatal or life-threatening SUSARs must be reported as soon as possible and at the latest within seven days of becoming aware of the reaction.
- Non-fatal or non-life threatening SUSARs, must be reported within 15 days of becoming aware of the reaction.
- A SUSAR which was originally considered to be non-fatal or non-life threatening which turns out to be fatal or life-threatening must be reported as soon as possible and not later than seven days after becoming aware of the reaction becoming fatal or life-threatening.

(Article 42(2), Clinical Trials Regulation.)

Under the Clinical Trials Directive, reporting of SUSARs by the sponsor follows the same principles under applicable European guidance (European Commission: Communication from the Commission: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (OJ 2011 C 172/1)). However, they must be reported not only through EudraVigilance but also by email to the ANSM.

In addition to the procedures above, and regardless of the applicable framework, the sponsor of a clinical trial on healthy volunteers in France must also report any of the following events as soon as possible at CTIS and to the ANSM (see Regulatory Authority):

- Serious adverse event.
- Expected serious adverse event.
- SUSAR.

(Article R. 1123-54, FPHC.)

Sponsors must submit annual safety reports to the competent authorities through CTIS (Article 43 and Annex 3(3), Clinical Trials Regulation). If the trial is governed by the Clinical Trials Directive, the reports must also be sent to the ANSM directly.

The sponsor must perform the following additional duties through EudraVigilance when the trial is governed by the Clinical Trials Regulation, or directly to the ANSM and the CPP (by electronic means or by post) when the trial is governed by the Clinical Trials Directive as transposed into French law:

- Notify any serious breach of the Clinical Trials Regulation or of the protocol within seven days of obtaining knowledge of the breach (Article 52, Clinical Trials Regulation).
- Report any unexpected events which affect the benefit-risk balance of the clinical trial but do not meet the definition of a SUSAR within 15 days from the date the sponsor became aware of the event at the latest (Article 53, Clinical Trials Regulation).
- Submit all inspection reports from third-country authorities concerning the clinical trial (Article 53, Clinical Trials Regulation).
- Report any urgent safety measure implemented in co-operation with the investigator following any unexpected event likely to seriously affect the benefit-risk balance of the trial, as soon as possible and within seven days of the date when the measures were taken at the latest (Article 54, Clinical Trials Regulation).

  For trials still governed by the Clinical Trials Directive, the competent ARS which delivered the authorisation for the trial site must be notified, as well as the ANSM and the relevant CPP (Article R. 1123-59, FPHC).

More generally, the sponsor is responsible for adequately monitoring the conduct of the trial, given its characteristics, including monitoring of:

- Whether the clinical trial is a low-intervention clinical trial.
- The trial's objective and methodology.
- The degree of deviation of the intervention from standard clinical practice.

(Article 48, Clinical Trials Regulation.)

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Additional reporting and monitoring requirements may apply, for example when the clinical trial involves an auxiliary medicinal product (Article 46, Clinical Trials Regulation).

Changes to the Clinical Trial

Once the clinical trial has been authorised, the sponsor can amend trial-related documents, such as the protocol. The applicable process for these changes depends on whether the relevant change is considered a substantial or non-substantial modification.

Substantial Modifications

A substantial modification is any change made after the clinical trial has been authorised and "which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial" (Article 2(13), Clinical Trials Regulation).

When the relevant change is considered a substantial modification, it must be approved prior to its implementation, as follows:

- Under the **Clinical Trials Directive** framework, all substantial modifications must be approved by the ANSM and obtain a favourable opinion from the relevant CPP (Article L. 1123-9, FPHC).

  In this respect, the ANSM refers to the European Commission guidance on the contents and process for obtaining these approvals (Order of 2 December 2016; European Commission: Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (OJ 2010 C 82/1) (Commission guidance CT-I)).

  While some substantial modifications require express approval from the ANSM, others must be submitted but will be deemed authorised in the absence of a decision from the ANSM within 35 days from the submission of a complete application (Article R. 1123-44, FPHC).

  The ANSM provides guidance on what type of substantial modifications require express approval in its notice to applicants (ANSM: [Former] Notice to Applicants for Clinical Trials on Medicinal Products: Part I, Annex 15).

- Under the **Clinical Trials Regulation**, the application for authorisation of the substantial modification must be submitted by the trial sponsor on CTIS.

  Where the trial takes place in several member states and the modification affects a document which applies to all member states (that is, it is included in Part I of the assessment report drawn up at the initial authorisation stage) both:

  – The application will be assessed by the reporting member state designated at the initial authorisation stage.

  – An assessment report will have to be prepared by the reporting member state and circulated to all relevant member states, which will then decide to authorise the modification or not in light of the report, with which they can disagree.

  Where the modification affects a document relevant for a single member state (included in Part II of the assessment report drawn up at the initial authorisation stage, such as the informed consent form), only the member state concerned assesses and decides on the authorisation of the application.

  (Articles 15 to 24, Clinical Trials Regulation.)

Non-Substantial Modifications

Non-substantial modifications do not require approval from the ANSM or the CPP. However, they must be notified of these changes by the sponsor (Article R. 1123-42, FPHC).

To date, the ANSM has not published a revised notice to applicants dealing with any substantial or non-substantial modifications for clinical trials governed by the Clinical Trials Regulation.

The sponsor can also choose to temporarily halt, or terminate early, a clinical trial, as follows:

- Under the **Clinical Trials Directive** as transposed into French law, temporary halts and restarts of the clinical trials must be handled as substantial modifications (see Substantial Modifications). The sponsor must therefore request approval from the ANSM and relevant CPP (ANSM: [Former] Notice to Applicants for Clinical Trials on Medicinal Products: Part I).

  For early termination, the sponsor must notify the ANSM and the relevant CPP, along with a relevant justification, within 15 days of early termination of the clinical trial (Article R. 1123-66, FPHC).

- Under the **Clinical Trials Regulation**, temporary halts and early termination must be notified through CTIS, including the reason for such action, within 15 days of the end of the trial (Article 37, Clinical Trials Regulation).

  If the trial does not resume within two years, it will be considered as having ended (Article 37, Clinical Trials Regulation).

  Restart of a trial following a temporary halt due to changes in the benefit-risk balance must be treated as a substantial modification (Article 38, Clinical Trials Regulation).

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End of the Clinical Trial

Under the French framework applicable to research involving human subjects, the sponsor must notify the ANSM and the CPP of the beginning and the end of the clinical trial, within 90 days (Articles L. 1123-11 and R. 1123-66, FPHC). The ANSM, specifically, must be informed of the end of the trial (which will generally be the date of the last visit of the last patient) in France as well as across the world. The sponsor must then finalise the final report of the clinical trial and submit the clinical trial summary report within a year of the end of the trial across the world to:

- EudraCT for publication at the EU Clinical Trial Register (see Register of Clinical Trials).
- The CPP.

(Article R. 1123-67, FPHC; ANSM: [Former] Notice to Applicants for Clinical Trials on Medicinal Products: Part I.)

In a similar (if not identical) way, under the Clinical Trials Regulation, the sponsor must notify competent authorities (namely, the ANSM and relevant CPP) of the end of a clinical trial:

- In a specific member state, within 15 days of the end of the trial.
- In all member states concerned, within 15 days from the end of the clinical trial in the last member state concerned.
- Across the world, within 15 days from the end of the clinical trial in the last of the member states concerned and third countries in which the clinical trial has been conducted.

(Article 37(1)-(3), Clinical Trials Regulation.)

Within one year of the end of the trial in all member states involved, the sponsor must submit:

- A summary of the clinical trial results to CTIS, as set out in Annex IV to the Clinical Trials Regulation.
- A separate summary which is understandable to laypersons, as set out in Annex V to the Clinical Trials Regulation.

(Article 37(4), Clinical Trials Regulation.)

If the trial is used to obtain a marketing authorisation for the IMP, the sponsor must also submit the clinical study report to CTIS within 30 days of any of the following:

- The marketing authorisation being granted.
- The procedure for granting the marketing authorisation being completed.
- The marketing authorisation application being withdrawn.

(Article 37(4), Clinical Trials Regulation).

The sponsor and investigator are also under an obligation to archive the clinical trial master file for at least:

- 15 years from the end of the trial under the former French framework (Article 2, Order of 8 November 2006).
- 25 years from the end of the trial under the Clinical Trials Regulation (Article 58, Clinical Trials Regulation).

Some additional monitoring and reporting requirements remain applicable once the trial has ended, such as:

- The reporting of serious adverse events by the investigator to the sponsor (Article 41, Clinical Trials Regulation).
- The reporting of SUSARs by the sponsor to the EMA (Article 42, Clinical Trials Regulation).

See Reporting Safety Information.

Decentralised or Hybrid Clinical Trials

There is no specific framework or guidance under French law applicable to decentralised or hybrid clinical trials. This type of trial is not prohibited *per se*, and it must comply with the general set of rules applicable to clinical trials. This may prove difficult, as the French regulatory framework applicable to research involving human subjects is not specifically adapted to the specificities of this type of trial.

Given the lack of France-specific guidance (except for Covid-19 related situations, for which guidance was issued but no longer applies), guidance adopted at European level provides some first insights on how decentralised or hybrid trials can be implemented (see HMA: Recommendation Paper on Decentralised Elements in Clinical Trials (13 December 2022) (European guidance)). The European guidance, however, does not always reflect national specificities. For instance, while the European guidance provides that electronic methods for signature of the informed consent form may be used where appropriate, in France, "e-consent" may be difficult to implement in practice, particularly given rules applicable to the processing of personal data, which do not specifically foresee the use of electronic means for collecting consent.

The European guidance does provide general insight on how decentralised trials can be implemented; for

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example, with respect to what type of information must be included in the clinical trial application about:

- The method of patient recruitment.
- Home health visits.
- At-home delivery of the IMP.
- Remote monitoring.

More generally, the European guidance emphasises that the sponsor remains responsible for the reliability and robustness of the data generated in the clinical trial, in compliance with applicable GCP (Articles 2(30) and 71, Clinical Trials Regulation).

The EMA has issued a guideline which provides further clarity on how computerised systems must be used to comply with this obligation in the context of clinical trials (EMA: Guideline on computerised systems and electronic data in clinical trials (EMA/226170/2021) (10 June 2021)).

Work is currently ongoing between French regulatory authorities to adapt applicable French rules to the specificities of decentralised or hybrid trials and to adopt related guidance.

Other Important Considerations in Clinical Trials

Data Privacy

In France, the General Data Protection Regulation ((EU) 2016/679) (GDPR) was incorporated into French law under Law No. 78-17 of 6 January 1978 (as amended), which historically regulates data protection issues at national level.

Data collected in the context of clinical trials includes health data which, given their sensitive nature, are subject to even greater protection under the GDPR. As a general principle, the processing of health data is prohibited (except in certain cases), particularly if the data subject has given explicit consent to the processing of personal data for one or more specified purposes, and particularly for scientific research purposes (Articles 4 and 6, Law No. 78-17).

Under Law No. 78-17, processing of health data in the context of a clinical trial may only be implemented where the data controller can guarantee that the processing complies with the applicable reference methodology issued by the French Data Protection Authority (*Commission nationale de l'informatique et des libertés* (CNIL)) relating to the processing of personal data in the context of health research requiring the collection of consent from data subjects (Deliberation no 2018-153 of 3 May 2018 approving a reference methodology relating to the processing of personal data implemented in the context of research in the field of health with the consent of the data subject (MR-001) (*Délibération no. 2018-153 du 3 mai 2018*)). The processing may be conducted without prior CNIL authorisation if the data controller (which should, in principle, be the sponsor) sends a declaration to the CNIL beforehand confirming compliance (Article 73, Law No. 78-17). If the processing does not comply with MR-001, prior authorisation from the CNIL must be obtained. (See CNIL: Health research authorisation application: information to be provided and criteria for approval (13 January 2023) (*Demande d'autorisation d'une recherche en santé : les informations à fournir et les critères d'octroi*)).

Where the trial site is a healthcare institution, a "sole agreement" must be entered into between the sponsor (and its contract research organisation (CRO) where there is one) and the trial site, the contents of which are defined in a national template (Articles L. 1121-16-1, IV, L. 1124-1, IV and R. 1121-3-1, FPHC). The template contains an appendix providing additional particulars on data protection and related responsibilities of parties (Order of 28 March 2022).

Although the CNIL has not, to date, issued additional guidance on the processing of personal data in the context of clinical trials (save for Covid-19-specific guidance), some guidance has been published, at European level, by the European Data Protection Board (EDPB), for example, with respect to the interplay between the provisions of the GDPR and the Clinical Trials Regulation (EDPB: Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR) (art. 70.1.b)) (Adopted 23 January 2019)).

Confidentiality

Under French law, there is no confidentiality requirement specific to clinical trials. Standard confidentiality rules therefore apply, such as doctor-patient confidentiality. Personnel in charge of quality control for the trial who have access to patients' individual data are held to a duty of professional secrecy, such as that applicable to French healthcare professionals (Article L. 1121-3, FPHC).

The Clinical Trials Regulation introduces specific transparency rules, under which information provided on CTIS is made publicly accessible, unless the information is considered confidential for one of the following reasons:

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- To protect personal data in accordance with the GDPR.
- To protect the sponsor's commercially confidential information, unless there is an overriding public interest in disclosing this information.
- To protect the confidentiality of communications between members states when assessing an application for authorisation of a clinical trial.
- To ensure effective supervision of the conduct of the trial by member states.

(Article 81(4), Clinical Trials Regulation.)

Requirements Related to IMPs

Under the Clinical Trials Regulation, as in the former framework, specific requirements apply with respect to the relevant IMP, and in particular its manufacturing, import, and labelling.

Manufacturing and Import

Under the Clinical Trials Regulation (as under the Clinical Trials Directive), the manufacturing and import of an IMP must comply with GMP, and relevant guidance on GMP, issued by the European Commission (Article 63, Clinical Trials Regulation; Commission Delegated Regulation on GMP for Investigational Medicinal Products ((EU) 2017/1569); European Commission: Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use (C(2017) 8179 final) (8 December 2017)). The EMA has also issued additional guidance on the handling and shipping of IMPs (EMA: Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice (EMA/INS/GMP/258937/2022) (14 September 2022)).

Similarly, under the Clinical Trials Directive as transposed under French law, the manufacturing of an IMP must comply with applicable GMP (Article L. 5121-5, FPHC: ANSM, Guide to Good Manufacturing Practice (29 December 2015) (*Guide des Bonnes Pratiques de Fabrication*)).

Labelling

Under the **Clinical Trials Regulation**, requirements for labelling vary depending on whether the IMP has been granted a marketing authorisation.

If the medicinal product has **not yet been granted a marketing authorisation** in the relevant indication, its labelling must comply with the requirements of Article 66 of the Clinical Trials Regulation, the objective being that the information provided ensures:

> "subject safety and reliability and robustness of the data generated in the clinical trial, while taking account of the design of the clinical trial, whether the products are investigational or auxiliary medicinal product, and whether they are products with particular characteristics."
>
> (Article 66(2), Clinical Trials Regulation.)

Additional specifications are provided under Annex VI to the Clinical Trials Regulation.

If the medicinal product has **already been granted a marketing authorisation**, its labelling must be that defined in the marketing authorisation (Article 67, Clinical Trials Regulation).

Under the **Clinical Trials Directive** framework, applicable labelling requirements are defined by Order (Order of 24 May 2006), with the ANSM providing additional guidance on the matter in its notice to applicants (ANSM: [Former] Notice to Applicants for clinical trials on medicinal products: Part I).

Payments and Incentives

Any person participating in research involving human subjects (including clinical trials of medicinal products) cannot receive any payment or incentive for their participation (Article L. 1121-11, FPHC). They can, however, receive reimbursement for the expenses incurred during their participation (such as travel costs), as well as compensation for constraints suffered (*indemnité en compensation des contraintes subies*), which must be set out in the clinical trial protocol (Article L. 1121-11, FPHC).

This compensation, payable by the sponsor, is only available to subjects:

- Who are not considered vulnerable (for example, when the subject is a minor, is imprisoned, or when they are under legal guardianship).
- When they are admitted in a healthcare institution for purposes other than their participation in the trial.

(Article L. 1121-11 al. 2, FPHC.)

The total amount of compensation payable to a clinical trial subject cannot exceed EUR6,000 over a period of 12 consecutive months (Order of 15 February 2023). This compensation can be made in kind, in which case the sponsor must evaluate the value of the advantages in kind provided to participants and justify their use based on the specificities of the trial conducted or those of the target population.

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Where the trial takes place in a French healthcare establishment, all additional costs incurred in relation to the trial must comply with the terms and conditions of the sole agreement to be entered into between the sponsor (and its CRO where it has one) and the trial site, the contents of which are defined in a national template (Order of 28 March 2022).

GxP

Under the Clinical Trials Regulation (as under the former framework), the clinical trial protocol must comply with good laboratory practice (GxP) to the extent applicable (Commission Guidance CT-1; Article 25(3), Clinical Trials Regulation). See also Ethical Guidelines and GCP.

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