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INFORMATIVE NOTE

HEALTHCARE, LIFE SCIENCES & PHARMACEUTICALS

Clinical trials in Portugal

Research and development ("R&D") of medicinal products is fundamentally important in peoples' daily lives. This is true both from an individual perspective – when considering the objective of identifying and treating pathologies (with a consequent increase in the quality of life of patients) – and from a collective perspective, when considering the role of R&D in controlling the spread of diseases and in eradicating them altogether.

In abstract terms, R&D activities can be defined as those carried out in humans (who may healthy or ill) to improve knowledge about pathologies, develop new methodologies for diagnosing them and, possibly, identify forms of treatment.

R&D activities are subject to legal and regulatory frameworks and, to carry them out, it is necessary to comply with certain requirements:

i) respect for the principle of human dignity and fundamental rights;

ii) adopting the measures necessary to protect and safeguard privacy, personality rights and the physical and mental integrity of the trial subjects, which inherently includes obtaining of their consent;

iii) compliance with applicable ethical parameters and applicable good practices;

iv) a prior assessment concluding that the potential benefits associated with the trial outweigh the foreseeable risks and inconveniences; and

v) obtaining the legally required approvals.

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In general, clinical trials are a universally recognised method to carry out R&D activities. They must be planned and controlled meticulously to ensure the scientific validity of the results.

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The legislation applicable to clinical trials conducted in Portugal is currently set out in Law 21/2014 of 16 April (amended by Law 73/2015 of 27 July and Law 49/2018 of 14 August), and it is commonly known as the Clinical Research Law ("CRL"). The CRL includes (i) the rules to conduct clinical trials with medicinal products for human use and which results from the incorporation into Portuguese law of Directive 2001/20/EC of the European Parliament and of the Council of 4 April, and (ii) the legislation on clinical research of medical devices, which results from the partial incorporation into Portuguese law of Directive 2007/47/EC, of the European Parliament and of the Council of 5 September.

Under the CRL, "clinical trial or trial" is defined as "any research conducted into human beings, intended to discover or confirm the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal products, or to identify the undesirable effects of one or more investigational medicinal products, or to analyse the absorption, distribution, metabolism and elimination of one or more investigational medicinal products, in order to ascertain their safety or efficacy".

In Portugal, conducting a clinical trial is specifically subject to:

i) the prior issuance of a positive opinion by the Competent Ethics Committee ("CEC");

ii) authorisation by Infarmed - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (the Portuguese National Authority for Medicines and Healthcare Products - "Infarmed") which is dependent on meeting the condition in (i) above.

"In Portugal, conducting a clinical trial is specifically subject to the prior issuance of a positive opinion by the CEC and authorisation by Infarmed."

The application for an opinion and the application for authorisation to conduct a clinical trial must be submitted by the sponsor (i.e., the natural or legal person, institute or entity responsible for the design, conduct, management or financing of the clinical trial) to the CEC and Infarmed, respectively, through the online platform of the National Clinical Trials Register ("RNEC").

Subject to certain situations provided for by law, the CEC has to give its opinion within 30 business days and state its position on the following aspects of the application submitted by the sponsor, among others: (i) the relevance of the clinical trial and the trial design, (ii) the assessment of the anticipated benefits and risks, (iii) the corresponding protocol, (iv) the material and human conditions necessary to conduct it, (v) the way of recruiting trial subjects, (vi) the time frame and conditions for clinical follow-up of subjects after completion of the trial, and (vii) the procedure for obtaining informed consent, including the information to be provided to trial subjects.

Once a favourable opinion has been issued and except for the situations requiring express authorisation as set out below, Infarmed's Governing Board must decide on the application for authorisation to conduct the clinical trial within 30 business days. However, during that period, it can request any additional documents, information or clarification it considers necessary to make its decision. Any such request will determine the suspension of the above period until the request is answered.

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"Infarmed can also present any well-founded objections to the application for authorisation which, in its opinion, could prevent its approval. Under these circumstances, the sponsor may – once only – change the contents of the application for authorisation previously submitted."

In addition to this, Infarmed can also present any well-founded objections to the application for authorisation which, in its opinion, could prevent its approval. Under these circumstances, the sponsor may – once only – change the contents of the application for authorisation previously submitted and must do so within the period granted by Infarmed.

If the change is not considered sufficient by Infarmed or if the sponsor chooses not to make any change to the initial application, the application will be rejected and the clinical trial may not be conducted.

After the start of a clinical trial, the sponsor may make changes to the corresponding protocol provided the prior assessment makes it possible to continue to conclude that the potential benefits outweigh the foreseeable risks and inconveniences. However, no changes may be made if they would impact the safety of the subjects or change the interpretation of the scientific evidence on which the conduct of the trial is based.

In these circumstances, the sponsor must ask the CEC to amend the protocol and the clinical trial may only proceed after (i) the CEC's issues an opinion in favour of it, and (ii) Infarmed has no well-founded objections. If the CEC issues an opinion in favour and Infarmed objects, the trial may only proceed if the protocol is adapted to the objections communicated or if the proposed amendment is withdrawn.

Except where the end of the clinical trial has been brought forward, the sponsor must notify the CEC within 90 days of the end of the participation of the last subject in the trial. In this context, it is also the responsibility of the investigator or sponsor to make available to the CEC the final results of the conduct of the clinical trial in the form of a summary of the final report.

In the current global pandemic caused by COVID-19, clinical trials have gained increased importance, particularly in terms of the research that is being carried out to bring effective drugs onto the market as soon as possible to combat the disease. In fact, the pandemic has put the scientific community and the pharmaceutical industry under intense pressure to design medicinal products that quickly, safely and effectively control the spread of COVID-19. As a result of this, the European Medicines Agency called for the necessary coordination and communication between the various entities that are developing or plan to develop vaccines and medicines to combat SARS CoV-2, and to provide a fee waiver for clinical trials with these purposes.

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In parallel, Infarmed has published several measures intended to mitigate the risks that the pandemic may pose to patients participating in clinical trials taking place while it continues, with a particular focus on:

- Discontinuation of treatment;
- Suspension of recruitment;
- Review of scheduled visits, with preference to be given, where possible, to remote visits;
- Centralised monitoring and review of source data;
- Direct home dispensing of experimental medication, with the principal investigator, the research team and the hospital pharmacy maintaining close and effective supervision of the process;
- Transfer between clinical trial centres, where good clinical practice and the General Data Protection Rules must be respected.

In this context, Infarmed agrees – without requiring prior notification or approval of a substantial amendment to the protocol – that clinical trial sponsors can make changes to the terms of their clinical trial authorisation to ensure the safety and protection of their subjects. However, this waiver does not apply to the above-mentioned interruption of treatment, which must be notified to Infarmed as an urgent safety measure.

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For this purpose, and in conjunction with the investigator and based on a risk analysis, the sponsor must assess and adopt measures to mitigate the risk of contamination for each clinical trial, based on a consideration of the characteristics of the trial, the trial site and the trial's epidemiological risk.

As a result, the sponsor must notify Infarmed within 4 months of the above period. This notification must be accompanied by a report that systematically documents the measures implemented and the deviations produced. It must also include an assessment of the implementation of the measures and their impact on the post-pandemic study.

Nonetheless, in cases where substantial changes that do not require immediate intervention by the investigator and sponsor may be involved, the sponsor must submit these to Infarmed as substantial changes through the common procedure. ■