GUIDANCE FOR THE TEMPORARY MANAGEMENT OF CLINICAL TRIALS PURSUANT TO EU REGULATION 536/2014 PENDING THE FULL IMPLEMENTATION OF THE MINISTERIAL DECREES REFORMING THE ETHICS COMMITTEES AND THE SINGLE FEE

INTRODUCTION

Regulation (EU) no. 536/2014 provides for the mandatory involvement of ethics committees in the review of "part II" (ethical aspects) of the trial application and the payment of one single fee at national level to cover for the costs of the activities of AIFA and of the ethics committee. For each trial, the review is performed by a single ethics committee, which must be independent from the clinical trial site. The ministerial decrees currently being finalized are aimed at allowing the application of these requirements.

In the period between January 31, 2022, date of full application of Regulation (EU) no. 536/2014, and the entry into force of the aforementioned ministerial decrees, it is however possible to submit a partial clinical trial application in Italy, relating only to "part I" of the dossier, for the assessment and approval of the clinical trial protocol and related technical documents. However, without the submission and approval of Part II of the application, the trial cannot be started at national level.

In order to allow the submission of part II of the clinical trial application as well, and to have a complete national authorization of these applications and an immediate start of the related trials in compliance with the requirements of the Regulation, a temporary management mode has been identified in accordance with the current legislation in force, which will be applicable from January 31, 2022 and until the ministerial decrees reforming the territorial ethics committees come into force.

A) TEMPORARY MODE

I. Compliance with the independence requirement of the ethics committee from the clinical trial sites

The ethics committee in charge of reviewing the trial as a single national ethics committee is identified among the ethics committees of the clinical trial sites NOT involved in the trial itself.

To this end, AIFA will publish on its website - in the section “European regulation on clinical trials”- the list of ethics committees, identified by the Regions among those currently existing, and available on a voluntary basis to review the clinical trial applications submitted through the EU portal. These ethics committees are preferably the single regional ethics committees, nominated by the Region itself, where possible providing for the abstention from the participation of the Medical Director or his delegate and the Scientific Director, in case of IRCCS.

If the sponsor fails to identify the single national ethics committee, AIFA identifies the ethics committee for the trial by applying an algorithm that allows adequate rotation with respect to the clinical trial sites and ethics committees previously involved, after consulting the Coordination Centre of the ethics committees, especially with regard to trials peculiar for their indication or complexity. The involvement is preferably limited to a narrow number of ethics committees, according with the indications of the Regions themselves.

II. Compliance with the single fee requirement

From January 31, 2022, the payment of a single fee at national level is mandatory for clinical trial applications.

If only part I of the dossier is submitted, sponsors can pay the first instalment of this fee, based on the current rates in force for applications submitted to AIFA.

However, if the ethics committee has already been identified, sponsors may pay the fee in a single instalment, including the amount due to the responsible ethics committee based on the fees currently in force for that ethics committee. If the ethics committee has not yet been identified, the amount relating to the ethics committee may be paid with a second instalment, and the proof of this payment can be uploaded to the EU portal during the validation phase of the application or, alternatively, as response to considerations during the assessment phase.

AIFA will then transfer the related fee to the ethics committee.

B) OPERATIONAL STEPS

The list of ethics committees available to review the clinical trial applications submitted according to the European Regulation pending the entry into force of the ministerial decrees, together with the related details is published on AIFA's website. This list will be regularly updated on the basis of communications received from the Regions.

The current ethics committees registered in OsSC are already registered in the EU portal and therefore they are already enabled to operate in the system. AIFA will promptly start specific training sessions for the use of the EU portal for the contact persons of the ethics committees (two) indicated for this purpose by the Regions, in order to allow immediate operation.

Following the publication of the ministerial decrees and the full start of the activities of the ethics committees for clinical trials, the clinical trials assessed according to the temporary mode will be automatically transferred for all subsequent activities to the ethics committee that will take over from the voluntary ethics committee within the same Region**.**