Agence nationale de sécurité du médicament et des produits de santé

Guide

Clinical Drug Trials submitted within the Pilot Phase to ANSM (French National Agency for Medicines and Health Products Safety) and the CPP (French Ethics Committee)

Practical Information Guide for Applicants

26 juin 2018 - Version 7.0

INFORMATIONS CONCERNANT L'EVALUATION DES ESSAIS CLINIQUES DE MEDICAMENTS SOUMIS DANS LE CADRE DE LA PHASE PILOTE SIMULANT LA MISE EN PLACE DU REGLEMENT (UE) N° 536/2014 DU PARLEMENT EUROPÉEN ET DU CONSEIL du 16 avril 2014 relatif aux essais cliniques de médicaments à usage humain et abrogeant la directive 2001/20/CE

AEC_DOC008A v.07

TABLE OF CONTENTS

I. INTRODUCTION 3

I.1. Scope of the Pilot Phase 4

I.2. Who does what between ANSM and the EC? 5

II. TEMPORARY PROCEDURES 6

III. PROCEDURE FOR IMPLEMENTING A DRUG TRIAL AS PART OF THE PILOT PHASE PROPOSED BY ANSM 7

III.1. Methods for dispatching dossiers 7

III.2. Dossier content / format 10

III.3. Evaluation deadlines 16

III.4. Validation of the application / acknowledgement of receipt 18

III.5. Dossier assessment 18

III.8. Final notification 22

III.9 Summary table of dialogue between the Sponsor / EC / ANSM apart from the IT portal of CNRIPH 23

IV. APPENDICES 24

Appendix 1: List of dossier components to be submitted to ANSM and EC 25

Appendix 2: Summary of trial protocol 27

Appendix 3: Financial and other arrangements 28

V. GLOSSARY 30

I. INTRODUCTION

European (EU) regulation No. 536/2014 of the European Parliament and Council dated 16 April 2014 on clinical trials on medicinal products for human use and repealing European Directive 2001/20/EC was published in the Official Journal of the European Union on 27 May 2014.

The entry into force of this regulation in the various Member States of the European Union, originally scheduled for May 2016, will be effective only with the provision of the European portal and the European database.

The European regulation essentially provides for the following:

- The implementation of a rapid, centralised and coordinated assessment procedure for applications for clinical trial authorisations and amendments as soon as this trial is being carried out in at least one European Union Member State This regulation establishes the single submission of the authorisation application by the clinical trial sponsor via a European portal grouping together all of the information and data relating to this trial, part of which will be accessible to the general public;

- A 2-part scientific and ethical assessment within specified deadlines:

    - part I – scientific: a *coordinated assessment between concerned Member States* leading to a single conclusion,
    - part II - ethical: an *assessment by each Member State concerned* leading to a national conclusion;

- the principle of a tacit authorisation and a single decision by the Member State concerned;

- greater transparency thanks to the publication of a large section of the Union database and thus public access to the inclusion process and results of trials carried out within the EEA (European Economic Area).

The application of this regulation imposes a new work organization for the competent authorities and Ethics Committees in Member States. In order to prepare for this process, essentially with regard to deadlines for assessing dossiers and coordinating with the 39 existing Ethics Committees (EC), the ANSM in conjunction with the EC is offering sponsors the opportunity to participate in a "pilot phase" in order to anticipate the next stages in the organisation and coordination of assessments carried out by ECs and the ANSM *per se*.

This "pilot phase" will give participants an idea of the new organisational structure enforced by this regulation whilst complying with current legislation.

The main issue in implementing this "pilot phase" for clinical trials involving medicinal products is to ensure that France is ready when the European Regulation comes into force.

A first phase of this experimental procedure was launched on 28 September 2015 with the collaboration of 21 volunteer CPPs out of the 39 existing ones.

Following the entry into force of Law No. 2012-300 of 5 March 2012 on research involving the human person (known as the Jardé Law), as amended by Ordinance No. 2016-800 of 16 June 2016 and Its implementing decree n ° 2016-1537 of 16/11/2016 relating to research involving the human person (JO 17/11/2016), this experimental procedure is now extended to all 39 CPPs.

I.1. Scope of the Pilot Phase

The pilot phase concerns:

- Clinical trials involving medicinal products (including radiopharmaceutical)
- All phases in drug clinical trials (phases 0, 1, 2, 3 or 4)
- All therapeutic areas
- **Initial clinical trial authorisation**
- All clinical trial sponsors (academic or private)

The pilot phase does not concern:

- Clinical trials involving medicinal products in the following cases:
    - CIM procedure ("Multiple Intermediate Correspondence" procedure)
    - Having been the subject of a previous submission as part of the VHP (Voluntary Harmonisation Procedure) whether France is the referent NCA or concerned NCA, if and only if France took part in this VHP.
- Obligations relating to the conduct and follow-up of clinical trials involving medicinal products including those submitted as part of the pilot phase (i.e. substantial amendments, reporting of serious adverse events, annual safety reports, new events) and at the end of the trial
- Clinical trials involving innovative medicinal products, i.e.
    - somatic cell therapy medicinal product,
    - gene therapy product
    - medicinal product derived from cell or tissue engineering
    - combined innovative medicinal product
    - innovative therapy medicinal products prepared on a non-routine basis
    - medicinal product, all or part of which comprises genetically modified organisms
- Clinical trials involving a health product (other than a medicinal product), especially medical devices, *in-vitro* diagnostic medical devices, cosmetics, cell therapy preparations, organs, tissues and labile blood products
- Clinical trials not involving health products (especially physiology, physiopathology, behavioural sciences and genetics)
- Non-interventional trials and research with minor risks or constraints (categories 2 and 3 of the Jardé Law)

I.2. Who does what between ANSM and the EC?

The competence of ANSM and the ECs in terms of clinical trials on medicinal products can be defined as follows:

	ANSM	EC
Currently (Articles L.1123-7 and L.1123-12 of the French Public Health Code)	**Safety of persons** **Scientific assessment** (especially the quality and safety of products used in research, conditions of use, etc.)	**Protection of persons** Information and consent Enrolment procedures / Exclusion periods / Compensation **Protocol** Methodological aspects with an ethical perspective **Resources** Investigators' qualifications / research centres
With the European Regulation	Part I - scientific The scientific assessment **primarily includes the methodological aspects***	Part II – ethical **Protection of persons** Information and consent Enrolment procedures / Exclusion periods / Compensation **Resources** Investigators' qualifications / research sites **Financial provisions**

* The following should be noted:

Within the scope of the European Regulation, it appears that the dossier comprises 2 parts (part I-scientific and part II-ethical) and the trial methodology is part of a coordinated European assessment (included in part I, which comes under the remit of the ANSM).

Following the entry into force of Law No. 2012-300 of 5 March 2012 on research involving the human person (known as the Jardé Law), as amended by Ordinance No. 2016-800 of 16 June 2016 and Its implementing decree n ° 2016-1537 of 16/11/2016 concerning research involving the human person (JO 17/11/2016), for trials relating to the medicinal product, evaluation of the methodological aspects remains within the competence of the EC until the implementation of the European Regulation.

II. TEMPORARY PROCEDURES

This pilot phase is optional.
Based on a voluntary approach, the sponsor can choose from two options:

1. The sponsor can apply the current legislation set by Articles L. 1121-1 and subsequent articles of the Public Health code transposing European Directive 2001/20/EC of the European Parliament and Council dated 4 April 2001 concerning the harmonisation of legislative, regulatory and administrative provisions of Member States relating to the application of Good Clinical Practices in carrying out clinical trials involving medicinal products for human use: authorisation and initial decisions, authorisation/decisions regarding substantial amendments and "vigilance" during clinical trials and the end of the trial).

2. The sponsor can choose to simulate application of the provisions stipulated in the European Regulation by following the pilot phase proposed by ANSM, which procedure is described in this document.

This optional procedure applies to the sponsors' application on a trial by trial basis.

The decisions taken by the ANSM and relevant EC within the scope of this pilot phase will be valid from a regulatory point of view and in accordance with current regulatory deadlines defined in the Public Health Code.

III. PROCEDURE FOR IMPLEMENTING A DRUG TRIAL AS PART OF THE PILOT PHASE PROPOSED BY ANSM

The European Regulation defines the methods for assessing clinical trials and the various stages involved in the evaluation of the latter (see document entitled, "(EU) REGULATION No. 536/2014 OF THE EUROPEAN PARLIAMENT AND COUNCIL dated 16 April 2014 on clinical trials on medicinal products for human use and repealing directive 2001/20 EC" available via the following link http://eur-lex.europa.eu/legal-content/FR/TXT/?uri=CELEX:32014R0536

III.1. Methods for dispatching dossiers

Within the scope of this pilot phase:

- D0 = date on which the dossier is received by both bodies.

III.1.1. Transmission to the EC

To obtain the random designation of an EC (Following the entry into force of Law No. 2012-300 of 5 March 2012 on research involving the human person (known as the Jardé Law), as amended by Order No. 2016-800 of 16 June 2016 and its implementing decree n ° 2016-1537 of 16/11/2016 concerning research involving the human person (JO 17/11/2016)), the sponsor must submit his complete file on the IS portal of the National Commission of Research Involving Humans : https://cnriph.sante.gouv.fr/ and trigger the random draw which will determine the concerned EC (whose identity will be transmitted to the sponsor and to ANSM on the adress phasepilote.reglement@ansm.sante.fr)

From then on and during the same day, the sponsor must also submit his file to ANSM (cf §III .1.2). The date of this dispatch will condition the day 0 (D0) – beginning of the instruction of the file.

CTA must be identified by the sponsors as applications submitted within the scope of the pilot phase.

The following addresses should be used for general questions relating to the pilot phase (and any anomalies experienced by EC):
l.lacoste@chu-poitiers.fr or eofrija@gmail.com
completing the "subject" field with the following information: **pilot phase question**

For requests for opinion on substantial amendments to clinical trials which have been evaluated within this pilot phase, it should be specified in the subject of the e-mail that the initial file was evaluated in the pilot phase.

The following should be noted: For general questions relating to the pilot phase and concerning EC aspects, the e-mails received via phasepilote.reglement@ansm.sante.fr will be transferred to the following e-mail addresses : l.lacoste@chu-poitiers.fr or eofrija@gmail.com

For questions relating to submission procedures on the IT portal, the following address must be used: DGS-RBM@sante.gouv.fr

For questions relating to the National Commission of Research Involving Humans, the e-mail address dgs-cnriph@sante.gouv.fr must be used.

III.1.2. Transmission to ANSM

The CTA must submitted to ANSM at the following address: phasepilote.reglement@ansm.sante.fr.

Eudralink messaging system
The Eudralink secure messaging system proposed by the European Medicines Agency (EMA) should be used (strong recommendation).

To access Eudralink, the user must first make a request to open an Eudralink account (nominative request) with the relevant EMA department by sending an e-mail to the eudralink@ema.europa.eu, an application form available through the link https://eudract.ema.europa.eu/docs/forms/Eudralink_Request.doc.

If you use the Eudralink secure method for sending e-mails, it is advisable to:
- set a message expiry date of 90 days and not to select password-protected dispatch
- attach dossier documents in a zipped format (zip or 7z file) without a password.

Use of the phasepilote.reglement@ansm.sante.fr mailbox is strictly limited to authorisation applications for clinical trials on **medicinal products** submitted within the scope of the pilot phase in preparation for the implementation of **the European Regulation relating to clinical trials involving medicinal products**

It is also very important to correctly complete the "subject" field with the following information:

	Subject of e-mail
Initial assessment request	**–AEC MED PP / Phase[(b)] / EudraCT No.[(a)] / Therapeutic Field / Concerned EC** For example: AEC MED PP / Phase 2 / EudraCT No. 2014-001450-56 / Oncology / Est I
Answers to validation[(d)]	**AR answers / ANSM ref.[(c)] / EudraCT No.[(a)]** For example: AR answer / MEDAECPP-2018-01-00025 / EudraCT No. 2014-001450-56
Answers to questions[(d)]	**CI answers / ANSM ref.[(c)] / EudraCT No.[(a)]** For example: CI answer / MEDAECPP-2018-01-00025 / EudraCT n° 2014-001450-56

(a) Specify the trial EudraCT number
(b) Specify the trial phase
(c) Specify the reference allocated by ANSM for the application
(d) Possibly formulated by ANSM following an assessment of the validation / an assessment of the initial application (question)

Means to implement the Unit in charge of early phase Clinical Trials

Further to the action plan announced by the Ministry of Health, the ANSM is about to implement a dedicated Unit in charge of early phase clinical trials
This Unit will handle all early phase medicinal clinical trials which are defined as First in human / early clinical trials including those which generate initial knowledge in humans on tolerability, safety, pharmacokinetics and pharmacodynamics of new active substances in humans[1]. These trials are often

undertaken in healthy volunteers but can also include patients. These are phase 1 or phase1/2 trials (as soon as phase 1 takes place in the French territory).
This Unit will not be in charge of clinical trials involving gene and cell therapy products, cells, tissues, organs, vaccines and medical devices.

In order to allow an optimal dispatching to the dedicated Unit, it is necessary to identify the type of clinical trial in the subject of all e-mail by displaying the mention “PREC”.

For example : AEC MED PREC PP / Phase[(b)] / EudraCT n°[(a)] / Therapeutic field / concerned EC

AEC MED PREC PP/ Phase 2 / EudraCT n° 2014-001450-56 / oncology / Est I

NB. Use of the phasepilote.reglement@ansm.sante.fr mailbox is strictly limited:
- to clinical trial authorisation applications submitted within the scope of the pilot phase in accordance with the methods described in this procedure;
- to responses to non-validation correspondence / correspondence relating to questions (substantiated objections) possibly asked by ANSM in relation to the dossiers submitted

Use the following address for requests for the authorisation of substantial amendments to clinical trials which have been authorised within this pilot phase ams-essaiscliniques@ansm.sante.fr
However, the subject of the e-mail should stipulate that the initial request was the subject of an assessment as part of the pilot phase.

For any other information relating to these clinical trials authorised during this pilot phase, such as :
- transmission of the annual safety report
- notification of the trial start (in France) and the end of the study
- transmission of clinical trial results

the following e-mail address should be used aec-essaiscliniques@ansm.sante.fr

The following address should also be used for general questions relating to the pilot phase: phasepilote.reglement@ansm.sante.fr completing the "subject" field as follows: **pilot phase question**

The mail received in the phasepilote.reglement@ansm.sante.fr mailbox will be sent to the relevant Division.

[1] Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1)

III.2. Dossier content / format

III.2.1. Content

The clinical trial authorisation (CTA) application dossier and the opinion request dossier are clearly defined in Appendix 1 of "(EU) REGULATION No 536/2014 OF THE EUROPEAN PARLIAMENT AND COUNCIL dated 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC" available via the following link:http://eur-lex.europa.eu/legal-content/FR/TXT/?uri=CELEX:32014R0536

It contains 2 parts:

- part I – Appendix 1 § B to J
- part II – Appendix 1 § K to P + R

Refer to *Appendix 1* describing all component parts of the dossiers submitted to ANSM and the EC.

III.2.1.1. Contents of authorisation application dossier submitted to ANSM within the scope of the pilot phase

The dossier includes most of the documents provided for within the current regulation transposing European Directive 2001/20/EC. For more information on this subject, the sponsor should consult "Advice to sponsors of clinical trials on medicinal products including innovative medicinal product therapy (IMT)" available at the following address on the ANSM website: http://ansm.sante.fr (section “Essais cliniques”).

a) In accordance with the European Regulation and European Directive

❖ **Appendix 1 of Regulation § B. COVER LETTER**

The "CTA application letter" template available at the following address on the ANSM website: http://ansm.sante.fr (section “Essais cliniques”) must be used.

Cases of low-intervention trials:
The sponsor is invited to specify whether he/she considers the clinical trial as a low level of intervention and to send confirmation justification of this claim, as required.

With regard to (EU) regulation No. 536/2014, "clinical trial with a low level of intervention" is a clinical trial that complies with all of the following conditions:

a) investigational medicinal products, excluding placebos, are authorised;

b) according to the clinical study protocol,

i) investigational medicinal products are used in accordance with marketing authorisation conditions;

Or

ii) the use of investigational medicinal products is based on convincing data and supported by scientific publications focusing on the safety and efficacy of these investigational medicinal products in one of the Member States concerned;

and

c) the additional diagnostic or monitoring procedures involve at most a risk or minimal additional constraint to ensure participants' safety compared to normal clinical practice in any Member State concerned;

Within the scope of this pilot phase:

It should be noted that this information is not required by the current regulation. Consequently, it will not be taken into account in the validation criteria governing CTA applications. However, the transmission of this information is important such that participating parties are familiar with this new information, which will be a new component in the implementation of the European regulation.

CTA application correspondence must be signed. Two cases can be considered:
- the applicant adds an electronic signature to the CTA application letter in PDF format;
- If the applicant is unable to add an electronic signature to the PDF version of this correspondence, he/she will transmit a scanned version (PDF format) of the manually signed page in the form, in addition to the unsigned PDF version.

❖ Appendix 1 of the Regulation § C. APPLICATION FORM

Pending the introduction of the European portal and European Union database, the sponsor will send the clinical trial authorisation application form obtained from the EudraCT database.

- A version in complete XML format, obtained via EudraCT (http://eudract.emea.eu.int). The shorter version (Core Data Set) proposed by EudraCT will not be accepted.

- and the corresponding PDF version or scanned version, duly signed.

Two cases can be considered:
- The applicant adds an electronic signature to the PDF format;
- If the applicant is unable to add an electronic signature to the PDF version of the form, he/she will transmit a scanned version (PDF format) of the manually signed page in the form, in addition to the unsigned PDF version.

❖ Appendix 1 of the Regulation § D. PROTOCOL

The protocol must be accompanied by a summary of the protocol in French as provided with the submission of the opinion request to the relevant EC (see *Appendix 2).*

The protocol is accompanied by the independent monitoring committee charter, if applicable.

The protocol must be signed by:
- the sponsor
- and either the coordinating investigator (for a multicenter trial, including multinational), or the principal investigator (for a single-center trial).

Two cases be envisaged:
- either the protocol includes the electronic signatures of the sponsor and the investigator in PDF format;
- in addition to the unsigned protocol, the sponsor transmits a scanned version (PDF format) of the protocol page containing the manually signatures of the sponsor and the coordinating investigator.

❖ Appendix 1 of the Regulation § E. INVESTIGATOR'S BROCHURE

If the investigational medicinal product is authorised and is used in accordance with the marketing authorisation (MA) conditions *(essentially in terms of indication, dosage, method of administration, population),* the summary of product characteristics (SmPC) constitutes the IB.

❖ Appendix 1 of the Regulation § F.DOCUMENTS RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICES FOR THE INVESTIGATIONAL MEDICINAL PRODUCT

❖ Appendix 1 of the Regulation § G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER

For each investigational medicinal product in the trial: study medicinal product, comparator and placebo.

❖ **Appendix 1 of Regulation § H. AUXILIARY MEDICINAL PRODUCT DOSSIER**

Currently referred to as "non-investigational medicinal product"

❖ **Appendix 1 of the Regulation § I. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)**

❖ **Appendix 1 of the Regulation § J. CONTENTS OF THE LABELLING OF THE INVESTIGATIONAL MEDICINAL PRODUCTS**

To be included for all **investigational** medicinal products (with or without a Marketing Authorisation), in accordance with current regulations.

Within the scope of this pilot phase, there is no intention to apply the provisions of Article 67 of the Regulation which stipulates a label in compliance with that of the MA when a MA has been granted for the medicinal product in question.

❖ **Appendix 1 of the Regulation § Q. PROOF OF PAYMENT OF FEE**

Since no tax is required in France, there is no need to provide proof of payment of duty.

b) **In accordance with current regulations** (will no longer be required with the application of the European Regulation):

- Import certificate for investigational medicinal products, if applicable

To conclude
The dossier to be submitted to ANSM must contain the following components of PART I:

Ref Appendix 1 of ER	Documents	A	B	C	D	Remarks
B	Cover letter	■			■	Template of CTA application letter for ANSM
C	Application form	■			■	Form obtained from the EudraCT European database (XML + PDF formats)
D	Trial protocol As well as: - protocol summary (see *Appendix 3*) - independent monitoring committee charter	■ ■	 ■		■ ■	Format and content defined by the European recommendation governing Good Clinical Practices
E	Investigator's Brochure or Summary of Product Characteristics (SmPC)	■			■	Format and content defined by the European recommendation governing Good Clinical Practices
F	Documents relating to GMP for the investigational medicinal product		■			
G	Investigational medicinal product dossier		■			
H	Auxiliary medicinal product dossier		■		■	
I	Scientific advice Paediatric investigation plan (PIP)		■ ■		■ ■	
J	Contents of the labelling of the investigational medicinal products	■				

	Import certificate for investigational medicinal products			■		

A: document required in all cases / B: document required if need be / C: requested in accordance with current regulations (will not be required with ER - European Regulation) / D: to be sent to the EC together with part II

III.2.1.2. Contents of opinion request dossier submitted to the EC within the scope of the pilot phase

For further details on the preparation of the dossier, the sponsor should consult the information available on the website of the CNCP at the following address:
http://www.cncpp.fr/?q=content/phase-pilote

a) In accordance with the European Regulation and European Directive

- **Appendix 1 of the Regulation § K. RECRUITMENT PROCEDURES**
- **Appendix 1 of the Regulation § L. INFORMATION FOR PARTICIPANTS, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE**

The sponsor is invited to forward the consent procedure that an element defined in Articles 29 to 35 of Regulation (EU) No 536/2014 and Annex 1 (§ L).

- **Appendix 1 of the Regulation § M. SUITABILITY OF THE INVESTIGATOR**
- **Appendix 1 of the Regulation § N. SUITABILITY OF THE FACILITIES**
- **Appendix 1 of the Regulation § O. PROOF OF INSURANCE COVER OR COMPENSATION MECHANISM**
- **Appendix 1 of the Regulation § P. FINANCIAL AND OTHER ARRANGEMENTS**

A financial description of the study must be provided in the form of a standard document describing financial study provisions (see *Appendix 3*).

- **Appendix 1 of the Regulation § R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION LAW ON DATA PROTECTION**

Within the scope of this pilot phase:

Must be transmitted to the EC in addition to the afore-mentioned documents:
- The covering letter (can use the CTA application letter model from ANSM for the opinion request dossier submitted to the ECs);
- The CTA application form:
- The protocol, protocol summary;
- The Investigator's Brochure and/or the SPC for investigational and auxiliary medicinal products;
- If applicable, the scientific advice given by a competent authority or EMA, information relating to a PIP.

b) In accordance with the current regulation (will no longer be required when the European regulation is introduced):

- The additional document at the request of the EC on the clinical trial

To conclude
The dossier to be submitted to the EC must contain the following items from Parts I and II:

PART I (column D)

Ref Appendix 1 of ER	Documents	A	B	C	D	Comments
B	Cover letter	■			■	Template of CTA application letter - ANSM
C	Application form	■			■	Form obtained from the EudraCT European database (XML + PDF formats)
D	Trial protocol As well as: - protocol summary (see *Appendix 3*) - independent monitoring committee charter	■ ■	 ■		■ ■	Format and content defined by the European recommendation governing Good Clinical Practices
E	Investigator's Brochure or Summary of Product Characteristics (SmPC)	■			■	Format and content defined by the European recommendation governing Good Clinical Practices
H	Auxiliary medicinal product dossier		■		■	
I	Scientific advice Paediatric investigation plan (PIP)		■ ■		■ ■	

PART II (must be in French)

Ref Appendix 1 of ER	Documents	A	B	C	Comments
K	Recruitment procedures	■			Including advertising announcements, printed documents, sound documents or videos and the procedures dealing with responses to these advertising strategies
L	Information leaflet Consent form Consent procedure	■			Adapted to suit the age and level of understanding of the persons concerned
M	Investigators' qualifications (suitability of investigators)	■			Including CVs (with French Medical Association Registration Number), duly signed and dated
N	Suitability of facilities	■			Justification of the suitability of human, material and technical resources for the clinical trial and compatibility unless authorisation granted to the place (L1121-13)
O	Certificate of insurance	■			European Regulation: Art. 76 Public Health Code: Art. L.1121-10 and Art. R.1121-4 to R.1121-9
P	Financial provisions	■			See *Appendix 3*
R	Proof of data processing compliance	■			Declaration of the sponsor or his/her representative certifying compliance with Regulation n°2016/679 known as General Data Protection Regulation (GDPR)
	Additional document at the request of the EC on the clinical trial	■		■	

A: document required in all cases / B: document required if applicable / C: requested in accordance with current regulations (will not be required with ER - European Regulation)

III.2.2. Format: Presentation of documents / Language

It is imperative that the sponsor respect the parts naming as described below.

III.2.2.1. ANSM

It is imperative that each of the items in the dossier appears in separate files and subfiles.

The documents must be identified by the sponsor and harmonised.

Ref Appendix 1 of ER	Documents	Identification
B	Cover letter	CORRESPONDENCE
C	Application form (xml and pdf)	FAEC
D	Trial protocol As well as - protocol summary (see *Appendix 3*) - independent monitoring committee charter	PROTOCOL SUMMARY DSMB
E	Investigator's Brochure Or Summary of Product Characteristics SmPC	IB
F	Documents relating to GMP for the investigational medicinal product	GMP
G	Investigational medicinal product dossier	DME
H	Auxiliary medicinal product dossier	DMA
I	Scientific advice Paediatric investigation plan (PIP)	DECISION
J	Contents of the labelling of the investigational medicinal products	LABELLING
	Import certificate for investigational medicinal products	IMPORT

The ANSM will accept documents transmitted in French or possibly English.

The following documents must be written in French:
- protocol summary
- Contents of the labelling of investigational medicinal products
- Import certificate for investigational medicinal products

III.2.2.2. EC

The documents must be identified by the sponsor and harmonised

Ref Appendix 1 of ER	Documents	Identification
K	Recruitment procedures	RECRUITMENT
L	Information Leaflet Consent Form Consent procedure	INFO-CO
M	Investigator's qualifications	CV
N	Suitability of facilities	EQUIP
O	Certificate of insurance	INSURANCE
P	Financial provisions	FINANCE
R	Proof of data processing compliance	DATA

All these documents must be transmitted In French.

III.3. Evaluation deadlines

Regulation No. 536/2014 states that the assessment of an authorisation application follows a precise schedule organised around several key dates.

Furthermore, the set dates for assessing clinical trial authorisation applications submitted within the scope of the pilot phase are based on an agenda similar to the European regulation with key dates that can be superimposed on those of the European regulation.

However, in order to comply with the current regulation (Public Health Code transposing European Directive 2001/20/EC), which imposes an evaluation deadline of 60 days, which cannot be exceeded, adjustments have been made in accordance with the participating parties (see *Appendix 4).*

Note that the key dates are counted in calendar days.

Within the scope of this pilot phase:

If a key date occurs on a weekend or public holiday, the relevant bodies will respond to the sponsor on the last working day before the theoretical key date. This also applies to sponsors and to the submission of answers to questions raised by both bodies.

The aim is to carry out acceptability validation within a maximum of 7 days, followed by an initial assessment no later than D33 (sending questions to the sponsor) in order to obtain a response from the sponsor, if additional information is required, by D45 at the latest with a final response from ANSM on D60.

In the event of an initial favourable response by both bodies (ANSM and EC): (D=day)

Stage	Key dates proposed within the pilot phase framework
Validation	On D7
End of assessment	On D33
Notification	+ 3 D = on D36

Therefore if the assessment has not highlighted any obstacles, the final response can be given before D60.

In the case of questions by at least one of the 2 bodies (ANSM and/or EC):

Stage	Key dates proposed within the pilot phase framework
Validation	On D7
Assessment with requests for substantiated objections by ANSM and/or requests for additional information by the EC	On D33
Sponsor's response	+ 12 D = on D45
Assessment of answers	+ 12 D = on D57
Notification	+ 3 D = on D60

Within the scope of this pilot phase:

The key dates have been set voluntarily within the scope of this pilot phase to simulate future deadlines concerning the assessment of applications under the European Regulation.

Deviations of key dates proposed within the scope of the pilot phase could be observed. In that situation, they will be followed-up.
The file cannot be rejected by the EC nor be excluded from the pilot phase because of these deviations.

Since the pilot phase is an experimental procedure based on the goodwill of sponsor, the key dates indicated cannot be legally challenged.

However, all of the participating parties (ANSM, EC, sponsors) shall make every effort to comply rigorously with the afore-mentioned deadlines and **the reporting of the final decision shall comply with the current regulation (i.e. within 60 days at most).**

III.3.1. ANSM

The overall deadline for assessing CTA applications is not changed in relation to the current regulation.

III.3.2. EC

Sponsors participating in the pilot phase shall answer the questions raised by the ECs within 12 days of receipt of the question mail (in accordance with the European regulation).

III.4. Validation of the application / acknowledgement of receipt

Purpose of the assessment of the validation of the application

The validation of the application will focus on the completeness of the dossier (administrative validation, i.e. checking the list of components to be submitted in support of the application, appropriate electronic version, documents drafted in the appropriate language).

Within the scope of the dossier validation assessment, the completeness of the dossier submitted will be checked by each body: ANSM and the EC for their respective section.

The validation of an application is examined by each body (ANSM and relevant EC) within 7 days of receipt of the application by mail.

A letter will be sent to the sponsor.

In case the application is not validated, the sponsor's answers must be sent according to the same procedure as that described in § III.1 of this document).

Within the scope of this pilot phase:

D0 = date on which the dossier sent by mail is received by both bodies (ANSM and EC)

If the dossier, submitted the same day, is considered not validated by 1 of the 2 bodies (ANSM and/or the EC):

- The sponsor should be contacted by telephone (or e-mail) within 3 days of receiving the dossier in order to request information.

- Validation correspondence is sent to the sponsor on D7. If the dossier is considered not validated by one of the 2 bodies, and if the sponsor wishes to continue participating in the pilot phase, it is proposed to withdraw the application from the 2 bodies and then to re-deposit the same research project with the ANSM and the initially designated EC (under the conditions set by the pilot phase, ie on the same day), in order to start a new assessment of the application with the same D0.

III.4.1. Correspondence regarding the validation of the application submitted to ANSM

If the dossier is validated, the validation correspondence will be accompanied by a document listing the theoretical key dates specific to the assessment of this application.

This correspondence will be sent by e-mail, by the concerned Division:
- To the sponsor
- To the relevant EC
- copy phasepilote.reglement@ansm.sante.fr

III.4.2. Correspondence regarding the validation of the application submitted to the EC

Validation correspondence templates will be available on the CNCP website for all ECs participating in this pilot phase: http://www.cncpp.fr/ (this document specifies the date of the session during which the file will be examined).

This correspondence will be sent by the EC concerned to the sponsor through IT portal and a copy of the document will be sent to phasepilote.reglement@ansm.sante.fr

III.5. Dossier assessment

III.5.1. Assessment scope by the ANSM

The assessment will be carried out to check the safety of persons taking part in the trial, paying particular attention to the safety and quality of the products used in the trial, in accordance with current standards, conditions regarding their use and the safety of subjects in view of the procedures implemented and the methods used as well as subject follow-up.

III.5.2. Assessment scope by the EC

The assessment will be carried out to ensure the validity of the trial, with particular reference to:

- protection of persons, especially the protection of subjects participating in the trial;
- the relevance of the research, the appropriate assessment of anticipated benefits and risks and duly justified conclusions.

The data will essentially document protection of persons (information and consent, recruitment procedures) and the qualifications of the investigators/suitability of research centres and financial provisions.

III.6. Correspondence from ANSM and/or EC in the event of substantiated objections or any questions

III.6.1. In the case of questions from the ANSM

This correspondence will be sent by e-mail, by the concerned Division :
- To the sponsor
- To the relevant EC
- copy phasepilote.reglement@ansm.sante.fr

As under current procedure, the sponsor will be asked to acknowledge receipt of the mail with questions that has been sent.

III.6.2. In the case of questions from the EC

This correspondence will be sent by the concerned EC to the sponsor through IT Portal and a copy of the document will be sent to the concerned Division [*] (copy phasepilote.reglement@ansm.sante.fr)
[*] the person responsible for monitoring the dossier in the relevant Division at ANSM, whose contact details (tel and e-mail) are given in the correspondence already issued by this division (e.g. acknowledgement of receipt).

III.7. Sponsor's responses to questions that may be asked by the ANSM and/or EC

The sponsor's responses to ANSM and EC requests must be sent respectively to ANSM and the EC in accordance with the milestone at D45 at the latest.

Presentation of documents

The documents should be gathered according to the subject's matter and questions raised:

- pharmaceutical data;
- non-clinical data;
- clinical data, etc.

III.7.1. Response sent to the ANSM

The sponsor's responses to ANSM must be sent to ANSM in accordance with the milestone at D45 at the latest.

E-mail responses should be sent to the following address: phasepilote.reglement@ansm.sante.fr

It is very important to complete the "subject" field in the e-mail providing information as indicated in paragraph III.1.1 of this document, in order to facilitate the administrative management of this correspondence.

III.7.2. Response sent to the EC

The sponsor's responses to EC must be sent to the IT portal within 12 days of receipt of the question mail (in accordance with the European regulation).

III.8. Final notification

It is proposed that:

- The relevant EC forwards its opinion on the clinical trial to the sponsor through IT Portal at the latest 1 to 2 days before the key reporting date and a copy of the document will be sent to the concerned Division[*] – copy phasepilote.reglement@ansm.sante.fr

[*] the person responsible for monitoring the dossier in the relevant Division at ANSM, whose contact details (tel and e-mail) are given in the correspondence already issued by this division (e.g. acknowledgement of receipt).

- The ANSM issues its decision together with opinion on EC concerned. This notification will be sent by e-mail by the Division concerned:
    - To the sponsor
    - copy to the EC concerned + phasepilote.reglement@ansm.sante.fr

III.9 Summary table of dialogue between the Sponsor / EC / ANSM apart from the IT portal of CNRIPH

	sponsor	EC	ANSM
Submission	- to Ansm **phasepilote.reglement@ansm.sante.fr** specifying the EC concerned - to the IT Portal		Mailbox **phasepilote.reglement@ansm.sante.fr** => Transfer to the concerned Division + copy EC concerned
Validation		This correspondence will be sent by e-mail, by the EC concerned: - To the sponsor - phasepilote.reglement@ansm.sante.fr	This correspondence will be sent by e-mail, by the concerned Division: - To the sponsor - copy to the EC concerned - copyphasepilote.reglement@ansm.sante.fr
Assessment / sending question		This correspondence will be sent by e-mail, by the EC concerned: - To the sponsor - copy concerned Division [*] - copyphasepilote.reglement@ansm.sante.fr [*] the person responsible for monitoring the dossier in the Product Division concerned at ANSM, whose contact details (tel or e-mail) are given in the correspondence already issued by this division (e.g. acknowledgement of receipt).	This correspondence will be sent by e-mail, by the concerned Division: - To the sponsor - copy to theEC concerned - copyphasepilote.reglement@ansm.sante.fr
notification		The EC concerned will forward its opinion on the CTA application by e-mail 1 to 2 days before the key reporting date: - to the concerned Division [*] - copy phasepilote.reglement@ansm.sante.fr [*] the person responsible for monitoring the dossier in the Product Division concerned at ANSM, whose contact details (tel or e-mail) are given in the correspondence already issued by this division (e.g. acknowledgement of receipt)	The ANSM shall report its decision together with the opinion reached by the EC concerned. This notification will be sent by e-mail by the concerned Division: - To the sponsor - To the relevant EC - copyphasepilote.reglement@ansm.sante.fr

Any communication between ANSM and EC must be formalized by completing the field "object" of the mail with the following words: **–AEC MED PP / ANSM ref. / N° EudraCT** and specifying according to the stages of the instruction: **admissibility, question, final opinion**

IV. APPENDICES

Appendix 1: List of dossier components to be submitted to the ANSM and EC

Appendix 2: Summary of trial protocol

Appendix 3: Financial and other arrangements

Appendix 4: Comparison of time-lines for assessing CT applications (European regulation / pilot phase)

Appendix 1: List of dossier components to be submitted to ANSM and EC

ANSM application dossier

PART 1

Ref Appendix 1 of ER	Documents	A	B	C	D	Comments
B	Cover letter	■			■	Template of CTA application letter - ANSM
C	Application form	■			■	Form obtained from the EudraCT European database (XML + PDF formats)
D	Protocol As well as: - protocol summary (see *Appendix 3*) - charter of the safety monitoring committee, if applicable	■ ■	 ■		■ ■	Format and content defined by the European recommendation governing Good Clinical Practices
E	Investigator's Brochure or Summary of Product Characteristics (SmPC)	■			■	Format and content defined by the European recommendation governing Good Clinical Practices
F	Compliance with GMP practice for the investigational medicinal product		■			
G	Investigational medicinal product dossier		■			
H	Auxiliary medicinal product dossier		■		■	
I	Scientific advice and Paediatric investigation plan (PIP)		■ ■		■ ■	
J	Contents of the labelling of the investigational medicinal products	■				
	Import certificate for investigational medicinal products			■		

A document required in all cases
B: document required if applicable
C: requested in accordance with the current regulation (will no longer be required with the European Regulation)
D: to be transmitted to the EC in addition to part II

EC application Dossier

PART I (column D)

Ref Appendix 1 of ER	Documents	A	B	C	D	Comments
B	Cover letter	■			■	Template of CTA application letter - ANSM
C	Application form	■			■	Form obtained from the EudraCT European database (XML + PDF formats)
D	Protocol As well as: - protocol summary (see *Appendix 4*) - charter of the safety monitoring committee, if applicable	■ ■	 ■		■ ■	Format and content defined by the European recommendation governing Good Clinical Practices
E	Investigator's Brochure or Summary of Product Characteristics (SmPC)	■			■	Format and content defined by the European recommendation governing Good Clinical Practices
H	Auxiliary medicinal product dossier		■		■	
I	Scientific advice and Paediatric investigation plan (PIP)		■ ■		■ ■	

PART II (must be in French)

Ref Appendix 1 of ER	Documents	A	B	C	Comments
K	Recruitment arrangements	■			Including advertising announcements, printed documents, audio documents or videos and the procedures dealing with responses to these advertising strategies
L	Information leaflet Consent form Consent procedure	■			Adapted to the age range and level of understanding of the persons concerned
M	Suitability of the investigator	■			Including CVs (with French Physician Order Registration Number), duly signed and dated
N	Suitability of the facilities	■			Justification of the suitability of human, material and technical resources for the clinical trial and compatibility unless authorisation granted for the place (L1121-13)
O	Proof of insurance cover	■			European Regulation: Art. 76 Public Health Code: Art. L.1121-10 and Art. R.1121-4 to R.1121-9
P	Financial and other arrangements	■			See *Appendix 3*
R	Proof that data will be processed in accordance with Union law on data protection	■			Declaration of the sponsor or his/her representative certifying compliance with Regulation n°2016/679 known as General Protection Data Regulation (GPDR)
	Additional document at the request of the EC on the clinical trial	■		■	

A document required in all cases / B: document required if applicable / C: request in accordance with the current regulation (will not be required with ER - European Regulation)

Appendix 2: Summary of trial protocol

The summary is a ***mandatory component document*** of any clinical trial application dossier.

Objective:

The summary must give every Committee member an ***intelligible summary of the clinical trial*** and should promote discussion.

Background

It must at least comprise the following information:

- identification of the protocol (title, reference), sponsor and investigator (coordinator);
- justification of the background to research;
- primary and any secondary objectives
- should highlight the anticipated benefits for participants and population;
- should highlight the risks faced by participants and the constraints to which they are subjected;
- number and characteristics of participants with the number of participants in France; the methodology selected: assessment criteria, study protocol design (possible flow-chart), type of analysis (descriptive, comparative), number of subjects required, intermediate analyses, discontinuation rules;
- the implementation of an independent monitoring committee or justification of its absence;
- justification of the choice relating to the duration for which participation in another trial is prohibited;
- provisional trial schedule;
- presentation of research sites and investigators' characteristics.

Form

- The summary ***must be written in French***;
- The document must be paginated, dated and allocated a version number;
- This document commits the sponsor.

Appendix 3: Financial and other arrangements

F - Financial and other arrangements
69. Brief description of how the trial is financed The trial is financed by: *(industrial sponsors: specify the sponsoring company)* (*institutional sponsors, specify all entities, origin of public/private funding)*
70. Information on financial transactions and compensation paid to participants and fees for investigators/site for participating in the clinical trial Participants' compensation: healthy volunteers or patients Investigators and sites (information regarding contracts concluded with sites and/or investigators)
71. A description of any other agreement between the sponsor and the site must also be submitted - For example, specify equipment hire contracts and other agreements

Appendix 4: Comparison of time-lines for assessing CTA applications (European regulation / pilot phase)

	European regulation	Pilot phase
Date received	**D0**	**D0**
Confirmation of validation	***+10 d = D10**	***+7 j = D7**
Receipt of sponsor's answers if not validated	****+10 d = D20***	
Confirmation of validation	****+5 d = D25***	
Assessment of dossier	***+26 d = D26 [1]**	***+19 d = D26**
Coordination	***+12 d = D38**	
Consolidation	***+7 d = D45**	
Finalising initial report and/or sending questions	**D45**	***+8 d = D33**
Clock stop	**Clock stop**	**non**
Receipt of sponsor's answers	***+12 d = D57**	***+12 d = D45**
Final assessment report	***+12 d = D79**	
Final coordination of assessment	***+7 d = D86**	
Completion of final assessment report	**D86**	***+12 d = D57**
Dispatch of notification / final decision	***+5 d = D91**	***+3 d = D60**

[1]*+50 days evaluation (if MTI)

total without question = 60 days

total if question = 91 days

total without question = 36 days

total if question = 60 days

V. GLOSSARY

CTA	Clinical trial authorisation
ANSM	French National Agency for Medicines and Health Products Safety
AR	Acknowledgement of receipt
IB	Investigator's Brochure
GMP:	Good Manufacturing Practice
EC	European Commission
IC	Intermediate correspondence (correspondence relating to questions)
CNCP	Conférence nationale des comités de protection des personnes - National Conference of Ethics Committees
CNRIPH	National Commission of Research Involving Humans
EC	Ethics Committee
DMA	Auxiliary Medicinal Product Dossier (or non-investigational medicinal product)
DME	Investigational Medicinal Product Dossier (comprising data relating to medicinal product(s) tested, comparator(s) and placebo(s)
EudraCT	European Clinical Trial Database
FAEC (CTA form)	Clinical Trial Authorisation Form
EudraCT number	Unique European identifier issued by the European Clinical Trial Database
PIP	Paediatric Investigation Plan
SPC	Summary of product characteristics
GDPR	Regulation n°2016/679 known as General Data Protection Regulation
EU	European Union
VHP	Voluntary Harmonisation Procedure (assessment of multinational Clinical Trial Applications in Europe) http://ansm.sante.fr/Activites/Essais-cliniques/CTFG-et-Evaluation-coordonnee-des-essais-cliniques-multinationaux-de-medicaments-au-niveau-europeen-VHP/(offset)/3

ANSM Division

ONCOH Product Division	Team concerned by medicinal products used in haematology, immunosuppressants in transplantation and nephrology
	Team concerned by medicinal products in oncology
	Team concerned by blood safety, blood products, cell therapy and radiopharmaceuticals
CARDIO Product Division	Team concerned by medicinal products used in cardiovascular disorders, thrombosis, metabolic, rheumatology, stomatology
	Team concerned by medicinal products used in gynaecology, endocrinology, urology, pulmonology, ENT, allergy
NEURHO Product Division	Team concerned by medicinal products used in neurology, psychiatry, anesthesia and drugs of addiction to alcohol
	Team concerned by medicinal products used in analgesics, non-steroidal anti-inflammatory drugs, ophthalmology and drug addiction to tobacco
	Team concerned by narcotic drugs, psychotropic drugs and drug addictions to drugs
INFHEP Product Division	Team concerned by medicinal products used in virology and gene therapy drugs
	Team concerned by vaccines and antibiotic, antifungal and antiparasitic medicinal products
	Team concerned by medicinal products used in dermatology, hepato gastro enterology and rare metabolic diseases
DPAI Authorization and innovation policies direction	Public policies and innovation process service (team concerned by the evaluation of “early phases clinical trials”)