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Adaptation of the Clinical Trials Directive

Recommendations on the Contents of a Dossier for the Request for Authorisation of the First Trials in Human Subjects

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Abstract

The European Directive on clinical trials of medicinal products will fall within the scope of the legislation of Member States on 1 May 2004. In France, this adaptation will be carried out by a public health bill concerning, among other things, the reform of the current Huriet-Sérusclat law, and by means of regulations. For trials concerning the initial administration of a product to human subjects, the group suggested the following recommendations:

- In French texts, to include a deadline of 30 days for the initial authorisation by the competent authority (Afssaps [Agence française de sécurité sanitaire des produits de santé]).
- To maintain an observed deadline of 20 days (35 official days) for the decision of the Ethics Committee (EC) [Committee for the Protection of Persons (CPP)].
- To obtain a more specific evaluation of the pharmaceutical dossier of the investigational medicinal product (IMP) from the competent authority.
- To provide both bodies with nonclinical and possibly clinical data concerning the IMP information of the participants and their consent.
- To follow the recommendations posted on the Afssaps website for the entire IMP dossier.
- To submit a protocol under the International Committee on Harmonisation (ICH) E6 format adapted for phase I and, possibly as a separate document, justification of a certain number of points (a total of ten) that are more specific to this trial phase to facilitate and improve the document review while also providing the expected guarantees.
- To limit the 'substantial' amendments to those provided for in the European guidelines.
- To break the blind for every serious event reported to the sponsor by the investigator, and report to the competent authority any serious adverse event related to the IMP or to the trial or without documented cause, while keeping ECs and investigators informed.

Furthermore, certain points concerning the authorisations for packaging, labelling and dispensing of the batches of medicinal products for clinical trials will need to be specified for these early studies.

All these recommendations are intended to help promote the development of studies involving the initial administration of medicinal products in France.

Keywords: clinical trial directive, phase I, transposition, drug, legal frame, good clinical practice

1. Introduction

The European Directive on clinical trials of medicinal products[1] was adopted in May 2001 and will fall within the scope of the legislation of the Member States on 1 May 2004 at the very latest. At the time of this round table meeting, a French public health bill focusing on reform of the current Huriet-Sérusclat law[2] in its IV title was in progress. One or several decrees or orders will also be necessary to establish certain points that are not outlined in the bill. Besides these legislative and regulatory aspects, there is the issue of the practical feasibility of the pro-

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visions as they are envisaged in the individual countries, specifically the procedures for the initiation, development and termination of the trial as established by the directive and its guidance documents.[3]

The challenges of this adaptation project focus on the need to maintain the appeal of France as a favourable place for conducting clinical trials, and particularly to continue to attract the international development of innovative medicinal products that will enable the medical community and asssociated experts to develop personal and local experience concerning these future products. As several surveys have shown,[4,5] the Huriet-Sérusclat law and the principle of notifying trials to Afssaps (Agence française de sécurité sanitaire des produits de santé) are part of a simple and predictable framework for trials that favours France. The continued differences between Member States concerning the transposition project may, on the contrary, be considered as an opportunity to consolidate this advance.

Phase I trials, limited in this sense to the initial administration of a new medicinal product in human subjects, represent an interesting and relatively simple working model, as well as a sensitive topic. Indeed, the start of phase I trials in France may result in the subsequent establishment of further trials using the same molecule.

The round table participants, who included academics, hospital specialists, and industry and legal experts, were aware of the challenges of the initial administration of a new active ingredient to healthy human subjects or patients (e.g., antineoplastic agents) or to specific populations (children). While keeping the specifics of these trials in mind, they formulated recommendations that aimed to optimise the implementation and development of such trials in France. Another objective was to facilitate the setting-up of a pilot phase by Afssaps.

2. Identification and Description of the Topic in France

It is useful to describe trials performed in France that involve the initial administration of medicinal products (Afssaps, unpublished data).

Only a fraction of trials currently registered with the Clinical Trials Unit of Afssaps under the classification 'phase I' is relevant.

While a slight decrease may be detected in the total number of trials on medicinal products performed in France between 1998 and 2002 (–17%), it is important to note that the proportion of phase I trials is itself stable. Of the 1227 trials of all phases registered in 2002, 297 or 24% were classified as phase I studies by the sponsors.

In 2002, 168 trials concerned new active ingredients (no marketing authorisation [MA] in either France or abroad), i.e. 57% of the total of registered trials. These 168 trials involved 110 active ingredients, of which 88 (81%) are exclusively studied as phase I; in other words, they would correspond to initial product administrations. We can see therefore that trials on initial product administrations represent barely 30% of registered phase I trials and 7% of all trials conducted nationally.

Moreover, 99% of phase I trials concerning new active substances are conducted by industry sponsors. In 2002, trials based on the criterion of sites authorised to conduct studies without direct individual benefit (DIB) were performed at private establishments in 64% of cases and at public establishments in 36% of cases. Forty percent of these authorised sites are located in Paris and the surrounding areas. Of the 1500 authorised sites for studies without DIB, 49 different sites were requested in 2002.

Phase I trials were performed at a single centre in 80% of cases, and of the 50 multicentre trials, half were international. In 2002, the number of participants in phase I trials was estimated to be 9600 in France, i.e. an average of 32 participants per trial.

This census was also able to show that approximately one of two phase I trials contains at least one amendment. This is an important fact, since the management of amendments regarded as 'substantial' stipulates a set of administrative constraints for the different players involved in the research. Their management will therefore be reflected in terms of the resources necessary for analysing these applications.

3. The Situation Abroad

The organisation of phase I trials abroad, both currently and in the future, was analysed by a subgroup of the round table by asking European subsidiaries of companies or persons responsible for evaluating clinical trials of Member States (appendix I) to complete a standard questionnaire. This survey has been published separately.[6]

It is notable that some countries more specifically interested in phase I trials announced a shorter time period for examining dossiers within the context of their adaptation project of the European Directive. These deadlines should be considered within the 'competitive' context as indicated below:

- The Netherlands: 15 days for the opinion from the Ethics Committee (EC) and the authorisation from the competent authority. It is envisaged that the EC will handle a significant part of the scientific evaluation concerning the product of the trial.

- Great Britain: 14 to 21 days for the competent authority. There is no precise indication as to whether the EC will provide its opinion within a deadline of fewer than 60 days.
- Germany: 30 days for the two opinions for a first product administration and 14 days for trials of subsequent phases.

Moreover, a pilot phase for phase I studies that is intended to test the feasibility of the system has been set up in Great Britain.

4. Recommendations for France

The proposals concern the contents of a dossier for the initial request for authorisation of a trial – the investigational medicinal product (IMP) dossier, the protocol, the subject's information sheet – in addition to the definition of amendments that are substantial to a clinical trial and the procedures for declaring serious adverse events (SAEs) within the context of these initial phase I trials.

The group considered the analysis of measures put in place by the other Member States and the situation of phase I trials in France.

4.1 Proposals Concerning the Authorisation of Clinical Trials

4.1.1 Deadline for Evaluation and Respective Competencies

The members of the round table recommended that a deadline of 30 days be included in the adaptation text for the initial authorisation and that the period of validation concerning the competent authority (Afssaps) be shortened. Currently, the average deadline observed for the EC (Committee for the Protection of Persons [CPP]) is 20 days (35 official days) and this should be maintained.

It appears especially essential for all to properly define the respective scopes of their activities.

After analysing the documents addressed to each of these bodies in accordance with the guidelines of the directive (table I), the group suggested the following distribution of activities: Afssaps to be specifically responsible for the complete evaluation of the IMP (quality, safety, methods for use in the trial); and the CCP to be responsible for aspects relating to the information on and protection of participants, and the adequacy of the facilities. The two bodies could be called on to express their opinion on the trial protocol.

4.1.2 Contents of the Initial Request Dossier

The dossier for the request for authorisation of a clinical trial consists of the following three principal elements:

- the trial protocol and its appendices;
- the subject/patient information sheet and the consent form;
- the investigational medicinal product dossier (IMPD).

Protocol

Principally, the content of the protocol will be based on the table of contents provided for in the 'Good Clinical Practices' (GCP), as presented in the International Committee on Harmonisation (ICH) E6 text adopted by the European Agency for the Evaluation of Medicinal Products (EMEA)[7] [appendix II].

It is important that certain aspects of these provisions are adapted and confirmed in phase I trials. These are as follows:

- the name and description of the IMP tested;
- the summary of the nonclinical data with clinical relevance for the trial;
- the summary of known or potential risks in humans;
- the justification of routes of administration, doses and the dosage regimen;
- the duration of participation for subjects;
- the description of the rules for trial discontinuation relating to both a subject and the trial;
- previous and concomitant treatments that are or are not allowed;
- quality control and assurance.

However, the group recommends that the following ten points be systematically completed for phase I trials, and that they possibly become the subject of a separate document:

- a general justification of the trial with a summary of information gathered on the IMP;
- justification of the galenic form and the route of administration;
- justification of the choice of the first dose administered;
- justification of the dose-escalation scheme;
- justification of the treatment duration for a subject in relation to the preclinical dossier;
- details of the objectives of the study (knowledge of doses used, pharmacokinetics, mechanism of action, interaction with other medicinal products, etc.);
- details and justification of criteria for evaluating efficacy and safety assessment in relation to preclinical data (target organs, duration of effect, etc.);
- justification of the duration of monitoring for each subject or patient;
- details and, if necessary, justification of the 'warning' procedures:
  - clinical (calling the resuscitation team)
  - methodology (breaking the randomisation code)
  - and procedures for discontinuing treatment for a subject or stopping the trial;

Table I. Suggested distribution of areas of expertise between Afssaps (Agence française de sécurité sanitaire des produits de santé) and the Committee for the Protection of Persons (CCP)

	Competent authority (Afssaps)	Ethics Committee (EC) [CPP]
Request form	Yes	Yes
Investigational medicinal product dossier (full or simplified)	Quality data	Nonclinical and clinical data (IB)
	Viral safety, GMO	
	Nonclinical and clinical data (IB or CTD format)	
	GMP data, authorisation of manufacturing and importing	
	Copies of other MS authorisations	
Trial dossier	Protocol and summary	Protocol and summary
	Justification of trial and overall benefit/risk evaluation by the sponsor	Justification of trial and overall benefit/risk evaluation by the sponsor
	Insurance	Insurance
		Ethical analysis by the investigator or the coordinator
Subject dossier	Participant's information	Participant's information and consent form
	Procedures of care management at the end of the trial	Opinion copy from other ECs
	Compliance with EMEA recommendations (paediatrics)	Protected persons (justification of inclusion)
		Processes for recruiting participants
		Compensation of subjects
		Exclusion period
		Procedures for informing subjects at the end of trial
		Procedures for care management at the end of the trial
Sites and investigators	List of principal investigators and coordinator	Quality of the site(s), authorisations for the research sites
		CV of coordinator and principal investigators, information on personnel and facilities

CTD = Common Technical Document; **CV** = curriculum vitae; **EMEA** = European Agency for the Evaluation of Medicinal Products; **GMO** = genetically modified organism; **GMP** = good manufacturing practices; **IB** = Investigator Brochure; **MS** = Member States.

- in the case of administration to a patient: justification for choosing a patient rather than a healthy volunteer.

Such a document could help speed up the receipt of the opinion, especially from the CPP.

Information and Consent

The current provisions already contain several essential and explicit elements. It is suggested that certain details be added concerning the following:

- the collection and preservation of biological samples, especially with regard to their future use;
- the means by which the subject could be informed of the global results at the end of the research;
- information allowing the subject direct access to insurance;
- the principle of separate consent for the ancillary studies, if these involve additional measures.

Investigational Medicinal Product Dossier (IMPD)

It was recalled that, in July 2003, Afssaps developed and posted on its website (www.afssaps.sante.fr) recommendations on the content of the parts relating to the pharmaceutical and nonclinical data for the IMPD in phase I trials. During the round table meeting, these recommendations as well as comments derived from public consultations were presented and discussed.

Certain particularly important points with regard to phase I trials emerged from the debate:

- Pharmaceutical quality: Overall, it concerns justifying administration to humans at this stage in the knowledge of the product's pharmaceutical quality. It is quite clear that studies with the aim of demonstrating quality are not yet complete, that the formulation of the medicinal product is only provisional, and that the dose administered in clinics is not defined. Nevertheless, safety of administration needs to be ensured by providing a description of the minimum necessary data, some of which are essential (table II). If the format selected by the guidance document is that of the 'Common Technical Document' (CTD),[8] the essential data will obviously entail all available information on the drug substance, the IMP (provisional), and the comparator product, including the placebo. Whenever possible, a cross-reference to the

Pharmacopoeia will be provided. All the relevant points relating to stability will be provided. An analytical method will need to be available and validated. Knowledge, even if only partial, of the principal impurities is required. In relation to the table of contents of the CTD, omission of any essential information needs to be justified. It is important to remember that, in the case of an MA, the IMPD is simplified. Thus, for the comparator, in the case of simple 'masking' and re-packaging, the product reference, product description (Summary of Product Characteristics [SPC]) and description of capsules will be accepted.

- Nonclinical part: Unlike the principal pharmaceutical data, the nonclinical data are generally included in every 'Investigator's Brochure'. By way of a reminder, the standard content of the Investigator's Brochure is described in the ICH GCP under the item 'Essential Documents'.[7] The theoretical format of the nonclinical part of the IMPD is also that of the CTD, but cross-references may be made with the Investigator's Brochure.

This section should describe the specific pharmacological data supporting the future indication of the product and, when known, the precise mechanism of action. It should also contain all the elements relating to safety pharmacology, describing the effect of the product on different organs (heart, central and peripheral nervous systems, kidneys, liver) and studies performed in certain body systems in relation to a particular exposure resulting from a specific concentration of the product in certain organs, e.g., the endocrine glands, testicles and ovaries, the eye, and the auditory system; hence the importance of radiolabelling studies. Data on pharmacokinetics and metabolism should be provided together with the metabolites likely to be observed in humans (and, ideally, the assay method used), such as those determined in studies in human hepatocytes. The following should also be provided: the 'toxicokinetic' data and the rationale for the choice of animal models, and the doses prescribed in the toxicology studies based on the analysis of this data; the single-dose toxicity data and repeat-dose toxicity to the species selected; the genotoxicity data (*in vitro* and *in vivo*) and the reproductive data – at least data relating to the segment of fertility studies (segment 1) with 'testicular staging'. Finally, data on local tolerability in relation to the route of administration (injection, inhalation in particular) should also be provided. The essential points of the discussion concerning the nonclinical data are summarised in table III.[9,10]

- Clinical part: At this stage, it is generally limited. Every previous product administration should be registered and duly

Table II. Data on pharmaceutical quality/phase I

Drug substance	Drug product
Manufacturing process (diagram)	Pharmaceutical development
Characterisation	justification of a new pharmaceutical form or the use of a new excipient
Control	Manufacturing and control process
specifications (even if provisional)	diagram of successive stages
analytical procedures (ref. Pharmacopoeia)	current controls
sufficient validation data (in order to ensure the methods are suitable)	Process validation
Viral safety	for sterile products (especially non-standard methods)
Batch analysis	for critical stage processes
Stability (available data)	Control of excipients
	reference to the European Pharmacopoeia or that of an MS or provide monograph or define specifications
	analytical procedures: reference to a Pharmacopoeia or provide a summary
	validation (non-essential)
	viral safety
	Control of drug product
	analytical procedures: reference to a Pharmacopoeia or provide a summary
	validation: provide sufficient validation data to ensure methods are suitable, batch analysis
	analytical characterisation of degradation products
	specifications: explain choice
	Stability
	possible cross-references with data on drug substances
	demonstrate for the expected duration of the trial by stating the approach adopted

MS = Member State.

Table III. Nonclinical data (points having been the subject of in-depth discussions)

Quality assurance and toxicology
It emerged from the discussion that, in the case of a lack of any final audited reports (especially toxicology), raw audited data available to the sponsor and a submission of an interim report would be considered as an acceptable minimum substitute.
Duration of the studies
If the product administration is limited to a single dose, the duration of exposure (toxicity known as 'subacute') will be 14 days in the two animal species. It was highlighted that these last two requirements were nevertheless 'higher' than those required by the US FDA.[9] For the rest, the length of exposure necessary in animals in order to move into the clinical stage is in agreement with the recommendations of the ICH M3.[10]
Assessment of radioactivity and analytical method
Concerning kinetics, the importance is stressed of having a radiolabelled pharmaceutical assessment in animals and a validated analytical method in order to be able to administer dosages in humans within the same or slightly delayed time-frame.

US FDA = US Food and Drug Administration; **ICH** = International Committee on Harmonisation.

described with respect to product safety (the number, nature and intensity of adverse reactions per subject and dose level). The data should also be available.

4.2 Proposals Concerning Substantial Amendments

By 'substantial', the guidance document[3] indicates any amendments that are likely to have a significant impact on the following:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial;
- the quality or safety of any IMP used in the trial.

Moreover, certain examples are provided (in attachment 5 of the guidance document).

The group's recommendation was to use the definition terms very precisely and in an inclusive way, namely: 'The sponsor should determine for each case whether the amendment is substantial by referring to the criteria of definition AND the provided examples'.

4.3 Proposals Concerning the Management of Adverse Reactions During First Product Administration Trials

Given that phase I trials have a collective objective which, allowing for some exceptions, does not conform to an individual therapeutic perspective, these trials should not involve any serious predictable risk for anyone participating. This is the reason for the following recommendations of the round table meeting:

- the investigator immediately reports any SAEs to the sponsor, without any exceptions;
- after lifting the systematic blinding, the SAE is reported by the sponsor to the competent authority insofar as it concerns the IMP, or the conditions of the trial (and in the case of any impact on the safety of participants), or insofar as no cause (for the SAE) can be determined;
- the investigators are informed as soon as possible;
- as outlined in the corresponding guidance document,[11] a trial safety report should be sent within a maximum of 90 days after the end of the trial.

4.4 Other Aspects of the Adaptation, and Specifically Logistical Aspects

4.4.1 Authorisation of Research Sites

Some countries will maintain or establish within their national system an authorisation for research sites. This is the case for France, Spain, Italy and Greece. It is likely that a similar recommendation may be actioned in Great Britain.

With regard to France, the revision project of the Huriet-Sérusclat law is to maintain authorisation for the sites that perform research that deviates from their primary remit of healthcare. *Ipso-facto*, the majority of sites where phase I studies are conducted should continue to be authorised. Nevertheless, this should not apply to the phase I trials in oncology conducted at specialist centres.

4.4.2 Register of Subjects

Great Britain and Germany have set up a pilot phase for establishing these subject registers. In France, the principle of the existing register for healthy volunteers should be renewed.

4.4.3 Laboratory Examinations

Certain countries request authorisation for sites where laboratory examinations are performed. This issue is being considered in France for the assays that fall outside of the usual tests carried out by the laboratories performing medical and biological analyses.

4.4.4 Insurance

Previously covered in France by the 'no-fault compensation' system, subjects participating in phase I trials, as is the case with subjects and patients in any clinical trial, will now be covered by the 'presumed fault' system. This will allow the sponsor, if nec-

essary, to withdraw liability should it not be responsible for the accident recorded.

The situation of subjects not covered by this type of insurance should be examined by the compensation committee responsible to the State under the principle of unknown therapeutic benefits in accordance with the law dated 4 March 2002.[12]

4.4.5 Compensation for Subjects

It is likely that the law will adapt the provision of the directive that establishes compensation to subjects for any 'constraints suffered'. It will be the responsibility of the CPP to evaluate whether the level of compensation is adequate, which will also be reported in the register of subjects.

4.4.6 Distribution System and Conditions of Use of Investigational Medicinal Products

Some questions remain unresolved, such as the conditions under which a phase I research centre may import, release, package and label the IMPDs. These are pharmaceutical activities that need to be performed by institutions authorised in this field. Discussions are underway that aim to determine whether or not authorisation of the research could apply, under certain conditions, to the manufacture of the product for the duration of the research only. Moreover, a system suitable for authorisation of packaging and labelling for research where the posology may not be known in advance (e.g. determination of the maximum tolerated dose), is being examined.

4.4.7 Transition Phase

As has been mentioned, certain countries (notably Great Britain) have set up a pilot phase of transition followed by the system finally selected.

France is launching a voluntary pilot phase, the details of which can be found on the Afssaps website (www.afssaps.sante.fr).

The aim of this pilot phase is to simulate the authorisation of a clinical trial by the Agency, allowing the different stakeholders to prepare the request dossier and Afssaps to prepare its evaluation within a period of 30 days. Afssaps circulates the list of documents to be provided and the procedure to be followed. This pilot phase is initially limited to phase I trials of medicinal products, with cell and gene therapies excluded.

An adjusted report is expected.

5. Conclusion and Summary of the Recommendations

The group issued recommendations enabling practical variations in the provisions of the European Directive of clinical trials, the adaptation of which in the legislation of the Member States should come into force during 2004.

The most significant of these recommendations are as follows:

- In the French texts, to include a deadline of 30 days for the initial authorisation of Afssaps and to maintain an observed deadline of 20 days (35 official days) for a positive decision from the CPP.
- To properly distribute the respective functions of Afssaps and the CPP, with evaluation of the medicinal product being the exclusive responsibility of Afssaps.
- To submit a protocol in the ICH format and adapted for the particular case of phase I trials, by specifically justifying the trial on the basis of the knowledge acquired regarding the product, the choice of the first dose and the dosage regimen, the measures for the protection of subjects and the conditions relating to warnings and termination of treatment or of the entire study. Ten principal elements could constitute a separate document.
- The content of the IMPD would follow the conditions posted on the website of Afssaps, by insisting on certain pharmaceutical (acceptable level of quality at this stage of product development) and nonclinical (pre-required and data proving to be especially useful in this type of trial) points.
- To follow precisely and exclusively the guidance document when submitting substantial amendments.
- To break the blind for every SAE reported by the investigator to the sponsor and to report to Afssaps every SAE related to the IMP or the trial, or even SAEs with no obvious cause, while also keeping the investigators informed.
- The remaining provisions set out in the directive or the adaptation texts will be applicable, but some unresolved questions remain concerning the authorisations allowed for the distribution system for IMPs, especially in these early studies.

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Appendix I. Transposition of the European Union Directive on clinical trials: Questionnaire

GLOBAL CONSIDERATION

Is the directive already transposed into your national regulation?

If no, specify when a draft of the new regulation has been released/is expected

Ethics Committees (ECs)

How will the ECs be organised within your country (e.g., Regional EC vs National EC, specialised EC, local EC)?

Is it planned to have a specific EC for Phase I trials?

What will be the time-frame for the evaluation of the application at the reception of the valid documentation?

Is it planned to have a specific procedure for Phase I? (see below)

Will the submission take place in parallel or not to the competent authority?

Will the application be submitted by the principal investigator/coordinator or the sponsor?

Is there any appeal procedure?

Competent Authorities

What will be the time-frame for the evaluation of the application at the reception of the valid documentation?

Is it planned to have a specific time-frame for Phase I studies ? (see below)

ISSUES SPECIFIC TO PHASE I STUDIES

I. Review by Ethics committee and competent authorities

Is it planned to have a specific procedure for Phase I?

In terms of :

- time frame
- specialised ethics committee (local?)
- documents

II. Content of the IMPD : *is there any recommendation on the content of the IMPD for phase I studies? If yes, can you specify where those documents are available?*

CMC documentation;

Nonclinical documentation;

Clinical documentation;

III. Protocol: *are there recommendations on the content of the protocol for phase I studies? If yes, can you specify where those documents are available?*

Subject recruitment

Are there specific recommendations relating to inclusion of minors in phase I studies?

For Phase I, is HIV/hepatitis serology asked in the screening of healthy volunteers?

For Phase I in cancerology, is it recommended to only include patients in therapeutic failure? Are there recommendations on the information given to the patients? Is a collective benefit versus an individual one mentioned?

Is there any specificity for Phase I in women?

IV. Logistics: *please specify the current situation and what is expected to change with the transposition of the Directive*

Is there a specific authorisation/certification of the site for phase I studies in terms of:

- facilities;
- equipment;
- lab;

Is there a national database for participants of phase I studies?

What is the content?

How long can a participant be included in the database?

May trial participants receive compensation?

If yes, how is (should) such a compensation (be) handled in the case of:

- healthy volunteers?
- non-healthy volunteers?

Is there a maximum amount to comply with (e.g. per year)?

Appendix I. Contd.

Supply of the investigational medicinal product
Will some Phase I study sites be authorised to import such products? If yes, specify the procedure:
Will Phase I study sites need a specific authorisation for (re)packaging/(re)labelling in case of extension of shelf life, packaging for escalation Phase I studies… ? In such a case, how do you consider the presence and the duties of the qualified person?
Insurance
What are the responsibilities and the obligations for the investigators in terms of insurance?
Is there any specificity in Phase I?
Biological samples
Are there specific provisions for storage, transport and analyses by a central lab in the context of clinical trials (i.e. need for any specific authorisation?)
V. Declaration of the end of study: *specific for Phase I?*
What are the requirements for both EC and CA? What will be the time-frame as regards the subsequent studies?
What is the content of the information to be given?
What is expected/should be performed with the transposition?

CA = competent authority; **CMC** = chemistry, manufacturing and controls; **IMPD** = investigational medicinal product dossier.

Appendix II. Protocol for a clinical trial of a medicinal product (International Committee on Harmonisation-Good Clinical Practice [ICH-GCP])

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)
1. General information
1.1. Title, protocol identifying number, and date
1.2. Name and address of the sponsor and monitor
2. Background information
2.1. Name and description of the investigational product(s)
2.2. A summary and findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial
2.3. Summary of the known and potential risks and benefits, if any, to human subjects
2.4. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s)
2.5. A statement of compliance protocol, GCP regulatory requirement(s)
2.6. Description of the population
2.7. Background for the trial
3. Trial objectives and purpose
4. Trial design
4.1. Primary and secondary endpoints
4.2. Type/design of trial, schematic diagram
4.3. Randomisation-blinding
4.4. Description of the trial treatment(s)
4.5. Expected duration of subject participation
4.6. Description of the 'stopping rules' or 'discontinuation criteria' for individual subjects, parts of the trial and the entire trial
4.7. Accountability procedures for the investigational product(s)
4.8. Maintenance of trial treatment randomisation codes and procedures for breaking codes
4.9. The identification of any data to be recorded directly on the CRFs
5. Selection and withdrawal of subjects
5.1. Inclusion criteria
5.2. Exclusion criteria
5.3. Subject withdrawal criteria
6. Treatment of subjects
7. Assessment of efficacy
7.1. Efficacy parameters
7.2. Methods and timing
8. Assessment of safety
9. Statistics
10. Direct access to source data/documents
11. Quality control and quality assurance
12. Ethics: description of ethical considerations relating to the trial
13–16. Data handling and record keeping, financing and insurance, publication policy, supplements

CRFs = case report forms; **GCP** = Good Clinical Practices.