



DIRECTORATE FOR EVALUATION OF MEDICINAL AND BIOLOGICAL PRODUCTS
Department on Evaluation of Clinical Trials and Special Status Medicinal Products

Clinical Trials Unit

CONDUCT OF CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE IN FRANCE

NOTICE TO SPONSORS OF CLINICAL TRIALS ON MEDICINAL PRODUCTS

PRACTICAL DOCUMENTS

EXAMPLES OF SUBSTANTIAL AND NON-SUBSTANTIAL AMENDMENTS
TO BE NOTIFIED TO AFSSAPS

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PRESENTATION OF THE DOCUMENT

SCOPE

N.B. This document only addresses the requirements of AFSSAPS (the French competent authority), and not those of the French Ethics Committees (CPP).

This document has two objectives:

1. to provide examples of amendments generally regarded by AFSSAPS as substantial, and examples of amendments generally regarded by AFSSAPS as non-substantial;
2. to specify, according to their nature, whether the substantial amendments must be notified to AFSSAPS for authorisation or for information only.

This list of examples is not exhaustive and has been drawn up based on AFSSAPS practical experience on amendments to clinical trials.

The examples given here complete those already provided by the European guidelines (cf. section Legal Basis : European provisions).

This list of examples may be extended and adapted, based on works led at the European level, notably those of the Clinical Trial Facilitation Group (CTFG).

TEMPLATE

Throughout this document, amendments are presented in the following format :

1 AMENDMENTS RELATIVE TO THE ORGANISATION OF THE TRIAL

NATURE	TYPE (for Afssaps)	COMMENTS
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1.1 Identification of the sponsor/ legal representative

① Change of sponsor

SAA or **SAI**
or **NSA**

Commentaire [AF1] : Si ce sont des numéro de code: remplacer Subject par Identification

Description of the change

Field for further details concerning the amendment, if needed.

Subject of the amendment

Mis en forme : Anglais (Royaume-Uni)

AFSSAPS type of amendment :

SAA Substantial Amendment to be notified to AFSSAPS for Authorisation

SAI Substantial Amendment to be notified to AFSSAPS for Information

NSA Non Substantial Amendment

BACKGROUND

LEGAL BASIS

EUROPEAN PROVISIONS

The two following European guidances provide examples of substantial amendments:

- the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial"^[1], published by the European Commission, lists the main types of substantial amendments;
- the "Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials"^[1], of the European Medicines Agency (EMA), gives examples of modifications relative to the pharmaceutical quality of investigational medicinal products.

FRENCH PROVISIONS

Pursuant to article L.1123-9 of the French Public Health Code, substantial amendments (SA) are understood to be those initiated by the clinical trial sponsor.

Article R.1123-35 of the French PHC defines substantial amendments as those having a significant impact on any aspect of the clinical trial, namely on the followings :

- the protection of clinical trial participants, including safety aspects,
- the scientific value of the trial,
- the quality or safety of any product used in the trial (investigational medicinal products and any other products used for the purpose of the research),
- the interpretation of the clinical trial documentation (e.g. the protocol, the investigator's brochure or the clinical trial authorisation form),
- the conduct or management of the trial.

An amendment is to be regarded as "substantial" when one or more of the criteria listed above are met.

It is up to the sponsor, based on the elements he holds, to decide whether or not to qualify an amendment as substantial.

NB:

However, AFSSAPS can be consulted by the sponsor as to the substantial or non-substantial nature of an amendment.

In addition, another regulatory text ("arrêté" dated on 19 May 2006, so called the "Substantial amendment ruling") defines the format and content of a request for authorisation of a substantial amendment to a clinical trial on a medicinal product for human use, to AFSSAPS, and to the Ethics Committees.

Lastly, practical information relative to the content, format and timetable for the assessment of an application for substantial amendment is provided in Volume 1 of the Notice to Sponsors of Clinical Trials^[1].

^[1] Available on the AFSSAPS website: www.afssaps.sante.fr

This section provides detailed information on several items mentioned in Volume 1 of the Notice to Sponsors (Section II. Modifications to the trial)

SUBSTANTIAL AMENDMENTS

All substantial amendments must be notified to AFSSAPS:

- either for authorisation [substantial amendment for authorisation (**SA**)], where the change relates to aspects of the clinical trial within the competence of AFSSAPS;

NB Substantial amendments introduced on the request of the competent authority or of the ethics committee of another Member State (or third party country) must be notified to AFSSAPS for authorisation.

- or for information [substantial amendment for information (**SAI**)]:
 - where the amendment arises from changes in information provided in the initial clinical trial application to AFSSAPS, which do not generally require an assessment by AFSSAPS (e.g. changes in the sponsor's contact details). Exceptionally, AFSSAPS may however ask for such amendments to be notified for authorisation and not for information only;
 - where the amendment relates to aspects within the sole competence of the CPPs. The sponsor should inform AFSSAPS of the substantial amendment once the CPP's opinion has been taken (cf. "SA ruling" and examples provided in the "Specific Cases" section of this document).

CHANGES OTHER THAN SUBSTANTIAL AMENDMENTS

► Non-substantial amendments

Non-substantial amendments (**NSA**) do not require notification to AFSSAPS (neither for authorisation nor for information). They should, however, be documented by the sponsor and be made available to AFSSAPS on request.

► Changes introduced on the request of AFSSAPS or the CPP

Amendments made following requests by AFSSAPS or the CPP should not be considered as substantial amendments in the sense of article L.1123-9 of the French PHC.

For instance, if, as part of the assessment of a clinical trial authorisation and pursuant to article R.1123-32, AFSSAPS asks the sponsor to make changes to the protocol, it will be up to the sponsor to send the amended protocol to the CPP for information (i.e. not as a notification of substantial amendment), once AFSSAPS's decision has taken place (cf. Volume 1 of the Notice to Sponsors - § 1.3.1 and § 2.3.2).

Similarly, when, as part of the assessment of the request for opinion on a clinical trial, and pursuant to article R.1123-24, the CPP asks the sponsor to modify the trial protocol, the sponsor should send this amended protocol to AFSSAPS, for information only, once the CPP has given its opinion.

The format and content of an application to AFSSAPS for an authorisation of a substantial amendment to a clinical trial on a medicinal product are determined by the "SA ruling".

All the items requested by the "SA ruling" must be provided, otherwise the application shall be deemed not receivable.

The documentation should include the following:

1. A covering letter of application for substantial amendment, including namely reasons for qualification as a substantial amendment;
2. The Substantial Amendment Form (cf. Volume 2 - "Application form for substantial amendment");

NB

For the purpose of traceability of the application for substantial amendment to AFSSAPS, the sponsor should allocate a code number to each substantial amendment. This code number must be reported on the SA application form (item E1 of the Substantial Amendment Form , as provided in Annex 2 of the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial", published in October 2005 by the European Commission).

3. A comparative table (before/after) comparing the changes made to the documents previously submitted, showing previous and new wording and highlighting the substantial changes, with their justification.

Examples of comparative tables are presented at the end of this document.

4. Where appropriate, the new version of modified documents, with updated number of version and date.
5. The supporting information for the proposed amendment, if not detailed in the covering letter or in the Substantial Amendment Form, including, where applicable, summary of new data, an updated overall risk/benefit assessment, possible consequences for subjects already included in the trial and possible consequences for the evaluation of the results ;
6. The clinical trial authorisation (CTA) application form, updated with the changes in the EudraCT application, with the updated XML file and Word, or pdf file, where appropriate.

SUBSTANTIAL AMENDMENTS REQUIRING AFSSAPS AUTHORISATION (SAA)

The procedures regarding SAA are described in Volume 1 of the Notice to Sponsors (cf. § 2.2.2).

AFSSAPS should give its opinion on **SAA** applications within 35 days, from the date of receipt of an application deemed to be complete. This period can be extended to 60 days for trials with cell therapy, xenogeneic cell therapy, gene therapy, or GMOs (cf. Volume 1 of the Notice to Sponsors - § 2.2.2.4.2.3.2).

Within this period, AFSSAPS:

- shall acknowledge receipt of the application,
- may request any additional information necessary for assessing the application, request changes to the application, notify the sponsor of reasoned objections,
- shall give a decision.

SUBSTANTIAL AMENDMENTS NOTIFIED TO AFSSAPS FOR INFORMATION (SAI)

AFSSAPS does not acknowledge receipt of SAI.

However, if a SAI application has been submitted to AFSSAPS and it appears to require authorisation, AFSSAPS shall inform the sponsor by post and examine the application in accordance with the terms defined in Volume 1 of the Notice to Sponsors (cf. § 2.2.4).

EXAMPLES OF AMENDMENTS TO BE NOTIFIED TO AFSSAPS

- Updated on 11.06.2008

The examples of amendments listed below correspond to a non-exhaustive list of modifications generally regarded as substantial or as non-substantial by AFSSAPS.

Among the examples of substantial amendments, some relate to changes generally requiring an authorisation, and others relate to changes to be notified to AFSSAPS for information only.

AFSSAPS may however request that specific substantial amendments be submitted for authorisation and not for information only. AFSSAPS may also be led to requalify as substantial an amendment initially considered non-substantial by the sponsor.

Data Sheet	SA SA submitted to AFSSAPS for authorisation	SAI SA submitted to AFSSAPS for information	NSA Non-substantial amendment
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1 AMENDMENTS OF GENERAL NATURE OR RELATED TO THE MANAGEMENT OF THE TRIAL (1/3)

NATURE	TYPE (for Afssaps)	COMMENTS
1.1 Clinical trial Identification		
① Change to the identification of the clinical trial specified in section A of the CTA application form(e.g. title of the trial, sponsor's protocol code number)	SAI	
1.2 Identification of the sponsor or of his legal representative		
① Change of sponsor	SA	
② Change of legal representative of the sponsor	SA	
③ Change of name / contact details of the contact person designated by the sponsor or his legal representative	SAI	
1.3 Applicant Identification		
① Change of applicant	SAI	
② Change of name / contact details of the contact person designated by the applicant	SAI	
1.4 Investigational Medicinal Product(s) (IMP) Identification		
① Change of name / code name of the IMP	SAI	
② Addition of the INN of the IMP	SAI	
1.5 General information on the clinical trial		
① Change in clinical trial phase	SAI	

1 AMENDMENTS OF GENERAL NATURE OR RELATED TO THE MANAGEMENT OF THE TRIAL (2/3)

Data Sheet	SAA SA submitted to AFSSAPS for authorisation	SAI SA submitted to AFSSAPS for information	NSA Non-substantial amendment
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NATURE	TYPE (for Afssaps)	COMMENTS
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1.6 Clinical trial sites / Investigators [for further details, see also section "Specific Cases"]

① Change of coordinating investigator or principal investigator in an existing site	SAI	
② Addition or withdrawal of a research site on gene therapy or cell therapy IMP(s)	SAA	For clinical trials with gene therapy or cell therapy IMP(s), the CTA includes the site authorisation (article L.1125-1 of the French PHC). Therefore, any SA relating to a research site requires AFSSAPS's authorisation.
③ Addition or withdrawal of a research site with IMP(s) other than gene therapy or cell therapy	SAI	For clinical trial site with IMP(s) other than gene therapy or cell therapy, the assessment of the site is under the competence of the CPP. Therefore, any SA relating to a CT site must be notified to the CPP for opinion, and for information only to AFSSAPS.
④ Changes relative to research site(s) located outside of France	NSA	
⑤ Changes relative to investigators located outside of France	NSA	

1.7 Technical Equipment / Service provider(s)

① Changes relative to technical equipment	SAI	The notification of these SAIs to AFSSAPS need not be immediate and can be made at the time of submission of a later SAA or SAI .
② Addition of technical equipment	SAI	
③ Change of service provider	SAI	
④ Change in transfer of trial related duties	SAI	
⑤ Change of name / contact details of the contact person for technical equipment / service provider	NSA	

1.8 Importer

① Change/addition of an importer <u>responsible</u> for the certification of the finished product in the EU	SAA	
② Change/addition of an importer <u>not responsible</u> for the certification of the finished product in the EU	SAI	

1 AMENDMENTS OF GENERAL NATURE OR RELATED TO THE MANAGEMENT OF THE TRIAL (3/3)

Data Sheet	SAA SA submitted to AFSSAPS for authorisation	SAI SA submitted to AFSSAPS for information	NSA Non-substantial amendment
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NATURE	TYPE (for Afssaps)	COMMENTS
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1.9 Site responsible for labelling

① Change of site responsible for labelling only	NSA	
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1.10 Clinical trial participants

① Change in planned number of subjects to be included	SAI	
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1.11 Duration of the clinical trial

① Change to the duration of the study, without change to the duration of exposure to the IMP nor to the duration of treatment with the IMP, but with <u>change to the monitoring</u> of the participants	SAA	
② Change to the duration of the study, without change to the duration of exposure to the IMP nor to the duration of treatment by the IMP, <u>without change to the monitoring</u> of the participants	SAI	

1.12 Other changes

① Change of insurance company	SAI	
② Changes in laboratory normal values	NSA	
③ Changes in clinical trial data collection documents	NSA	E.g. CRF changes
④ Addition of a new country participating in the clinical trial	NSA	

2 AMENDMENTS RELATED TO THE PHARMACEUTICAL QUALITY OF THE IMP (1/3)

Data Sheet	SAA SA submitted to AFSSAPS for authorisation	SAI SA submitted to AFSSAPS for information	NSA Non-substantial amendment

NATURE	TYPE (for Afssaps)	COMMENTS
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2.1 Amendments related to the quality of the active substance

2.1.1 Manufacturing process for active substance of biological origin

① Change of manufacturer and/or change to the manufacturing process, and/or size of the batch and/or analytical method(s) for the active substance, that may have a significant impact on the safety of the CT participants	SAA	
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2.1.2 Manufacturing process for active substance of chemical origin

① Changes in the manufacturing process resulting in the presence or discover of new impurities	SAA	
② Change to the size of the batches	NSA	

2.1.3 Stability of the active substance of chemical or biological origin

① Extension of the duration of stability	NSA	These changes are of under the responsibility of the sponsor, who is in charge of performing the evaluation and validation.
② Re-test period	NSA	However, the sponsor should notify to AFSSAPS, as a new event likely to have an impact on the safety of the CT participants, any deterioration (e.g. occurrence of toxic impurities, precipitation of an injectable drug)
③ Withdrawal of a test and/or a specification which is no longer justified with regard to the stability	NSA	E.g. withdrawal of the "residual solvents" parameter of the specifications for the stability of the active substance

2 AMENDMENTS RELATED TO THE PHARMACEUTICAL QUALITY OF THE IMP (2/3)

Data Sheet	SAA SA submitted to AFSSAPS for authorisation	SAI SA submitted to AFSSAPS for information	NSA Non-substantial amendment
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NATURE	TYPE (for Afssaps)	COMMENTS
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2.2 Amendments related to the quality of the finished product or placebo

2.2.1 Manufacture of the finished product

① Change of manufacturer or formulation, and/or change in the manufacturing process, and/or the size of the batch, and/or the analytical method(s), and/or the site of primary packaging for the finished product, that may have a significant impact on the safety of the CT participants	SAA	
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2.2.2 Manufacture of the placebo

① Change of formulation likely to have a significant impact on the safety of the CT participants	SAA	
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2.2.3 Stability of the finished product or placebo

① Extension of the duration of stability (including after opening or reconstitution of the IMP)	NSA	<p>These changes are of under the responsibility of the sponsor, who is in charge of performing the evaluation and validation.</p> <div style="border: 1px solid red; padding: 5px;"> <p>However, the sponsor should notify to AFSSAPS, as a new event likely to have an impact on the safety of the CT participants, any deterioration (e.g. occurrence of toxic impurities, precipitation of an injectable drug)</p> </div>
② Restriction of the storage conditions motivated by a safety issue	SAA	
③ Change to the storage conditions relative to logistical aspects (without impact on the safety of the CT participants)	NSA	

2 AMENDMENTS RELATED TO THE PHARMACEUTICAL QUALITY OF THE IMP (3/3)

Data Sheet	SAA SA submitted to AFSSAPS for authorisation	SAI SA submitted to AFSSAPS for information	NSA Non-substantial amendment
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NATURE	TYPE (for Afssaps)	COMMENTS
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2.2.4 Packaging and labelling of the IMP (including packaging of the placebo)

① Change of IMP dispensing system	SAA	
② Change of packaging of an IMP, where the IMP is a gene therapy or cell therapy drug	SAA	
③ Change of packaging of a non-liquid or non-pasty IMP, where the IMP is not a gene therapy or cell therapy drug	NSA	
④ Change to secondary packaging	NSA	

2.2.5 Other modifications related to the quality of the IMP or of the placebo

① Withdrawal or modification of a filter to be placed on the perfusion line upon administration of the drug	SAA	E.g. cases of monoclonal antibodies
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2.3 Amendments in viral safety data

① Modification to data presented in the viral safety file	SAA	The format of the viral safety package is defined in articles 5 and 6 of the ruling of 24 May 2006 fixing the content, the format and the content of the request for a CT authorisation with a medicinal product for human use.
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3 AMENDMENTS RELATED TO THE NON-CLINICAL PART OF THE APPLICATION

Data Sheet **SAA** SA submitted to AFSSAPS for authorisation **SAI** SA submitted to AFSSAPS for information **NSA** Non-substantial amendment

NATURE	TYPE (for Afssaps)	COMMENTS
① Change to the protocol following a new non-clinical event	SAA	Impact on risk/benefit assessment of the clinical trial
② New non-clinical data likely to have a significant impact on the safety of participants and/or on the protocol of the trial	SAA	
③ New non-clinical data unlikely to have an impact on the safety of participants and/or on the protocol of the trial	NSA	
④ Modifications made to the non-clinical data presented in the investigator's brochure having a significant impact: - on the safety of patients, - and/or on the CT protocol,	SAA	See Section "Specific Cases"

4 AMENDMENTS RELATED TO THE CLINICAL PART OF THE APPLICATION (1/2)

Data Sheet

SA A
SA submitted to AFSSAPS for
authorisation

SA I
SA submitted to AFSSAPS for information

NSA
Non-substantial amendment

NATURE	TYPE (for Afssaps)	COMMENTS
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4.1 General information concerning the protocol

① Change of signatory of the protocol for the sponsor	NSA	
② Update of the contact details of the medical director in the protocol	NSA	

4.2 Objectives of the trial / Endpoints / Design of the trial

① Modification to the main objective of the trial	SA A	
② Addition of an interventional ancillary study	SA A	E.g. pharmacokinetics or pharmacogenetics sub-study.
③ Change to the primary endpoint and/or a secondary endpoint likely to have a significant impact on the safety of CT participants	SA A	E.g. addition of an invasive test * Item E.5 of the CTA form to be updated in the event of change to the primary endpoint.
④ Change to the primary endpoint and/or a secondary endpoint without impact on the safety of CT participants	SA I	* Item E.5 of the CTA to be updated in the event of change to the primary endpoint.
⑤ Change to the design of the trial (e.g. addition of an arm / addition of a placebo group)	SA A	

4.3 Selection of trial participants

① Change to the inclusion / non-inclusion criteria (including the age of the participants)	SA A	
② Change to the number of subjects to be included at a given site, without impact on the total number of subjects expected to be included in the trial	NSA	
③ Extension to the period of recruitment <u>with</u> change to the duration of the clinical trial	SA I	
④ Extension to the period of recruitment <u>without</u> change to the duration of the clinical trial	NSA	

4.4 Treatment(s) administered

① Change in the mode of administration of the IMPs	SA A	
② Change of dose	SA A	
③ Addition of new dose ranges	SA A	
④ Change in the duration of exposure to the IMP	SA A	
⑤ Change of comparator	SA A	
⑥ Modification to the list of concomitant treatments prohibited / authorised	SA A	

4 AMENDMENTS RELATED TO THE CLINICAL PART OF THE APPLICATION (2/2)

Data Sheet	SAA SA submitted to AFSSAPS for authorisation	SAI SA submitted to AFSSAPS for information	NSA Non-substantial amendment
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NATURE	TYPE (for Afssaps)	COMMENTS
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4.5 Monitoring of clinical trial participants

① Change to the monitoring	SAA	E.g. addition/deletion of clinical examinations, biological examinations and appointments
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4.6 Monitoring of the clinical trial

① Addition or withdrawal of an independent data monitoring committee	SAA	
② Change in the independent data monitoring committee	SAI	

4.7 Changes to the investigator's brochure

<p>Modifications to the clinical data presented in the investigator's brochure likely to have an impact on :</p> <ul style="list-style-type: none"> - the safety of the CT participants, - and/or the CT protocol, - and/or the assessment of the expectedness of a suspected serious adverse effect (where the IB is the reference document). 	SAA	
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4.8 Other changes to the protocol

① Temporary halt of a clinical trial	SAA	See Section "Specific Cases"
② Restart of the clinical trial after a temporary halt	SAA	See Section "Specific Cases"
③ New clinical safety data relative to the IMP(s), reported from a clinical trial or not, likely to have a significant impact on the safety of the participants and/or on the trial protocol	SAA	
④ New clinical safety data relative to the IMP(s), reported from a clinical trial or not, without impact on the safety of the participants and/or on the trial protocol	SAA	
⑤ Change in the definition of the end of trial	SAI	

SPECIFIC CASES

MODIFICATIONS TO THE INVESTIGATOR'S BROCHURE (IB)

The investigator's brochure (IB) is one of the documents part of the application for a clinical trial authorisation. In France, the format, content and procedures for updating an IB are detailed in the ruling of the 19 May 2006, relative to the content and format of a brochure for the investigator for biomedical research relating to a medicinal product for human use (hereinafter called the "IB ruling").

Pursuant to article 4 of the above mentioned French IB ruling, the IB must be updated:

- at least once a year (annual update),
- when a new event occurs, as mentioned in article L.1123-10 of the French PHC.

Only changes deemed substantial by the sponsor need to be notified to AFSSAPS as part of an application for substantial amendment.

Regarding aspects under the competence of AFSSAPS, changes to the IB are deemed to be substantial when they have a significant impact:

- on the safety of the CT participants,
- and/or on the CT protocol,
- and/or on the assessment of the expectedness of a suspected serious adverse effect (where the IB is the reference document).

In the application for substantial amendment to AFSSAPS, the sponsor should:

- NB**
- clearly identify, in a comparative table (before/after), the changes that may have a significant impact on the safety of the participants, and/or on the protocol, and/or on the determination of the expectedness of the adverse effects,
 - for changes with potential impact on the participants safety but not on the protocol, explain the absence of impact on the protocol.

If the modifications to the IB are not substantial, they need not be subject to an authorisation request nor to transmission to AFSSAPS for information.

Similarly, the annual update of the IB need not be systematically sent to AFSSAPS, but only where this update constitutes a substantial amendment.

MODIFICATIONS TO THE SUBJECT INFORMATION LEAFLET^[3] (at the sponsor's initiative)

The assessment of the subject information leaflet is within the sole competence of the CPPs, pursuant to the provisions of article L.1123-7 of the French Public Health Code (PHC).

Article 2 of the French SA ruling specifies that, "if the substantial amendment relates to items of the application on which either AFSSAPS or the CPP rules, the sponsor shall submit the request for substantial amendment only to the organisation concerned. In this case, the sponsor shall inform the second body of the changes after receipt of the decision of the first."

With regard to the above, when the subject information leaflet is amended on the initiative of the sponsor, it is up to him:

- to submit this modification for opinion to the concerned CPP;
- then, once the opinion of the CPP has been given, to send this opinion to AFSSAPS for information only, together with the substantial amendment form, specifying that the change(s) concern(s) the subject information leaflet, without attaching the amended version of the subject information leaflet.

^[3] Information document intended for people participating in the biomedical research (article L.1122-1 of the French PHC).

MODIFICATIONS TO THE LIST OF INVESTIGATORS

Pursuant to article L.1123-7 of the French PHC, the assessment of the qualification of the investigator(s) is within the sole competence of the CPPs.

Therefore, only the opinion of the CPP needs to be sought when the list of investigators is amended.

However, AFSSAPS should be kept informed of these modifications for the reasons mentioned above insofar as they have an impact on the information provided in the clinical trial authorisation application form (items G.1 and/or G.2 relative to investigators).

Therefore, when the list of investigators mentioned in the CTA form is amended, the sponsor should:

1. submit the change(s) to the CPP for opinion, attaching for this purpose the curriculum vitae of the investigator(s) ;
2. then, once the opinion of the CPP has been given, send to AFSSAPS for information:
 - the opinion of the CPP,
 - the substantial amendment form,
 - the updated CTA, from EudraCT (in xml and Word or pdf formats)

without attaching the curriculum vitae of the investigator(s).

MODIFICATIONS TO THE CLINICAL TRIAL AUTHORISATION (CTA) APPLICATION FORM

Some of the information relative to the CT feature only in the CTA form (e.g.: information on the legal representative of the sponsor, information on organisation(s) to which the sponsor has transferred certain trial related duties).

Any change made to this information should be considered substantial and according to their nature, notified to AFSSAPS either for information or for authorisation (cf. section "Examples of amendments to notify to AFSSAPS").

INFORMATION ON TEMPORARY HALT OF A CLINICAL TRIAL

A temporary halt of a clinical trial consists in:

- stopping the recruitment of new participants in this trial;
- and/or interrupting the treatment of all or some of the subjects already included in the trial.

Any decision by the sponsor to temporarily halt the trial is subject to:

- firstly, immediate information of AFSSAPS and the concerned CPP, preferably by email or fax;
- secondly, and at least within 15 calendar days from when the trial is temporarily halted, application for a substantial amendment authorisation by AFSSAPS (Clinical Trials Unit by email to ams@afssaps.sante.fr), and for opinion by the concerned CPP.

Lastly, to restart the trial, the sponsor must obtain both the authorisation from AFSSAPS and a favourable opinion from the concerned CPP.

CHANGES FOLLOWING A NEW EVENT / URGENT SAFETY MEASURES

The onset of (a) new event(s) may require the sponsor to take appropriate urgent safety measures to protect the subjects against immediate hazard.

If the onset of a new event leads to urgent safety measures and to changes in the conduct of the trial, including its temporary halt, the sponsor must:

- immediately inform AFSSAPS and the concerned CPP of the new events and the measures taken, preferably by email or fax;
- and, at least within 15 calendar days from the establishment of the urgent measures, notify as a substantial amendment AFSSAPS and the concerned CPP for respective authorisation and opinion.

If the onset of the new event leads to the end of the trial, the sponsor must inform AFSSAPS and the concerned CPP immediately. The sponsor should notify this as a Declaration of End of Trial, in accordance with the terms described in part IV "End of Trial" of Volume 1 of the Notice to Sponsors.

CHANGES RELATED TO RECRUITMENT ARRANGEMENTS

Pursuant to article L.1123-7 of the French PHC, the assessment of recruitment arrangements is within the sole competence of the CPPs.

Consequently, when the modalities of recruitment of participants are changed, the sponsor should:

1. submit this change to the concerned CPP for opinion, with a description of the new recruitment arrangements;
2. then, once the CPP's opinion has been given, send to AFSSAPS for information :
 - the opinion of the CPP,
 - the substantial amendment form,
without attaching the description of the new recruitment arrangements.

CHANGES RELATIVE TO THE STATISTICAL ANALYSIS OF THE CLINICAL TRIAL

Pursuant to article L.1123-7 of the French PHC, the assessment of the planned statistical analyses is within the sole competence of the CPPs.

Consequently, when the methodology of the trial is modified, for the reasons mentioned above, the sponsor should:

1. submit this change to the concerned CPP for opinion, together with the amended trial protocol;
2. then, once the CPP's opinion has been given, send to AFSSAPS for information :
 - the opinion of the CPP,
 - the substantial amendment form,
 - the amended protocol.

CHANGES AIMING AT CLARIFYING CLINICAL TRIAL DOCUMENTATION OR CORRECTING TYPOGRAPHICAL ERRORS

Changes aiming at :

- clarifying clinical trial documents (e.g. protocol, IMPD), without any impact on the safety of the trial participants,
- correcting typographical errors,

should be sent to AFSSAPS for information only.

The notification of such changes to AFSSAPS need not be immediate and can be done at the time of submission of a later **SAI** or **SAA**.

EXAMPLES OF COMPARATIVE TABLES

(HIGHLIGHTING SUBSTANTIAL AMENDMENTS)

Two examples of tables presenting substantial modifications to previously submitted documents, by showing previous and new wording and the reason for change, are provided hereafter.

In any case, it is strongly recommended to submit, in addition to the tables, a summary of the principal changes

Mis en forme : Anglais
(Royaume-Uni)

- **Example 1 : recommended format when the number of substantial changes is limited**

Document concerned: [Name of document]

N° and date of the previous version: [to be completed]

N° and date of the new version: [to be completed]

Initial wording ^[1]	Amended or new wording ^[2]	Reason/Justification for change
Chapter/section concerned: 5.2.1 Inclusion criteria Inclusion criterion N°2 Male or female subjects aged 18 to 70 at the time of the screening visit	Chapter/section concerned: 5.2.1 Inclusion criteria Inclusion criterion N°2 Male or female subjects between 18 and 70 below 75 years of age at the time of the screening visit Addition of inclusion criterion N°8: HgbA_{1c} >9	To be detailed here, if the justification does not appear elsewhere ^[3]

- **Example 2 : recommended format when the substantial changes are numerous**

Document concerned: [Name of document]

N° and date of the previous version: [to be completed]

N° and date of the new version: [to be completed]

Section concerned: Inclusion criteria

The following text ^[1]:

Male or female subjects aged between 18 and 70 at the time of the screening visit

Is replaced with ^[2]:

Male or female subjects aged ~~between 18 and 70~~ **below 75 years of age** at the time of the screening visit

Reason/Justification for change: to be detailed here, if this justification does not appear elsewhere ^[3]

[1] | Note there the initial wording.

Note there the amended wording :

[2] - by striking through the deleted text , where appropriate,

- by adding the new text, where appropriate, preferably in **bold italics**, or by highlighting (avoid the colour yellow).

[3] | If the justification for the substantial changes, is already detailed elsewhere in the documents submitted (e.g. in the SA letter), please indicate here where this justification can be found.

LIST OF ABBREVIATIONS

AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé (French Competent Authority)
IB	Investigator's Brochure
EC	Ethics Committee
CPP	Comité de Protection des Personnes (French Ethics Committee)
CRF	Clinical Research Form
CRO	Contract Research Organisation
PHC	Public Health Code
CTA	Clinical Trial Authorisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
NSA	Non-Substantial Amendment
SA	Substantial Amendment
SAA	Substantial Amendment for Authorisation
SAI	Substantial Amendment for Information