

Part II Document Harmonisation Guidance

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1. Introduction

This guidance document is aimed at supporting sponsors of Clinical Trials when submitting applications under *Clinical Trials Regulation (EU) No 536/2014*; herein referred to as ‘the Regulation’. However, this guidance is also relevant under Directive 2001/20/EC and may be used in advance of the Regulation applying. The Regulation defines two parts of a clinical trial application, Part I and Part II. This guidance document relates to the submission of Part II elements of the application only.

This is a general guidance which relates to a set of harmonised documents which have been endorsed by the EU Clinical Trial Expert Group. These templates have been developed based on the requirement set out in the Regulation and are therefore compliant with the Regulation. However, where it was deemed appropriate, and where participating Member States were in agreement, the templates also include additional fields which are intended to support sponsors in submitting a comprehensive clinical trial application. This is notwithstanding that further information may also be requested from sponsors which is additional to the information requested in the templates.

The aim of providing a set of harmonised documents for sponsors is to facilitate the application process by providing a single set of documents which should be broadly applicable across all EU Member States and therefore sponsors are encouraged to use these templates in clinical trial applications. However, sponsors are advised to also refer to national guidance when submitting an application in each Member State. This is because individual Member States may have national expectations and requirements in terms of the information which is to be provided. On the other hand, some members states, instead of implementing national requirements decided to use these or (slightly) adapted versions of these templates.

2. Investigator Curriculum Vitae (CV)

2.1. The suitability of investigators should be assessed under the Part II assessment, as defined under Articles 7 and 49 of the Regulation. In this context, ‘The Investigator’ is taken to be the following;

Either;

Principal Investigator - an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site

Or;

Investigator - an individual responsible for the conduct of a clinical trial at a clinical trial site

Therefore, documentation in the application of the suitability of investigators under Article 7 of the Regulation is limited to principle investigator at each site and is not required for other investigators involved in the trial unless national requirements specify otherwise. Other individuals involved in conducting the clinical trial should also be suitably qualified to perform their task (Art 49) and this aspect is covered in the site suitability declaration (Annex I N67).

2.2. The harmonised CV template includes fields to complete which cover all the required information defined in Annex I, Section M, Paragraph 65 of the Regulation.

2.3. National requirements regarding the signature on the CV (electronic, wet, none) vary, sponsors should follow the national requirements.

3. Declaration of Interest

3.1. When assessing the suitability of investigators, consideration should also be given to whether there are any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators. In this context, 'The Investigator' is taken to be the following;

Either;

Principal Investigator - an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site

Or;

Investigator - an individual responsible for the conduct of a clinical trial at a clinical trial site

Therefore, documentation in the application of conditions which may influence the impartiality of investigators is limited to the principle investigator at each site unless national requirements specify otherwise.

3.2. The harmonised Declaration of Interest template includes fields to complete which cover all the required information defined in Annex I, Section M, Paragraph 66 of the Regulation.

4. Site and Facilities Suitability

4.1. The Suitability of the site and the facilities should be assessed under the Part II assessment, as defined under Article 7 of the Regulation.

4.2. The harmonised site suitability template includes fields to complete which cover all the required information defined in Annex I, Section N, Paragraph 67 of the Regulation.

4.3. The information which is required to assess the suitability of the sites and facilities will vary between different Member States. This is due to varying national legislation and policy which applies in different Member States. Some Member States will require a signed declaration only

and some Member States will require additional information to that which is explicitly requested in the harmonised template. It is therefore essential to confirm the information which will be required (and the template to be used) when submitting to each Member State.

5. Recruitment and Informed Consent Procedure

5.1. The appropriateness of how subjects will be recruited into the trial and arrangements for obtaining informed consent should be assessed under the Part II assessment, as per Article 7 of the Regulation.

5.2. Where the trial will involve the recruitment of subjects through advertisement, copies of the advertising material should also be submitted, including any printed materials, and audio or visual recordings. This should include information about the procedures proposed for handling responses to the advertisement. This includes copies of communications used to invite subjects to participate in the clinical trial.

5.3. The harmonised template is intended to be used to describe the recruitment and informed consent procedure only. In addition to information about the procedure, all information given to subjects (or, where applicable, to their legally designated representatives) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent.

5.4. When e-consent methods are accepted in the member state, and where the trial proposes to use e-information or e-consent methods, this should be clearly stated and in compliance with national legislation. The information should be submitted in such a way that the information can be suitably assessed.

5.5. Where the template refers to an impartial witness, this requirement may *either* relate to the trial due to the subject population (e.g. trials with a treatment for a musculo-degenerative disease) *or* relate to individual trial subjects due to individual circumstances (e.g. illiteracy).

5.6. The harmonised template includes fields to complete which cover all the required information defined in Annex I, Section K, Paragraph 59 and Section L, Paragraph 62 (a) – (e).

6. Compensation for trial participants

6.1. The appropriateness of providing compensation to trial participants is assessed under the Part II assessment, as defined under Article 7 of the Regulation.

6.2. Compensation generally includes but is not limited to reimbursement of costs related to trial participation (e.g. travel, accommodation, meals), for loss of earnings due to trial participation and for monetary and non-material loss or damages (e.g. discomfort and suffering).

6.3. Financial incentive to participate in trials might be accepted exceptionally in justifiable cases (e.g. for patients who had stopped trial treatment (due to medical advice, lack of effectiveness, side effects etc) but are asked to continue follow-up visits to allow for a valid intent to treat analysis). Some Member States do not accept the payment of financial incentive for participation.

6.4. Please note that for trials which involve minors or incapacitated subjects, no incentive or financial inducement may be given to the subjects or their legally designated representatives except for compensation of expenses or loss of earnings directly related to the participation in the trial. A small token of appreciation is not considered an incentive, but needs to be explicitly allowed by the ethics committee (see also Q&A 9.1).

6.5. In certain, justifiable cases, conditional compensation could be acceptable. At all cases, it must remain proportionate with the associated expenses and/or loss of earnings due to trial participation. For example, in case of complex trials, when stages are predefined, it could be acceptable to pay compensation per stages (to participate in a screening platform and additional compensation if the patient tests positive for certain markers and starts trial treatment).

6.6. Compensations (including incentives) with appropriate justification should be assessed and approved by the evaluating ethics committee. Compensations must not be used to compensate for compromising participants' right and safety and should not lead to undue influence. Sponsors need to make Ethics Committees aware of any conditions linked to compensations.

6.7. Description of any other financial agreement between sponsor and the site as well as of compensation paid to the investigators and/or sites shall be submitted separately (Annex I P70, 71).