(d) have knowledge of the risk analysis of the ATIMP (see section 12(d));

(e) have knowledge of the requirements for storage, handling, administration, and destruction or disposal of the ATIMP including any hazard to those handling the product and close contacts and the risk to the environment;

(f) have knowledge on the use, application, implementation or administration of the ATIMP and the requirements for clinical, efficacy and safety follow up;

(g) ensure that the particular requirements for the application of the ATIMP, such as standardisation of surgical procedures and training of the healthcare professionals involved, are communicated to the investigator site team including the surgeons or other specialists involved;

(h) inform the trial subject and where applicable their legal representative of the particular issues that arise for ATIMPs. In particular, both the informed consent form and any other written information to be provided to the subjects should include explanation of the following:

- The arrangements for traceability including provisions for subject data protection and confidentiality (see section 7);
- The arrangements for follow up before and after the end of the trial, including after subjects withdraw from the study and including the information (alert card) to be provided to the subject for use in the event of problems arising after the end of the trial (see section 8.2);
- The inconveniences of long term follow up, where applicable (see section 8.2);
- The definition of the end of the trial and its relationship to the follow up after the end of the trial (see section 8.2);
- The irreversible nature of the ATIMP, where applicable;
- The need, where applicable, for the presence of a representative of the sponsor for assistance during the administration of the ATIMP and the rationale for this;
- Risks and precautions including for example those related to shedding in the context of ATIMPs involving gene therapy;
- Guidance on how to communicate risks to close contacts and offspring where they could be at risk and information on any follow up involving them.

12. SPONSOR

In the context of clinical trials with ATIMPs sponsors should:

(a) establish and maintain a system for traceability (see section 7.1 and 7.2.1);

(b) keep their part of the traceability records for the required period (see section 7.3);

(c) implement the appropriate adverse event and adverse reaction reporting process as required by the legislation in the context of ATIMPs (see section 8.1);

(d) ensure that an ongoing risk analysis, based on existing knowledge of the type of product and its intended use, is performed and provided to the investigator involved in a clinical trial with that ATIMP, through the investigators brochure or updates to it and to the patient through the informed consent or updates to it (see section 8.2);

(e) for combined products, the risk analysis and risk management plan of the device part should be shared with the investigators;

(f) identify the need for, duration and the nature of clinical, safety or efficacy follow-up required, including after subjects withdraw from the study (see section 8.2);

(g) establish the particular requirements for the application of the ATIMP, such as standardisation of surgical procedures and training of the investigator involved;

(h) train the investigator in the requirements for storage, handling, administration, and destruction or disposal of the ATIMP including hazards to those handling the product and close contacts and the risk to the environment;

(i) train the investigator on the use, application, implantation or administration procedures of those ATIMPS that may require specific concomitant therapy and may involve surgical procedures that could have an impact on the safety or efficacy of the product. Information on the standardisation and optimisation of these procedures during clinical development should be provided. The sponsor should also identify when their personnel need to be involved in these procedures and describe this in the protocol or associated document that is included in the application to the competent authority and ethics committee and in the agreements with the clinical investigator site;

(j) consult the national competent authorities for biosafety, where applicable.

13. PROTOCOL

50. The following should be considered by the sponsor in relation to the content of the protocol:

(a) Variabilities in the nature of ATIMPs and the diseases for which they are used that need to be foreseen in the protocol design. The protocol should foresee any necessary flexibility that may be required for the handling of this variability inherent in the use of certain ATIMPs, for example:

- The acceptable range of cell numbers and cell viability at the time of administration to subjects;

- Appropriate windows of acceptability for inclusion and exclusion criteria.

(b) Where an ATIMP contains human cells or tissues, the protocol should contain a brief overview of:

- Confirmation that the donation, procurement and testing of the human tissues and cells are in conformity with the relevant Regulations, as referred to in Article 3 of the Regulation 1394/2007;

- The donor type and whether the donation is part of the trial process;

- The criteria for suitability of the donated material to comply with defined requirements.

(c) Where an ATIMP incorporates a medical device (i.e. a combined advanced therapy medicinal product), the protocol should contain a brief overview of:

- Characteristics, performance and purpose of the device;

- Confirmation that this product is in conformity with essential requirements with the regulations referred to in article 6 of the advanced therapy regulation.

- Rationale for combination of ATIMP and medical device to aid understanding of the effect of each individually and in combination.

(d) Detailed instructions to ensure blinding of the trial where needed (e.g. where the person responsible for randomization of the subjects to treatment has to remain blind or where the person involved at the clinical site in the preparation of the ATIMP cannot be blinded whilst the person responsible for the administration of the ATIMP needs to be blinded);

(e) Traceability procedures and documentation (see section 7);

(f) Information on any particular requirements for safety reporting, including during follow up after the end of the trial (see section 8.1):

(g) The definition of the end of the trial and its relation to the follow up after the end of the trial (see section 8.2);

(h) Information on the follow up strategy expected for the ATIMP (including follow-up after the end of the trial) with the rationale and objectives based on appropriate risk assessment (see section 8.2);

(i) Specific requirements relating to subjects withdrawn from the trial at their own initiative or that of the investigator, in particular relating to the follow-up strategy (see section 8.2);

(j) Information on the application of the ATIMPs when this application may require specific concomitant therapy and may involve surgical procedures that could have an impact on the safety or efficacy of the product. This includes information on the standardisation and optimisation of the processes involved including where applicable the surgical procedures;

(k) Information on whether the presence of a representative of the sponsor experienced in the administration of the ATIMP needs to be present during the application of the ATIMP to the subject and the rationale for this;

(l) Instructions on any local preparation or reconstitution required;

(m) In case of ATIMPs involving gene therapy, information on viral shedding and any precautions required should be provided where applicable;

14. INVESTIGATOR BROCHURE

51. The following should be considered by the sponsor in relation to the content of the Investigator Brochure:

(a) A description of the scope and sufficiency of existing information and its limitations;

(b) Information obtained from ongoing risk analysis based on existing knowledge of the type of product and its intended use including risk associated with the application method (e.g. surgery, concomitant medication, associated devices);

(c) Information on the risk management plan (for marketed products);

(d) Information on the risks due to product failure;

(e) Information on the product safety handling, containment and disposal;

(f) Information on short and long term safety issues particular to ATIMPs such as infections, immunogenicity/immunosuppression and malignant transformation as well as those related to medical devices for combined ATIMPs.

15. ESSENTIAL DOCUMENTS

52. As regards the keeping of records, the rules as set out in Directive 2001/20/EC and 2005/28/EC apply. The traceability records should be kept for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor.

53. Before, during and after completion or termination of the trial each party (see section 7.2) should hold the necessary information available at all time to ensure bidirectional traceability, linking the donor information at the procurement site to the ATIMP and the clinical trial subject information at the clinical trial site to the ATIMP, whilst ensuring the data protection legally required for both the donor and the clinical trial subject.

15.1. Before the Clinical Phase of the Trial Commences

54. During this planning stage the following documents should be generated and should be on file before the trial formally starts:

(a) File of the tissue/blood establishment, manufacturer, sponsor and investigator/institution: Details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice vers;

(b) File of the sponsor:

– The documentation used to determine the follow up strategy;

– The follow up strategy expected for the ATIMP (including follow-up after the end of the trial) with the rationale and objectives based on appropriate risk assessment.

15.2. During the Clinical Conduct of the Trial (see also Annex)

During the clinical conduct of the trial the following documents should be on file:

(a) File of the tissue/blood establishment or animal facility:

– Traceability records linking the donor/animal source to the donated material;

– Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa.

(b) File of the manufacturer:

– Traceability records linking the donated material to the manufactured ATIMP;

– Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa.

(c) File of the sponsor:

– Traceability records linking the manufactured ATIMP to the clinical trial site and from the clinical trial site to the patient code;

– Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa;

– Any update to the documentation used to determine the follow up strategy;

– Any update to the follow up strategy expected for the ATIMP (including follow-up after the end of the trial) with the rationale and objectives based on appropriate risk assessment.

(d) File of the investigator/institution:

– Traceability records linking the manufactured ATIMP delivered to that clinical trial site and from the clinical trial site to the patient code, patient identification and medical file;

– Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa.

15.3. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 15.1 and 15.2 and kept by each respective party should be in the file with the following:

(a) File of the tissue/blood establishment/animal facility: Final traceability records linking the donor/animal source to the donated material;

(b) File of the manufacturer: Final traceability records linking the donated material to the manufactured ATIMP;

(c) File of the sponsor:

– Final traceability records linking the manufactured ATIMP to the clinical trial site and from the clinical trial site to the patient code;

– Follow-up procedures, contact information and data collected, to document the conduct of the clinical follow-up, safety follow-up and efficacy follow-up required.

(d) File of the investigator/institution:

– Final traceability records linking the manufactured ATIMP delivered to that clinical trial site and from the clinical trial site to the patient code, patient identification and medical file;

– Follow-up procedures, contact information and data collected, to document the conduct of the clinical follow-up, safety follow-up and efficacy follow-up required.

ANNEX - TRACEABILITY RECORDS

By Tissue Establishments/Procurement Organisation:

As outlined in Annex VI of Directive 2006/86/EC implementing the human tissue and cell Directive 2004/23/EC.

By Blood Establishments:

As outlined in Annex I of Directive 2005/61/EC implementing the blood directive 2002/98/EC.

By Animal Facilities:

By analogy with Annex VI, of the Directive 2006/86/EC implementing the human tissue and cell Directive 2004/23/EC:

- Source animal identification
- Donation identification that will include at least:
  - Identification of the animal facility
  - Animal ID number
  - Date of procurement
  - Place of procurement
  - Type of donation (e.g. single v multi-tissue; living v deceased)
- Product identification that will include at least:
  - Identification of the animal facility
  - Type of tissue and cell/product (basic nomenclature)
  - Pool number (if applicable)
  - Split number (if applicable)
  - Expiry date
  - Tissue/cell status (i.e. quarantined, suitable for use etc.)
  - Description and origin of the products, processing steps applied materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety.
  - Identification of the facility issuing the final label
- Identification of user facility and distribution dates:

- Date of distribution/disposal
- Identification of the user facility

By the Manufacturers:

- Information on the material received from the Procurement organisation, tissue establishment or animal facility as applicable:
  - Identification of the tissue establishment/animal facility/any intermediaries if applicable
  - Type of tissue and cell/product (basic nomenclature)
  - Pool number (if applicable)
  - Split number (if applicable)
  - Tissue/cell status (i.e. quarantined, suitable for use etc.)
- ATIMP identification that will include at least:
  - Tissue/cell status (i.e. quarantined, suitable for use etc.)
  - Description and origin of the products, processing steps applied materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety.
  - Identification of the sponsor, contract research organization or investigator/institution to whom the product is supplied
  - Product name/code
  - Pharmaceutical form, route of administration, quantity of dosage units and strength
  - Batch and/or code number
  - Trial reference code
  - Trial subject identification number
  - Expiry date
  - Date of distribution/disposal
  - Release of the finished product by the Qualified Person

By the sponsor:

According to section 8 of the Note for guidance on Good Clinical Practice[29] the following essential documents should be kept by the sponsor before, during and after the conduct of the trial:

- Shipping Records for IMP (8.2.15, 8.3.8):
- Certificate of analysis of the IMP (8.2.16, 8.3.9)
- Treatment allocation and decoding documentation (8.2.17, 8.4.6
- IMP accountability at the site (8.3.23, 8.4.1), including final disposition of both used and unused product.

These records contain information relevant for traceability purposes and at least the following minimum data set from these records should be kept for 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor:

- Identification of the manufacturing site
- Identification of the investigator/institution that used the ATIMP
- Product name/code
- Pharmaceutical form, route of administration, quantity of dosage units and strength
- Batch and/or code number
- Trial reference code
- Trial subject code
- Expiry date
- Date of application

In addition, the last version of the Investigator Brochure and the protocol should be retained for the same period to provide information about the product and its application.

By investigator and institution responsible for human application

According to section 8 of the Note for guidance on Good Clinical Practice[30] the following essential documents should be kept by the investigator before, during and after the conduct of the trial:

- Shipping Records for IMP (8.2.15, 8.3.8):

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29 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

30 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

- Certificate of analysis of the IMP (8.2.16, 8.3.9)
- Treatment allocation and decoding documentation (8.2.17, 8.4.6
- Subject identification code list (8.3.21, 8.4.3)
- IMP accountability at the site (8.3.23, 8.4.1) including final disposition of both used and unused product.

These records contain relevant information for traceability purposes and at least the following minimum data set from these records should be kept for 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor:

- Identification of the investigator/institution,
- Identification of the sponsor and contract research organization where applicable,
- Identification of the manufacturing site,
- Product name/code,
- Pharmaceutical form, route of administration, quantity of dosage units and strength,
- Batch and/or code number,
- Trial reference code,
- Trial subject code,
- Subject identification code list (8.3.21, 8.4.3) (links the name of the subject to the trial subject code),
- Expiry/retest date,
- Date of administration,

The subject medical records should also contain the product name/code, the trial reference code, trial subject code and administration dates and dose in order to ensure that a link can be made back to the identity of the product and the further traceability records of the investigator and sponsor.

The investigator site should also retain records of any product that was unused or destroyed and of its final status.

HMA
Heads of Medicines Agencies

Clinical Trials Facilitation Groups

Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications

Version 2

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1 Abbreviations

CA	competent authority
CT	clinical trial
CTFG	clinical trial facilitation group
CTA	clinical trial application
EC	ethics committee
EU	European Union
FIH	first in human
HMA	EU Heads of Medicines Agencies
MN-FIH	multinational first in human
GNA	grounds for non acceptance
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
MA	marketing authorisation
MC-CT	multicentre clinical trial
MS	member state
MN-CT	multinational clinical trial
NIMP	Non IMP
NCA	national competent authority
P-NCA	participating national competent authority
PIP	paediatric investigational Plan
RFI	request for further information
VHP	voluntary harmonisation procedure
VHP-C	VHP-Coordinator
VHP-SA	substantial amendment of a positive Voluntary Harmonisation Procedure

2 Introduction

The EU Heads of Medicines Agencies (HMA) agreed in 2004 to establish a clinical trials facilitation group (CTFG) to co-ordinate the implementation of the EU clinical trials directive 2001/20 EC across the member states
This document is produced by the CTFG in order to propose a harmonised procedure for assessing multinational clinical trials (CT) by the National Competent Authorities (NCA) in EU. The changes of this new version of the guideline were approved by the HMAs during the November 2009 Meeting in Uppsala; Sweden.
This document should be read in conjunction with other EU-published guidelines (see also Section References).

The main changes in v2 with respect to v1 refer to:
a) the acceptability of all CTs with at least 3 concerned MS;
b) deletion of the *"Pre-procedural step" or "Request for VHP"* phase in the procedure, and
c) the inclusion of substantial amendments in the scope of the VHP.

The CTFG is open for discussions on further improvements especially in respect of handling substantial amendments. Any suggestion in this respect should be sent to VHP-CTFG@VHP-CTFG.eu indicating on the message reference "suggestion for improvement of VHP".

3 Background/Rationale

The Directive 2001/20/EC, (the "EU Clinical Trials Directive"), relating to the implementation of good clinical practice in the conduct of clinical trials (CT) on medicinal products for human use, defines a multi-centre clinical trial (MC-CT) as a CT conducted according to a single protocol but at more than one site, and therefore by more than one investigator. The trial sites may be located in a single Member State (MS), in a number of MS, or in one or more MS and additionally in third countries. This document relates to a MC-CT with trial sites in several MS, referred to as multinational CTs (MN-CTs) throughout this document.
In the context of the implementation of Directive 2001/20/EC and with the aim to harmonise the conduct of CTs within EU MS, the EU-Commission has issued detailed guidances and information regarding major aspects of clinical trials, such as the format of requests to Competent Authorities (CA) and of CT information to be submitted to Ethics Committees (EC), the reporting of adverse reactions arising from CT, the documentation on the quality of the Investigational Medicinal Product (IMP) and the European clinical trial database EudraCT (EudraLex - Volume 10 Clinical trials guidelines).
To coordinate the implementation of Directive 2001/20/EC across the MS at an operational and national level, the EU Heads of Medicines Agencies have set up the Clinical Trials Facilitation Group (CTFG). This is another major step for the achievement of harmonisation of CTs in Europe.

With the translation of the Directive into national laws and regulations, divergent practices between the different MS remain in areas such as:

- Distribution of duties between the CAs and the ECs
- Content, format or language requirements
- Timelines for the review of a CT application
- Different application dates by the sponsor in the different MS
- Human resources and workload vs. the number of applications per NCA

Regarding a MN-CT, for which an application is filed in several MS as the authorisation of a CT is subject of national legislations, the assessment of the same Clinical Trial Application (CTA) for a given MN-CT might result in varying final decisions. Country-specific modifications might occur due to changes requested by the different NCAs and ECs; a CT might even be approved in one MS and rejected in another. Such situations not only may jeopardize the scientific value of clinical trial results due to country-specific modifications but also are hardly understood by the public, since the levels of protection of clinical trials participants should be the same in all European countries.
Further to October 2007, CTs Conference organised by the European Commission and EMEA, the importance of maintaining the following general principles for the conduct of clinical research in the European Union has been recognised:

- Protect clinical trials participants
- Ensure high-quality research in the EU
- Contribute to a favourable research environment in EU
- Bring innovative medicines to patients as quickly as possible

For these reasons, the need to harmonise MN-CTs in Europe in order to ensure the protection of participants as well as the scientific value of CTs by the means of harmonising NCAs' processes and practices relating to MN-CTs (about 30% of CTs in EU), has become a priority for the CTFG. Thus, the organisation of coordinated assessment of multinational CTAs through the Voluntary Harmonisation Procedure (VHP) has been

a major objective of the CTFG work plan for 2008-2010. This procedure has been set up within the current legal frame-work for CTs.

On the basis of the experience with the VHP in 2009, the CTFG developed a new version of the VHP: the procedure has been modified in order to streamline the assessment, to enlarge the scope of the pilot phase and to shorten the timelines. For each VHP, one of the participating NCA takes the lead in the scientific consolidation of the letter with grounds for non-acceptance.
Procedures as for example assessment reports and rapporteurships from the decentralised procedure are discussed to be included in the VHP.

4 Scope and general principles

On the one hand, a harmonisation procedure of the assessment occurring after the application of a CT in the different MS is foreseen difficult to achieve and may even be counterproductive by adding an additional step at the end of an already lengthy process. On the other hand, taking into account the current legal framework, each NCA remains responsible for the approval of a CTA in its own country. Therefore, a harmonisation procedure for the assessment of MN-CT applications is proposed i) before the initial phase of the national process, and ii) on a voluntary basis.
The NCAs will be giving CTAs involving First in human (FIH)[1] or with "critical" products,[2] and the VHP in general, a priority in their daily work.

The main objectives of the assessment of the CT are to ensure the quality of the IMP and the safety of the trial subjects.

Due to the volume of MN-CTs to be assessed every year and bearing in mind that CTA decisions remain a competence of each NCAs, an incremental process is proposed with an initial pilot phase.

During the pilot phase, all MN-CTs involving not less than 3 MS are eligible to undergo the VHP.

During the pilot phase no fees will be charged for VHPs or VHP-SA; the costs of the NCAs will be covered by the national applications to the NCAs.

5 Definitions

- VHP-Coordinator (VHP-C): the CFTG representative of the NCA in charge of coordinating the VHP for CTAs

[1] First in human (FIH) MN-CTs and particularly CTs with investigational medicinal products with known or anticipated risk factors as described in EMEA/CHMP/SWP/294648/2007
[2] investigational medicinal products (limited community expertise e.g. IMP with novel mode of action, novel manufacturing process, novel administration and storage requirements, links to a class of medicinal products with recognised safety concerns, unresolved pre-clinical abnormal findings, for instance monoclonal antibodies interfering with immune regulation, and advanced therapies) or "critical" MN-CTs (e.g. for limited trial populations e.g. orphan diseases, less common types of cancer, paediatric diseases with small numbers of participants, diseases with small numbers of participants or unmet medical needs), based on NCA's judgement and endorsed by the CTFG

- Participating NCAs (P-NCAs): the NCAs concerned by the CT and wishing to participate to the VHP on a voluntary basis

- The "VHP applicant": a sponsor, whoever is submitting a request for VHP of a MN-CT to the CTFG

- Request for VHP: the letter from the VHP applicant, requesting a planned MN-CT to undergo the VHP. The applicant should describe the key features of the CT and indicate which EU countries will be involved in the MN-CT. The request for VHP should also contain all the documentation required for the assessment of the CTA through the VHP. The content of the VHP application is detailed under section "Format and content of the VHP application"

- Leading NCA: The NCA responsible for coordinating the response to the applicant.

6 Outline of the proposed procedure

The VHP will comprise three phases:

- Phase 1: Request for VHP and validation of the application
- Phase 2: Assessment step: review of a CTA by the NCAs of the participating MS
- Phase 3: National step, with formal CTAs to all concerned NCAs

Phase 1 and 2 are actually composing the submission phase to the CTFG. Phase 3 is the formal submission of a CT to each NCA according to the national regulations.

6.1 Request for VHP and validation of the application

In the request for VHP, the applicant should shortly describe the key features of the CT and indicate which EU countries will be involved in the MN-CT. The request for VHP should also contain all the documentation required for the assessment of the CTA by the MS.

6.1.1 At any time, the applicant informs the VHP-C by sending the request for VHP to VHP-CTFG@VHP-CTFG.eu via E-mail/Eudralink, highlighting important features of the MN-CT and the documentation required for the assessment of the CTA

6.1.2 Upon receipt of the request and VHP-documentation, the VHP-C creates a new file in the VHP database and allocates a VHP number

6.1.3 The complete VHP-documentation is forwarded electronically by VHP-C to the P-NCAs immediately after receipt

Within 5 working days after receipt, the VHP-C informs the applicant whether all requested MS will participate. Validation of the dossier will also be performed and the applicant will be informed of any deficiencies or, if complete, the start date of the VHP.

All timelines in the VHP are calendar days with one exception: the 5 working days between initial submission and confirmation by the VHP-C (0) and the 5 working days when submitting VHP-substantial amendment (VHP-SA)(7.1).
In those MS declining participation in the VHP, a national CTA in parallel to the VHP or after the VHP is possible.

6.2 VHP CTA assessment step

Of note, the timelines proposed hereby are maximum timelines. Whenever possible for the P-NCAs, the timelines can be shorter.
Important: during the entire VHP, any contact from the applicant to the P-NCA should be avoided and the VHP-C being the only contact for the applicant to ensure that all P-NCA receive identical information.

6.2.1 VHP Assessment Step I (Day 1-Day 30)

- In the absence of grounds for non acceptance (GNA)/ request for further information (RFI),
  - a statement will be sent by the VHP-C to the applicant (copy to all P-NCAs), not later than day 30, stating that no GNA/RFI have been expressed by any P-NCA during the VHP assessment phase and that the P-NCAs unanimously consider the CTA (with date & version #) acceptable for this MN-CT
  - The final step, i.e. submission of a CTA in each participating MS, can then start (See Section 6.3 National step)

- In case of GNA/RFI:

- A consolidated list of GNA will be forwarded to the applicant by the VHP-C via E-mail/Eudralink on day 30 with a request for response to the GNA/RFI and/or for the revised CT documentation by E-Mail/Eudralink by day 40 at the latest
- If the applicant decides to proceed, the VHP assessment step II starts on receipt of the responses together with a revised CT documentation by the VHP-C.
- The VHP file will be closed with a notice to the applicant and the P-NCAs if no response from the applicant is received within the allotted time

6.2.2 VHP Assessment Step II (Day 40-Day 60)

The applicant's response document is immediately dispatched by the VHP-C to all P-NCAs for review. After a 7-day period, the VHP-C compiles the P-NCAs assessments.

➢ If consensus is achieved, i.e. the revised version of the CTA is considered approvable by all P-NCAs on day 50, the VHP-C sends to the applicant a statement by electronic mail (copy to all P-NCAs), mentioning that all GNA/RFI have been resolved and that the P-NCAs unanimously consider the revised CTA (with date & version #) as approvable.
The final step, i.e. submission of a CTA at each participating NCA, can start (See Section 6.3 National step).
➢ If no consensus is among the P-NCAs a teleconference will be organised (between day 50 and day 57), during which all P-NCAs are invited to express their views and possible solutions to the remaining issues so that a final decision can be given at the end of the meeting:
- Unanimous decision of the MS that the revised version of the CTA is approvable: an electronic letter to the applicant will be sent on day 60, mentioning that all GNA/RFI have been resolved and that the P-NCAs unanimously consider the re-

vised CTA (with date & version #) as approvable. Comments to facilitate the national submission in the MS might be added. The final step, i.e. submission of a CTA in each participating MS can start (See Section 6.3 National step).

- Unanimous decision of the MS that the revised version of the CTA is not approvable: an electronic letter will be sent to the applicant on day 60 with the remaining GNAs and proposed solutions for national submissions or a VHP-resubmission. Comments to facilitate national submissions in the MS or a VHP-resubmission might be added (See Section 6.3 National step).
- In the case that not all P-NCA agree, that all GNA/RFI have been resolved, the open points and the names of MS, which consider GNA/RFI as unsolved, will be forwarded to the applicant. Also the list of MS, which consider all GNA/RFI as resolved, will be forwarded. The open points have to be resolved before or in the national procedure, the timelines for the submission of the CTA (20 days, see Section 6.3) and the approval by the NCA (10 days, see Section 6.3) do not apply for the MS with unsolved GNA.

6.3 "National step" Formal CTA

The acceptability statement following the VHP does not imply that the MN-CT is authorised by the P-NCAs. Once the applicant has been notified that the CTA is considered acceptable (at the end of the VHP assessment Step I or II), a CTA has to be submitted in each participating MS as outlined in the Clinical Trial Directive (2001/20/EC) and in 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 (ENTR/F2/BL D 2003. current version).*

In his covering letter for the CTA, to the NCAs the sponsor should remind the NCAs that this MN-CT has undergone the VHP and add the E-Mail with the VHP approval. Generally, no changes between the final CTA and the CTA approved during the VHP will be accepted.

However, if at the end of the VHP process, a NCA has considered GNA as unsolved or if the solutions proposed by that NCA are not acceptable for the sponsor, the sponsor may decide to skip the filing of a CTA in that MS.

Or, if the sponsor decides to apply in a MS that was initially not part of the VHP, the NCA of the new MS may accept the decisions taken in the VHP, without changes by the sponsor to the documents that have been agreed in the VHP.

Submissions of the CTA to the NCAs should not be later than 20 days after receipt of the VHP acceptability statement by the applicant.

It is agreed by the MS, that after a positive VHP a decision of the NCA should be issued within 10 days and that no scientific discussion on the agreed documents of the VHP (e.g. Protocol, IB, IMPD) will be started again.

The applicant should notify a list of the dates of authorisation of the MN-CT to the VHP-C, when available.

7 Substantial amendments

Substantial amendments (SA) of CTAs that have undergone a VHP can be submitted to the VHP-C at any time, under the condition, that the CTAs have already been approved by the P-NCAs. The date of the national approvals should be given in the cover letter together with summary information on the content of the SA.
The notification should be made in accordance with the current version 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.* The amendment form of annex 2 of the guideline should be used and appropriate documents to assess the changes of the CT should be added. To facilitate the assessment of the changes, all changed documents (e.g. IMPD, IB and Protocol) should be submitted with the changes highlighted or with a comparative table before-after. When changes are complex and affecting several parts of the document, the complete document with track changes as well as a clean copy with the final version should be submitted.
Like the documents of the original VHP, SAs should be submitted via E-Mail to the VHP-C.

7.1 Timelines of substantial amendments

The submission of SAs to the VHP-C is possible at any time. Within the 5 working days after the submission, the submitted documentation will be validated and the applicant will be notified via E-mail of any deficiencies or of the start of the VHP-SA. If the Dossier is not complete, additional information will be requested by the VHP-C and this should be submitted by the applicant within 3 days.
The result of the assessment will be communicated to the applicant within 20/35 days after a valid request. In case of a rejection, the reasons (GNA) will be sent to the applicant. GNA can not be addressed during the VHP-SA by the applicant, but a resubmission addressing the GNA with the shorter timeline for approval (20 days) is endorsed.
In case of a positive statement by the VHP-C, the applications to the P-NCA should be filed according to the national regulations within 10 days. The approval by the NCA should be issued within 7 days after the valid request (see the flow chart on VHP-SA for detailed timelines).

8 References

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal L 121, 01/05/2001. p34 – 44
- 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. ENTR/F2/BL D (2003) Rev 2 or newer versions
- Detailed guidance on the European clinical trials database (EUDRACT Database) as required by Article 11 and Article 17 of Directive 2001/20/EC, CT 5.1 Amendment describing the development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset. April 2004
- Guideline on strategies to identify and mitigate risks for first-in-man human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/294648/2007

9 Appendices

9.1 Flow-charts

9.1.1 Flow chart Voluntary Harmonisation Procedure

Phase 1	Request for VHP	
Any time	Electronic submission of request and CTA documentation to VHP-C via E-Mail/Eudralink (VHP-CTFG@VHP-CTFG.eu) Forwarding of the CTA documentation to the P-NCA	
Within 5 working days after receipt at VHP-C	Information to the applicant on the acceptance by NCAs and on the date of start (DAY 1) of the VHP phase 2 Or, Compilation of formal deficiencies of the VHP dossier, if applicable: if needed, the missing information will be requested by the VHP-C and should be submitted within 3 days	
Phase 2	VHP CTA assessment step I	
Day 1	Start of VHP	
Day 30	If no GNA or RFI: information (VHP-C) of the applicant on acceptance	End of VHP and start of phase 3 →National step
Day 30	In case of GNA and/or RFI: transfer of GNA/RFI by VHP-C to the applicant and the P-NCAs (Response has to be submitted within 10 days)	
	Day 40 – Day 50 VHP assessment step II	
Day 40	Deadline for electronic submission of additional documentation and revised CTA to VHP-C by the applicant	
Day 50	If the revised CTA is considered approvable: information (by the VHP-C) of the applicant on acceptance	End of VHP and start of Phase 3 →National step
Day 60	If a revised CTA approvable after internal discussion : - Information of the applicant by the VHP-C on acceptance	End of VHP and start of Phase 3 → National step
	Revised CTA not approvable : - End of the VHP: Letter to the applicant with details of GNAs	
	Disagreement between MS on GNAs: - List of MS that are ready to approve the CTA and list of MS with open points	
Phase 3	National step	
Within 20 days of receipt of approvability statement	Submission of the formal CTA (as agreed during the VHP with the requested changes, where applicable) to each P-NCA with the letter of decision on VHP	
Within 10 days of valid CTA[3] After P-NCA's decision	Procedure and decision according to national laws Information of the VHP-C by the applicant on the outcome of the national CTAs (with respect to the VHP decisions)	

[3] The 10 days can relate to CA decisions only. In MS where the CAs have to forward the CTA to EC or other committees different timelines for the decisions might result.

9.1.2 Flow chart VHP of substantial amendments (VHP-SA)

Phase 1	Request for VHP-SA	
Any time	Electronic submission of request and substantial amendment documentation to VHP-C via E-mail/Eudralink (VHP-CTFG@VHP-CTFG.eu) Forwarding of the SA to the P-NCA	
Within 5 working days after receipt at VHP-C	Information to the applicant on the date of start of the VHP-SA phase 2,. Or, Compilation of formal deficiencies of the VHP-SA dossier, if applicable (if needed the missing information will be requested by the VHP-C and should be submitted within 3 days)	
Phase 2	VHP-SA CTA assessment step	
Day 1	Start of the VHP for substantial amendments	
Day 20	If no GNA within the assessment of the VHP-SA were raised by the P-NCA: information (via VHP-C) of the applicant on positive decision	End of VHP SA and start of phase 3 →National step
Day 35	If GNA existed, but were resolved after internal discussion: information (via VHP-C) of the applicant on positive decision	End of VHP SA and start of phase 3 →National step
Day 35	In case of rejection: transfer of reasons (GNA) by VHP-C to the applicant and the P-NCAs.	
Phase 3	National step	
Within 10 days of receipt of approvability statement	Submission of the formal substantial amendment to every P-NCA including the letter of decision on VHP SA	
Within 7 days of valid SA[4] After P-NCA's decision	Procedure and decision on SA according to national laws Information of the VHP-C on the outcome of the national CTAs (with respect to the VHP SA decisions)	

Shorter timelines are possible for resubmissions

[4] The 7 days can relate to CA decisions only. In MS where the CAs have to forward the CTA to EC or other committees different timelines for the decisions might result.