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Collaboration in international trials

The HOVON working group decides if it wants to participate as co-sponsor in an intergroup trial or if it wants to invite a group as co-sponsor to a HOVON trial. Before a final decision is made, the HOVON Board has to be informed and approve the collaboration.

HOVON prefers to limit international collaboration to study groups only. Participation of individual sites outside the Netherlands or Belgium has to be approved by the HOVON executive board. Individual sites may participate if this is essential for the timely completion of the trial, if it is in the interest of the development of future collaboration structures or if the working group has another compelling reason to invite the site to participate.

It is the responsibility of the Principal Investigator to negotiate the distribution of responsibilities in the international trial.

The HOVON manager will review the financial aspects of the collaboration and draw up a contract to document the collaboration agreements.

Negotiating the distribution of responsibilities in international trials

When negotiating the distribution of responsibilities in an international trial, the topics listed below should always be included. The HOVON manager and the HOVON Data Center should be involved in the decision-making of the Principal Investigator, to ensure the financial and practical feasibility.

For most topics there is a HOVON preference. A preference means that any other arrangement has to be discussed with the HOVON board, HOVON manager or HOVON Data Center first to review the feasibility. Please note that preferences are valid both ways – regardless if HOVON is acting as primary sponsor or co-sponsor – unless specified otherwise.

If in an intergroup trial the co-sponsor is a study group that operates internationally, the responsibilities of that co-sponsor involve all countries where it conducts the trial.

Responsibilities are assigned to the primary sponsor or co-sponsor. The (co-) sponsor may delegate some or all of the resulting tasks to a data center or CRO.

1 Submission to Ethics Committee and Competent Authority

Discuss the arrangements for obtaining EC and CA approval for the trial and for any amendments. Discuss the arrangements for required regulatory reporting.

HOVON preference is that:

- submitting the trial and amendments for approval to the national Ethics Committee and Competent Authority according to national laws and regulations is the responsibility of the co-sponsor in each country (for international collaboration with individual sites this is the coordinating investigator).
- submitting trial reports to the national Ethics Committee and Competent Authority according to national laws and regulations is the responsibility of the co-sponsor in each country (for international collaboration with individual sites this is the coordinating investigator).
- the primary sponsor provides to the co-sponsor all documents that are required for submission to the EC and CA and that are not country specific. This includes but is not limited to:
  - Protocol
  - Product information: Investigators Brochure, IMPD or SPC

- EudraCT application form, to be adapted by co-sponsor for all items that are country specific
- EudraCT notification of amendment form, to be adapted by co-sponsor for all items that are country specific
- EudraCT notification of the end of trial form, to be adapted by co-sponsor for all items that are country specific
- Annual progress report
- Annual safety report
- End of trial report

2 Trial documents

Discuss the arrangements regarding trial documents. This includes but is not limited to:

- Protocol. HOVON preference is that the co-sponsor will use the original protocol as provided by the primary sponsor without any adaptations. The co-sponsor may write an addendum to the protocol to describe country specific trial procedures. The co-sponsor may write an addendum with a translation of the protocol in the local language. The content of any addendum has to be discussed with and approved by the primary sponsor. Any addendum to the protocol has to be submitted to the national EC and CA for approval (see also topic 1).
- Patient information letter and informed consent form (ICF). HOVON preference is that the primary sponsor provides a study template in English. The co-sponsor in each country (for international collaboration with individual sites this is the coordinating investigator) will write a country specific ICF template by translating the study template and adapting the ICF to comply with national regulations. The country specific ICF template has to be submitted to the national EC and CA for approval (see also topic 1).
- CRF. HOVON preference is that the co-sponsor will use the CRF or e-CRF provided by the primary sponsor without any adaptations (see also topic 6).

Please note that the preferences regarding protocol and CRF do not exclude the possibility that study groups contribute to the design of the protocol and CRF in an early stage of trial development.

3 Safety

Discuss the arrangements regarding SAE reporting, SAE evaluation and SUSAR reporting. For annual safety reports, see topic 1.

HOVON preference is that:

- all SAE information is stored in the database of the primary sponsor.
- in intergroup trials the co-sponsor should have access to the SAE data from patients included by their participating sites.
- all SAE information is reported on the SAE form provided by the primary sponsor.
- sites report any SAE directly to the primary sponsor.
- any correspondence regarding an SAE report (including queries and answers) is handled directly between the primary sponsor and the sites.
- evaluation of reported SAEs is the responsibility of the primary sponsor.
- it is the responsibility of the primary sponsor to create a SUSAR report from any SAE that is evaluated to be a SUSAR; this report should be in an internationally accepted format, i.e. CIOMS form.

- it is the responsibility of the primary sponsor to provide SUSAR reports to all co-sponsors.
- it is the responsibility of the primary sponsor to submit SUSAR reports to all Competent Authorities and Health Authorities according to applicable national laws and regulations.
- it is the responsibility of the co-sponsor (for international collaboration with individual sites this is the coordinating investigator) to submit SUSAR reports to the national Ethics Committee.
- it is the responsibility of the co-sponsor (for international collaboration with individual sites this is the coordinating investigator) to submit SAE reports or line listings to the national Ethics Committee if this is required by national laws and regulations.
- for intergroup trials the co-sponsor will send SUSAR reports to the participating sites in their country.

4 Monitoring

Discuss the requirements and arrangements regarding monitoring of the trial.

HOVON preference is that:

- HOVON will only arrange for monitoring visits to HOVON sites located in the Netherlands and Belgium.
- the quality of trial conduct in HOVON sites located in the Netherlands and Belgium is monitored by means of Site Evaluation Visits. Arranging study specific monitoring visits is only possible after permission by the HOVON board.
- for international trials where HOVON acts as primary sponsor the responsibility for monitoring the trial lies with the co-sponsor (for international collaboration with individual sites this is the coordinating investigator). Monitoring by the co-sponsor should be performed according to the monitoring plan provided by HOVON.

5 Randomization

For intergroup trials, discuss the procedure for including and randomizing patients in the trial.

HOVON preference is that:

- all patients are enrolled in the enrolment system of the party holding the clinical database, usually the primary sponsor.
- in intergroup trials the co-sponsor should have access to the enrolment data from patients included by its participating sites.

6 Data collection and data management

Discuss the arrangements for data collection and data management in the trial.

HOVON preference is that:

- all data from the trial are stored in the database of the primary sponsor.
- in intergroup trials the co-sponsor should have access to the data from patients included by the participating sites from its group.
- all data are reported on the case report form (CRF or e-CRF) provided by the primary sponsor.
- sites send the (paper) CRF directly to the primary sponsor.

- any correspondence regarding the CRF data (including queries and answers) is handled directly between the primary sponsor and the sites.
- evaluation and cleaning of reported data (central data management) is the responsibility of the primary sponsor.
- the primary sponsor should provide to the co-sponsor a report on the status of data collection at least twice a year.

7 Study drug

Discuss the arrangements for supply and distribution to the sites of study drug. Take into consideration that different countries may have different legal requirements for issues such as importing study drug from another country and labeling.

HOVON preference is that the co-sponsor arranges the distribution of study drug to their sites directly with the national representative of the involved pharmaceutical company and informs the primary sponsor of the agreements that are made.

8 Site initiation and site management

Before a site can include patients, a set of site documents has to be collected. Each trial has a specific set of documents, which includes items such as a local approval and a signed protocol signature page. There may be other requirements before a site can start, for example a completed site initiation visit. During the trial information has to be exchanged with the sites and updated documents collected.

In an intergroup trial, it has to be clear who will be responsible for:

- Collecting the site documents
- Filing the site documents during and after the trial
- Tracking if all requirements for site initiation are fulfilled
- Deciding when the site is allowed to start
- Collecting new versions of site documents during the trial
- Informing the sites about trial issues during the trial
- Answering questions from the site during the trial

HOVON preference is that the co-sponsor is responsible for all site initiation and site management activities for their sites. Site documents may be sent to the primary sponsor for archiving after the end of trial.

9 Legal and finance

Always discuss the arrangements regarding the trial insurance according to national laws and regulations. Also discuss any other legal and financial issues.

10 Trial specific issues

Discuss any arrangements for trial specific issues. For example central reviews (cytogenetics, imaging results), quality of life survey, side studies, central lab procedures, etc.

Summary for international collaboration with sites from Belgium in trials where HOVON acts as primary sponsor.

HOVON will by default take on all sponsor responsibilities for Belgian sites similar to Dutch sites, with the exception of:

- Country specific ICF (topic 2)
- SUSAR and SAE reporting to national Ethics Committee (topic 3)

Summary for international collaboration with individual sites in trials where HOVON acts as primary sponsor.

HOVON will by default take on all sponsor responsibilities for such sites similar to Dutch sites, with the exception of:

- National EC/CA submissions and reporting (topic 1)
- Country specific ICF (topic 2)
- SUSAR and SAE reporting to national Ethics Committee (topic 3)
- Monitoring (topic 4)