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Installing a DSMB

An independent Data Safety and Monitoring Board (DSMB) should be installed for all HOVON trials where HOVON is the primary sponsor.

If the relevant working group has valid arguments why installing a DSMB is not necessary given the design of the trial, the HOVON Board will review their proposal and decide whether this can be accepted. In such cases, the protocol should always contain clear and specific stopping rules.

During a randomized trial none of the participants, including the Principal Investigator and co-investigators, should be informed of the interim results split by arm. The DSMB protects trial participants from bias by knowledge of the interim results.

In both randomized and non-randomized trials there may be a concern of conflicting interests when difficult decisions about the continuation of a trial have to be made by the investigators participating in that trial. This can be avoided by an independent review of the interim results by a DSMB.

The content of this policy only applies to trials where HOVON acts as primary sponsor. However, if HOVON wishes to participate as co-sponsor in an intergroup trial, the relevant working group should take into consideration if the primary sponsor has made satisfactory arrangements to ensure the safety and validity of the trial such as installing a DSMB.

Criteria for the constitution of the DSMB

A DSMB consists of at least three members, with at least one statistician and two physicians.

The members of a DSMB are invited on personal title on the basis of their expert knowledge of the disease involved or the research methodology. Members of a DSMB should have ample experience with (randomized) clinical trials.

The members of a DSMB may not be involved in the trial, work at the HOVON Data Center, be a member of the HOVON board, or work in a hospital department participating in the trial.

The members may not have a conflict of interests due to ties with a company involved in the trial.

The members should agree to keep all trial information confidential.

Persons can be members of various DSMB's, especially for related and/or successive trials.

Distribution of responsibilities when installing a DSMB

The Principal Investigator of a trial should ensure that the DSMB is installed before the start of the trial and that relevant information regarding the DSMB is included in the protocol.

The working group will select and invite candidates to become a member of the DSMB. This task may be delegated to the Principal Investigator.

Once the DSMB members have been selected, the Principal Investigator will provide their names and contact details to the Trial Manager.

Candidate members will receive from the Trial Manager the protocol of the trial and the DSMB charter. The Trial Manager will assist the Principal Investigator in preparing the DSMB charter.

The charter should contain a declaration of the tasks required of the DSMB members for the trial, which should be based on this policy document and trial specific DSMB tasks described in the protocol.

Candidate members will be asked to sign the DSMB declaration of membership form provided to them if they accept DSMB membership and have no conflict of interests.

The DSMB elects a chairman from among its members and informs the Trial Manager of the person elected as DSMB chair.

Once the candidate members have agreed to join the DSMB by returning the signed DSMB declaration of membership form, they will receive from the Trial Manager a formal letter of appointment by the HOVON Board.

The Trial Manager ensures that all documents and correspondence regarding the DSMB installment are filed in the Trial Master File at the HOVON Data Center.

Task of the DSMB

The DSMB will advise the Principal Investigator, co-investigators and the chair of the working group in writing about the continuation of the trial.

The DSMB will review the general progress and feasibility of the trial, the quality and completeness of the data, adverse events and safety, and differences in results between the arms of a randomized trial. The DSMB will consider if there is any concern regarding the safety and well-being of trial subjects or regarding the scientific validity of the trial results.

The DSMB will base her advice on the reports provided by the statistician. The DSMB is free to take into consideration external information, such as the (interim) results of other trials or literature reports.

Scheduled interim analyses and stopping rules

The protocol of a randomized trial states the intended frequency and the endpoints of interim analyses. It also contains stopping rules, taking into account the sequential character of the interim analyses.

These stopping rules serve primarily as guidelines to the DSMB. As all possible events that may cause closure or modification of a trial cannot be listed in advance, the DSMB is free to deviate from these guidelines. The statistician in the DSMB shall see to it that the relevant statistical aspects are adequately taken into account in the DSMB's recommendations.

Unscheduled interim analyses

Trial data are reviewed on an ongoing basis by the central data manager and statistician and in case of SAE reports, also by the Principal Investigator. This may give rise to a concern about the results of the trial, for example if there appear to be more deaths or SAE’s in the experimental arm of the trial. Such concern may be a cause for an additional unscheduled interim analysis. The conditions for an additional interim analysis should be stated in the protocol or in the statistical analysis plan of the trial.

Reports provided to the DSMB

The type and frequency of reports to be provided to the DSMB should be described in the protocol.

These reports are made by the trial statistician and are unblinded with respect to study arm in case of a randomized trial.

The DSMB will always review the reports of the scheduled and unscheduled interim analyses.

If the scheduled interim analyses occur less frequently than once a year, the DSMB will also review at least annually a report with tabulated safety data (Adverse Events, Serious Adverse Events and SUSARs) and tabulated progress data (such as number of patients enrolled, number of patients off treatment categorized by reason, data collection status).

The advice of the DSMB will be included in the annual safety and progress reports to the Ethics Committees.

The protocol should also state up to which time point these reports will continue, e.g. until all patients have ended protocol treatment or until all patients have reached the phase of (low risk) maintenance treatment.

The statistician makes a concept for the contents and structure of the reports well in advance of the first DSMB meeting and presents this concept, without actual data, to the DSMB for review. The DSMB may request to include additional tables and diagrams in the report or to adjust the presentation or structure of the report.

In the confidential part of their advice the DSMB may recommend the statistician to make an adjustment in the next report.

DSMB meetings

The Trial Manager of the trial will inform the DSMB well in advance of the time points when the interim reports will become available and request the DSMB to schedule their meetings accordingly.

The interim reports shall be forwarded by the statistician to the DSMB's members at least seven days before a scheduled meeting of the DSMB. All information supplied to the DSMB is strictly confidential.

In addition to the preplanned meetings additional ad hoc meetings are possible if interim results require such a meeting or on request of the DSMB. The DSMB may request additional data to be collected or additional analyses to be performed, which will be discussed in an additional meeting.

Meeting support

Meetings will be held in the form of teleconferences, unless the interim results give the DSMB members reason to discuss the matter face-to-face.

The DSMB chair may request the Trial Manager to provide assistance in arranging the meeting facilities.

Presence of DSMB members, statistician and Principal Investigator

Preferably all DSMB members should be present at each DSMB meeting. If circumstances prevent this at least one statistician and one physician member should be present and the other members should provide their opinion to the DSMB chair in writing prior to the meeting. If in that case the DSMB members present determine there is cause to make changes to the trial, a new meeting with the complete DSMB should be scheduled as soon as possible.

At the start of meetings of a DSMB, the Principal Investigator and co-investigators may be present to present specific questions and points of special interest or concern to the DSMB. The statistician is present to clarify the interim report and to answer questions from the DSMB.

The investigators have to leave before the DSMB discuss any confidential information. On the DSMB's request, the statistician may remain present during the entire meeting.

Recording meeting minutes and results

The DSMB chair will ensure that meeting minutes are made at each meeting.

The DSMB will compose a formal written advice based on the meeting outcome. The DSMB advice consists of a public part, intended for the Principal Investigator, co-investigators and the chair of the working group, and optionally a confidential part intended for the study statistician.

The confidential part intended for the statistician may contain recommendations for additional analyses or methods of reporting. This part may contain unblinded study-arm-specific information.

The public part contains recommendations in general terms. These recommendations are to be formulated without any unblinding. The public part may refer to the confidential part.

Each written advice will be dated and signed by the chairman of the DSMB and sent or given to the trial statistician. The statistician will immediately forward the public part of the written advice to the Principal Investigator, co-investigators, the chair of the working group and the Trial Manager.

Filing records of DSMB meetings

A copy of the reports provided to the DSMB, the DSMB meeting minutes and the confidential part of the DSMB advice should be filed and kept confidential by the trial statistician until the end of the trial and then transferred to the Trial Master File before archiving.

The public part of the DSMB advice is filed in the Trial Master File.

Follow up of DSMB recommendations

The DSMB may make any recommendations they deem necessary to protect the safety and well-being of trial subjects or safeguard the scientific validity of the trial results.

This may include but is not limited to changes in the trial design or treatment or test schedule, changes in the data collection and analysis plan and even prematurely terminating the trial or a treatment arm of the trial.

The Principal Investigator, co-investigators and chair of the working group will inform the DSMB and the HOVON Board in writing to what extent the recommendations will be followed.

If the advice leads to premature termination of the trial or a treatment arm, the HOVON Policy “Premature termination of a trial or investigational site” applies.

The recommendations of the DSMB are not binding. However, the Principal Investigator, co-investigators and chair of the working group should provide a written motivation to the DSMB members and the HOVON board if they decide to deviate from the DSMB recommendations. The HOVON board has to approve the deviation.

A copy of the correspondence should be sent to the statistician and Trial Manager to be filed in the Trial Master File.

Informing investigators and ethics committees

The participants of a trial will be informed in writing of the public advice of the DSMB and the resulting corrective actions regarding the continuation of the trial (if applicable). This is the responsibility of the Principal Investigator in cooperation with the Trial Manager.

The DSMB advice and resulting corrective actions should be included in the Annual Safety Report for the Competent Authorities and Ethics Committees.

If the DSMB advice leads to changes in the trial or if the advice arrives shortly after an ASR was sent, the Ethics Committee should be informed in writing without delay. This is the responsibility of the Principal Investigator in cooperation with the Trial Manager.

Data and safety monitoring in absence of a DSMB

If no DSMB is installed, the results of the interim analyses and any points of concern regarding the trial should be discussed with the HOVON board.

This discussion should be recorded in the meeting minutes. A copy of these minutes should be sent by the Principal Investigator to the Trial Manager for filing in the Trial Master File.