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Adaptation of previous policy "Duration of follow up"

Data collection in HOVON trials

During a HOVON trial data are collected for the following purposes:

- To enable statistical analysis of the trial endpoints
- To monitor the safety of the trial
- To monitor the conduct of the trial

Only relevant data should be collected. The collection of redundant data should be avoided.

The Principal Investigator should discuss with the trial statistician what are the most appropriate and efficient endpoints for the trial and which data are needed for those endpoints.

Collecting additional data for the purpose of exploratory analyses and/or meta analyses should be limited to the most relevant data and should not involve data available from other sources such as registries.

The trial protocol should make a distinction between procedures required to generate trial data and procedures required for adequate patient care only. Where possible, procedures for patient care only should be described in the protocol as “according to local policy” or “recommended”. This will limit the occurrence of unnecessary protocol deviations.

Priorities in data cleaning

Limiting data collection to essential data will also limit the number of queries.

In addition, the Principal Investigator together with the trial statistician and the data center team should establish priorities for data cleaning. The effort spent to retrieve missing data or resolve discrepancies should be in proportion to the importance of the data.

The following priorities are a general guideline:

Data directly related to primary and secondary endpoints and the incidence of serious or severe (grade 3 - 4) adverse events should have priority 1. Queries should be raised until all discrepancies are resolved or it is clear beyond doubt that correct data can not be retrieved.

Other safety data should have priority 2. If a query on these data does not provide a satisfactory solution, a re-query may be raised up to two times until the issue is closed as unresolvable.

Data on protocol compliance have priority 3. In case of an unsatisfactory query answer, it may be re-queried only once.

Any additional data, if collected at all, should not be queried.

Duration of follow up in HOVON trials

For all HOVON trials the duration of follow up data collection should be specified in the protocol.

The maximum duration of a trial insurance policy is set at 8 years. Therefore maintenance treatment or follow up visits with study specific tests should be limited to a maximum of 8 years after start of the trial (see paragraph “Relationship between follow up and maintenance treatment duration and trial insurance” for details) This limitation does not apply to the collection of observational follow up data.

In addition to the limitations of the insurance, the maximum allowed follow up duration for individual trial patients is as follows:

- Phase I trials: up to 6 months after the last protocol treatment received by the patient
- Phase II trials: up to 5 years after the date of enrolment of the patient
- Phase III trials: up to 10 years after the date of enrolment of the patient

If the Principal Investigator wishes to have a longer follow up duration in the protocol, this should be discussed with and approved by the HOVON executive board.

No approval is required to include a shorter follow up duration in the protocol.

If a trial or treatment arm is terminated prematurely, the Principal Investigator and the trial statistician should determine which data still need to be collected. Usually there will be no need to collect post-treatment follow up data. Also see the HOVON policy “Premature termination of a trial or investigational site”.

Considerations regarding follow up duration and data collection

It is advised to limit the duration of follow up to the interval needed to perform the analyses as described in the protocol. This may for example include an analysis of long-term effects at 10 years after start of treatment. Collecting follow up data that will never be used for analysis and publication would be a waste of resources.

It is advised to limit the data collected during follow up to those data needed to perform the analyses as described in the protocol. If for example the planned analysis of long-term effects after 5 years will be limited to overall survival, it is not necessary to collect detailed information on remission status.

Please be aware that if the protocol prescribes a specific frequency of follow up visits and specific tests that need to be performed at follow up visits, any deviation from this schedule by the local investigator is a protocol deviation. Consider if the planned analysis of the follow up data actually require such a strict schedule. It may be sufficient to collect “observational” data of follow up visits that are performed by the site according to their local regular care policy. It could also be an option to define a strict follow up schedule for a limited time which is then followed by observational “long-term follow up visits” for the remainder of the follow up duration. The strict follow up schedule could for example be limited to the follow up interval that will be included in the primary endpoint analysis, which is usually 1 year of follow up.

Considerations regarding the duration of maintenance treatment on protocol

Please be aware that if the protocol prescribes the continued use of maintenance treatment until disease progression as part of the protocol treatment schedule, some patients may remain on protocol for a very long time, even exceeding the specified duration of follow up data collection. After a certain amount of time, data from maintenance treatment will no longer be relevant for the trial endpoints since there will be no more analyses of maintenance data.

When designing the trial, consider up to which time point maintenance treatment is relevant for the trial objectives and endpoints. After that point, it could be an option to end maintenance treatment as part of the protocol treatment schedule: continuation of treatment is no longer obligatory and no more detailed maintenance data is collected, only follow up data.

From an ethical standpoint it may be necessary that provisions are made and described in the protocol that allow patients that benefit from the treatment to continue after the end of the protocol treatment schedule. This depends on the nature of the disease, the patient population and the treatment used in the trial and should be decided by the Principal Investigator. In such a case, continued availability needs to be ensured for medication without a marketing authorization or medication that is not reimbursed by healthcare insurance. An arrangement could be made for continued delivery to the hospital by the manufacturer, on “named patient” basis for medication without a marketing authorization.

From a safety standpoint, the protocol should then include the advice to report any serious adverse reactions to the medication occurring after the end of protocol treatment to the manufacturer similar to regular care procedures. The manufacturer can then handle the event as a spontaneous product safety report according to their standard procedures.

Relationship between follow up and maintenance treatment duration and "end of trial"

All HOVON trials should apply the default definition of "end of trial" as the time when the last patient has finished the last patient visit. This means that "end of trial" is reached after the last follow up visit. For a trial with an indefinite duration of maintenance treatment according to the protocol treatment schedule, "end of trial" is reached after the last follow up visit or after the end of maintenance treatment of the last patient, whichever comes last.

"End of trial" signals the end of the administrative and regulatory reporting requirements. The trial can be shut down and archived. Limiting the duration of maintenance as protocol treatment and the duration of follow up to the interval needed to perform the planned analyses and meet the study objectives, will avoid wasting valuable resources on trial activities that do not yield any meaningful study results.

Relationship between follow up and maintenance treatment duration and trial insurance

Any procedure or treatment that is different in nature or frequency from regular patient care may cause harm to the patient that is considered related to trial participation. This means maintenance treatment as part of the protocol schedule and any non-standard procedure during follow up (including increased frequency of standard tests) needs to be covered by the trial insurance policy. If this is not covered by trial insurance, HOVON as sponsor would be liable for such claims.

The maximum duration of a trial insurance policy is set at 8 years.

Therefore the duration of maintenance treatment on protocol and the duration of follow up visits that are different from regular care should be limited to a maximum of 8 years after start of the trial. This is of specific importance for phase III trials.

Continuation of medication after the trial and observational follow up visits according to local policy do not require coverage by the trial insurance policy.

Both the protocol and the patient information letter should make a distinction between maintenance treatment on and off protocol and non-standard versus observational follow up visits. The patient information letter should indicate at which point coverage of the trial insurance ends.

Summary of general recommendations

For each trial careful consideration is required which data should be generated and collected.

The scientific relevance of the data should be weighed against the practical consequences.

The protocol and CRF of a previous trial may serve as a helpful starting point, but should not be copied without thoroughly reviewing if all items fit the specific purpose of the new trial.