Title:	**Risk based quality management of clinical trials**	
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Scope of this policy

The requirements in this policy apply to clinical trials that are a HOVON trial and for which HOVON is the primary sponsor.

It is applicable prospectively for each trial that is approved as a HOVON trial by the executive board and assigned a HOVON trial number after the effective date of this policy, 01 September 2016.

Mandatory Quality Risk Management Plan

For each trial as defined in the scope of this policy, a Quality Risk Management Plan (QRMP) is mandatory. It is also mandatory to apply the risk mitigation strategies from the QRMP in the execution of the trial.

A draft version of the QRMP needs to be included by the Principal Investigator in the review of a new trial by the HOVON executive board, as described in the HOVON Guideline for Initiating a HOVON trial. This is required to ensure that the PI is aware of the need to perform a risk assessment and to demonstrate that risk factors have been taken into account during the design of the trial.

The first version of the QRMP needs to be final prior to inclusion of the first patient in the trial.

It is the responsibility of the Principal Investigator to ensure that the QRMP for the trial is finalized before inclusion of the first patient in the trial, and that risk mitigation strategies are implemented in the trial.

The final first version of the QRMP for new trials needs to be reviewed by the HOVON Protocol Uitvoerbaarheids Commissie (PUC).

Risk mitigation strategies from the QRMP need to be implemented before the trial activity they are related to can start. For the most part this means that the risk mitigation strategies also need to be implemented prior to inclusion of the first patient in the trial.

Principles of risk based quality management

Risk based quality management can be viewed as an analogy to targeted therapy in the treatment of oncology patients: instead of treating every trial with the same set of measures to monitor and safeguard the quality of the trial, you apply measures that are specific to the properties of an individual trial.

To be able to effectively apply risk based quality management, you first need to analyze the trial to identify the correct targets. In other words, a risk assessment. Once you have identified what can go wrong in the trial and why, you can choose an effective method to mitigate those specific risks. This is something you probably already do subconsciously when designing a trial.

What is new with the implementation of this policy, is that risk assessment and risk mitigation is transformed into a structured process that is documented.

The benefit of a structured process is to decrease the risk of “blind spots”. It requires you to make conscious decisions and by documenting those decisions they can be reviewed and reproduced.

Risk assessment and risk mitigation measures influence the planning and organization of a trial. This means that it will also influence the trial budget. That is why the risk assessment needs to start at a very early stage of trial design.

Process outline of applied risk based quality management

The HOVON Template for Quality Risk Management Plan will be used to write the QRMP. Use the template for guidance and documentation of the process.

1. Identify the risks
   Review all aspects of the trial with a multi-disciplinary team. The team should consist of at least the Principal Investigator and the trial manager. It is advised to include a central data manager and a monitor, and if necessary consult other specialists on specific topics, such as a statistician, ICT, safety, local site management. Always involve the HDC quality manager in the process.
   Ask yourself the questions, what is different in this trial compared to a "common" HOVON trial? What could go wrong in this trial because of that?
   A "common" HOVON trial is defined by the following characteristics:
   - It is a phase II or phase III open label trial (no blinding/placebo)
   - It concerns a familiar diagnosis that has been the subject of HOVON trials before
   - Only patients 18 years and older are included, able to give consent for themselves
   - The trial uses a single ICF plus one optional pre-study ICF
   - The protocol combines a "background" treatment that is standard therapy, with a new IMP, as a combination treatment or as maintenance. In a randomized trial the control arm is standard therapy.
   - The IMP in the trial is a marketed product, or an SCT protocol that has been used before
   - Only sites from the Netherlands, Belgium and Luxembourg participate, or,
   - Sites from other countries participate under affiliation of a familiar co-sponsor such as SAKK or Nordic group
   - All operational tasks are delegated to the HOVON Data Center (TM, CDM, Safety Desk), as well as statistics

2. Weigh the risks
   For each risk that you have identified, ask yourself two questions:
   What is the probability that this will happen?
   If it happens, how much will it affect patient safety or the validity of the trial results?
   The combination of these two factors determines the weight of the risk. This step is done with the same team as step 1.

3. Decide how to handle the risks
   This step can be done in the "core" team, consisting of the Principal Investigator and the trial manager. Always involve the HDC quality manager in the process.
   Depending on the weight of the risk, decide if and how you will mitigate the risk.

4. Implementation and execution
   Steps 1 to 3 result in the Quality Risk Management Plan. The risk mitigation activities described in the QRMP now need to be implemented in the planning and organization of the trial by the trial team, and executed accordingly. The risk mitigation activities become an integral part of the design and management of the trial.
   The implementation is recorded in a manner that is appropriate for each activity, in trial documents that are part of the Trial Master File. For example in the protocol, data management plan, statistical analysis plan, monitoring plan, study manuals, DSMB charter.
   The execution of activities is also recorded in the appropriate trial documents or systems. For example monitor visit reports, study reports, trial database, correspondence.

5. Evaluation and adaptation
   The QRMP is not a one-off document. During the course of a trial it may be necessary to

re-assess the risks and adapt the risk mitigation activities accordingly, leading to a new version of the QRMP.
An obvious reason is a substantial amendment, which will always require a review of the QRMP to determine if it is still valid. Also, the accumulation of information from monitoring activities may lead to new insights in the probability of certain risks.

PUC review of QRMP

As outlined before, the HOVON Protocol Uitvoerbaarheids Commissie (PUC) needs to review the first version of the QRMP of new trials.

The PUC needs to receive the current trial protocol, CRF, ICF and study manuals prior to or at the same time as the QRMP.

The purpose of the review is to assess if risks have been missed, to assess if the weight of the risks is realistic and to assess if proposed risk mitigation strategies are feasible and likely to be effective in practice.

It is mandatory for the Principal Investigator to include in the QRMP any additional risks identified by the PUC.

Comments on the weight of risks and on risk mitigation strategies are to be considered an advice by the PUC. The Principal Investigator may decide not to follow this advice. The rationale for this decision needs to be recorded in the Trial Master File.