HDC ALERT

Subject	**Eligibility in HOVON trials**
Date	10 November 2020
Ref. Nr.	HDC_ALERT2020-4

Dear HOVON PIs and Site Principal Investigators,

Recently there have been some issues and debate about eligibility of patients for a trial, specifically in situations where there seems to be a discrepancy between the protocol criteria and regular medical practice. With this ALERT HOVON will clarify their policy on this point and provide best practice guidelines for both Site PIs participating in HOVON trials and Principal Investigators initiating HOVON trials.

Regulations on the matter of eligibility are very clear. Patients that do not meet the eligibility criteria specified in the protocol cannot be included in a trial.

HOVON will adhere to the regulations and does not accept any exceptions on the protocol eligibility criteria.

In some cases the protocol criteria may seem to be unnecessarily restrictive compared to regular practice. But even if the site PI has discussed the situation with the Principal Investigator and the Principal Investigator agrees with the arguments of the site PI, the patient *cannot be included* as an exception at that time. The protocol criteria should first be amended and approved by the Ethics Committee before any patient can be included according to the new criteria.

Why is it so important to strictly adhere to the eligibility criteria?

The purpose of eligibility criteria is to ensure the safety of patients participating in the trial, as well as to ensure that only patients are included from the population the trial was designed for.

Bypassing the eligibility criteria will risk the safety of the patient.

Also, the Ethics Committee has approved the trial as ethically acceptable to be performed as described in the protocol. Performing the trial in patients that do not fulfill the protocol eligibility criteria has not been approved. Performing a trial without approval of an Ethics Committee is a violation of laws and regulations.

This means that if the patient comes to harm this may have serious liability consequences for the involved site PI.

Furthermore, inclusion of multiple ineligible patients will risk the outcome of the trial. Ineligible patients are excluded from analysis and may cause an underpowered study. If undetected, the presence of patients with characteristics the trial was not designed for will muddle the data and possibly lead to wrong conclusions about the effect of the treatment in the population the trial was actually intended for.

What are best practice guidelines regarding eligibility criteria for Site PIs?

Site PIs should not include patients that do not fulfill all eligibility criteria.

Participating investigators should personally review if a patient fulfills the eligibility criteria. If the actual administrative enrolment of patients is delegated to supporting trial staff, a local procedure should be implemented that ensures that only patients are included with a documented confirmation of the responsible Site PI that the patient fulfills the eligibility criteria. For example a signed and dated checklist that is handed to the research nurse and filed in the Investigator File after inclusion.

Participating Site PIs should ensure that the source documents (medical file) are complete so that there is proof that all eligibility criteria were met at the time of enrolment. This includes test results and notes of reviews and discussions with other investigators.

If a patient is not eligible due to a single lab value that is marginally out of range and it is not necessary to start treatment immediately, repeat the test to see whether it returns to an acceptable value. The same goes for lab values that are not within the timeframe as indicated in the protocol. Check if the patient is interested in participating and willing to repeat the test. If the repeated test is within range / within the time frame of the eligibility criteria, the patient can then be included. Document this process in the patient medical file.

What are best practice guidelines regarding eligibility criteria for PIs?

If a site PI consults the Principal Investigator about an issue of eligibility, the PI should not endorse that the Site PI includes the patient if it is not entirely clear that the patient fulfills all eligibility criteria.

Principal Investigators should take careful consideration when writing the eligibility criteria for a trial. The criteria have to be clear and precise. The criteria have to be in balance with regular medical practice and with the specific risks of the trial, and not unnecessarily restrictive.

For example: consider if you really want to exclude all patients with an ASAT value of > 2 x ULN, so that a value of 2.05 x ULN means the patient is not eligible, or that you just want to

exclude patients with clinically confirmed liver dysfunction and require further tests to check this if ASAT is > 2 x ULN. Same goes for time frames stipulated in the protocol. Do you really want to exclude patients that had their bone marrow taken 22 days ago, while the protocol indicates that the bone marrow should not be older than 3 weeks.

If an eligibility criterion is only applicable in specific circumstances, this should be clearly specified in the protocol.

For example: liver dysfunction is an exclusion criterion *unless* it is attributable to the disease under study.

If this assessment is difficult, the protocol may further specify a description of tests that have to be done to rule out another cause for the liver dysfunction. It may also include the requirement to consult the PI to confirm that the dysfunction can indeed be attributed to the disease under study. The tests and/or the discussion with the PI should be documented in the medical file.

Thank you for your attention and please do not hesitate to contact us in case of questions!

Kind regards,

HOVON Data Center (HDC)

hdc@erasmusmc.nl