Requirements (re)start clinical trials, including clinical trials in CRUs

Due to the COVID-19 pandemic and the restrictive measures in force as defined by the Dutch Government to control the pandemic, all clinical trials are put on hold, except COVID-19 related trials or trials concerning severe diseases for which no satisfactory treatment is available. Considerations and decisions for clinical trials which were either put on hold or allowed to continue, should subsequently have been documented as part of a risk analysis (benefit-risk) and archived in the investigator site file (ISF).

The European Guidance "Management of clinical trials during the COVID-19 (Coronavirus) pandemic" and the corresponding documents of the Health and Youth Care Inspectorate (IGJ) and the Central Committee on Research Involving Human Subjects (CCMO) are still in full force. The Dutch Government frequently evaluates the current situation and announces, under conditions, relaxing measures.

In case of any unexpected increase of the spread of the virus, previous decisions leading to relaxing measures can be revoked. In that case all considerations and the steps to be taken at that time should be documented. During an inspection the policy of the health care institution, the considerations and decisions (in accordance with legislation and regulations in force and the situation in the health care institutions at that moment) should be verifiable.

Based on the latest relaxing measures by the Government and the (slowly) restarting of regular care, the IGJ and CCMO see, in advance of European decisions thereon, opportunities for the (re)start of clinical trials, including clinical trials in clinical research units (CRUs).

In collaboration with the CCMO and with input from relevant stakeholders[1]) the requirements below were formulated for the (re)start for clinical trials that were put on hold.

- The research location/institution in charge of the (re)start of clinical trials, based on the institutional policy.

- De principal investigator (PI) revised and evaluated, whether or not in collaboration with the head of the department, the study-specific risk analysis and documented the process (in the ISF).

- Upon (re)starting a clinical trial, the burden for supportive services and the regular patients flow should be taken into account; the basic principle is that this will not or hardly lead to any extra patient movements. In addition, the consequences of potential downscaling (again) due to a (local) increase of COVID-19 infections should be considered

- The rights, safety and wellbeing of trial participants, other patients and staff at the research location/institution should prevail.

- The (re)start of a clinical trial should be approved by the management (e.g. care group manager, head of department or other authorised person or (temporary) structure/group (e.g. COVID-19 team)).

- At the institutional level an (overall) risk analysis should be conducted and evaluated, in order to demonstrate central oversight of the impact on ongoing and new to start clinical trials. A positive outcome of the evaluation of this risk analysis is a prerequisite for a possible (re)start of a clinical trial or a group of clinical trials. In case of consecutively (re)starting clinical trials, the new situation (of already restarted trials) should be the starting point.

- To ensure central oversight, the board of directors of the health care or research institution, or another body mandated to do so, should approve in writing the (re)start of clinical trials,

[1] NFU, NVMETC, NVZ, STZ

taking into account that continuity of regular care in the health care institution is ensured and interference with the necessary care for COVID-19 patients is avoided. This is should not be a new local feasibility analysis.

- The (re)start of a clinical trial **without** substantial changes[2] compared to a previously approved research dossier, should be sent in as a notification to the medical research ethics committee (MREC) and the competent authority (in case of clinical research with medicinal products).

- The (re)start of a clinical trial that **does** involve substantial changes[2] to the research dossier (i.e. amendments), should be submitted, following the procedure in force, for review and approval by the MREC and the competent authority (in case of clinical research with medicinal products).

- The study-specific risk analysis should in both above cases (notification or submitting a substantial change (= amendment) be part of the package provided to the MREC.

Note: The (re)start of clinical trials does not automatically imply the restart of monitoring. Also for monitoring visits, there should be no/hardly any extra "movements" in the health care institution. In the exceptional case where an on-site monitoring visit is considered crucial, such visit should not interfere with patient care. The health care institution/department defines (and documents) the extent to which monitoring can be restarted, based on the institutional policy and governmental (restrictive) measures in force at that time.

[2] Substantial changes are changes that might have a substantial effect on either the safety or the rights of the trial participants or the reliability and robustness of the research data.