➢Newsletter➢

Onderwerp: **Breaches**
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As of January 31, 2022, the regulation (EU) No. 536/2014 (Clinical Trial Regulation, CTR) applies for conducting clinical trials with drugs.
Under this regulation, HOVON as a sponsor has a primary responsibility for determining whether any breach meets the definition of a **serious breach** in a clinical trial.
With this newsletter, we would like to shed some light on the terms and abbreviations associated with serious breach reporting, as well as explain the process of serious breach reporting.

Definitions
Protocol deviation (PD): any change, divergence, or departure from the study design or procedures defined in the protocol, consent document, recruitment process, or study materials originally approved.
Serious breach: any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.
Suspected serious breach: an incident which at the time of communication from investigators or from service providers to the sponsor has not yet been assessed by the sponsor to be a serious breach.

Protocol Deviation (PD)
An important protocol deviation is not equivalent to the definition of a serious breach, and therefore an important protocol deviation is not necessarily also a serious breach and vice versa.

Nevertheless, deviations that are considered important, even if they are not classified as serious breaches, should still be documented and reported in the eCRF, as they may have an impact on the analysis of the data. However, not every (important) deviation from the protocol needs to be reported as a serious breach.

According to Good Clinical Practice (GCP), the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. Deviations that do not significantly affect the safety and/or the rights of the patient or the reliability and robustness of the data generated in the trial should be documented (in source documentation) to ensure that appropriate corrective and preventive actions to be taken.

Identifying a (suspected) serious breach
While conducting a clinical trial, even the most experienced and diligent research teams may deviate from the approved protocol or experience unexpected events. Research teams should identify, evaluate, and address these deviations and unexpected events in order to prevent them from occurring again and hence protect the rights, safety, and welfare of patients, as well as the integrity of the research data.

HOVON breach coordinators should be notified as soon as possible after an important deviation / unexpected event occurs.

NOTE: For reporting a suspected serious breach, HOVON provided a guideline which can be found on the HOVON website: https://hovon.nl/en/general-trial-info/trial-execution/serious-breaches.

HOVON serious breach assessment team
Once a suspected serious breach is reported, HOVON breach coordinators will assign an assessment team. Their role is to determine whether the suspected serious breach qualifies as serious. This involves conducting a detailed analysis of the breach, determining its severity, the root cause and, if applicable, recommending appropriate corrective and preventive actions.

A root cause analysis (RCA)
It is the responsibility of HOVON as a sponsor to thoroughly perform a root cause analysis (RCA) to identify the cause of the serious breach and to assess the impact of the breach on the reliability and robustness of the trial data, as well as the impact on a trial patient's safety and/or rights.

An RCA is the process of identifying and documenting the root cause of the issue and the downstream effect on the causal chain. An RCA will focus on identifying underlying problems that contribute to errors, rather than focusing on mistakes made by individuals. For this, HOVON uses the 7W's-method: Who, What, Where, Which (by which), Way (in what way), When and Why. This assessment will be documented in the HOVON "Breaches database" in ALEA. The final report will be uploaded in CTIS. The site will receive a copy of the final report, which must be filed in the Investigator Site File (ISF) of the study.

Corrective And Preventive Action (CAPA)
Once aware of a (suspected) serious breach, immediate **corrective actions** should be taken. The deviation must be documented, including why it occurred, and the immediate corrections taken to address the deviation or event.

Preventive actions are necessary to ensure that the problem does not reoccur. An example is to create and document a process or standard operating procedure (SOP). Then, train on the process, implement the process, evaluate the process, and amend the process as necessary.
Identify the actions taken to address the root cause, the individual (role) responsible for taking the actions, and where to document the actions.

Evaluation
It may be necessary for HOVON as a sponsor to implement preventive measures to avoid similar breaches in the future (please keep in mind to update the trial compliance procedures and/or documents). In some cases, it is necessary to implement preventive actions that are study transcending or to address systemic issues and ensure the integrity and safety of future trials. Depending on the CAPA if needed, an Effectiveness Check will follow.

Did you know that:

- *Reporting of the serious breach through the CTIS should be done by HOVON as a sponsor within **7 calendar days** of becoming aware of a serious breach?*
- *All steps in the CAPA procedure, including actions taken e.g. (re) training on current or improved processes, **need to be documented**, as the appropriateness of the decisions and actions taken by the sponsor may be examined during any process triggered by the notification of the serious breach, for example during GCP inspections?*