SOP 26a Associated Document 1 Pharmacovigilance Definitions

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Clinical Trial of an Investigational Medicinal Product Definitions

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Event of Special Interest (AESI): An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g. regulators) might also be warranted. (Based on CIOMS VI)

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Code Break/Unblinding: Code break involves unblinding a participant so that the treatment allocation is made known. This can be single (just to research team) or double (to research team and participant; be cautious not to unblind others involved in the study)

Day '0': The day the Chief Investigator (CI) (or delegated team) first becomes aware of the event. In some cases Day '0' maybe when significant new information is received by the CI on an existing event that alters the assessment.

Please note in this case the CI (or delegated team) is representing the sponsor.

Investigator's Brochure (IB): The IB is a comprehensive document that summarises the known information about an IMP. It is a compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the trial. According to ICH GCP the purpose of the IB "to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures." The IB is of critical importance throughout the drug development process and is updated with new information as it becomes available. Once the drug has a marketing authorisation in any EU member state, the summary of product characteristics (SmPC) is accepted as an adequate replacement for the IB where the drug is used according to the terms of this authorisation.

Investigational Medicinal Product (IMP): An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including products already with a marketing authorisation.

Non-Investigational Medicinal Product (NIMP): Products that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) that may be supplied to subjects participating in a trial and used in accordance with the protocol. For instance, some clinical trial protocols require the use of medicinal products such as support or rescue/escape medication for preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These medicinal products do not fall within the definition of an IMP and are called NIMPs.

Reference Safety Information (RSI): The RSI documents are used to assess the expectedness of SAEs for clinical trials. In clinical trials the RSI is documented within the summary of product characteristics (SmPC), or the investigator brochure (IB) and the protocol.

Serious Adverse Event (SAE): Any adverse event or adverse reaction that:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect.

Note: Some medical events may jeopardize the subject or may require an intervention to prevent one of the above characteristics or consequences. These should also be considered as 'serious' in accordance with the definition.

Serious Adverse Reaction (SAR): Any adverse reaction that is classed as serious in nature and where there is evidence to suggest a causal relationship between the drug and the adverse event.

Summary of Product Characteristics (SmPC): The SmPC is a document that relates to a marketed medicinal product. It contains a description of the product's properties and the conditions attached to its use. This document is important as it describes all known expected adverse reactions. The holder of the marketing authorisation of the medicinal product will routinely update the SmPC based on receipt of new information.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse reaction that is classed as serious in nature and which is not consistent with the information about the medicinal product in question. In the case of a licensed product, the summary of product characteristics (SmPC) for that product. In the case of any other investigational medicinal product, the Investigator's Brochure (IB) relating to the trial in question. Note: to fulfill the definition of SUSAR there must be suspicion of a causal relationship between the event and the IMP.

- UK relevant SUSARS: The Medicines and Healthcare products Regulatory Agency (MHRA) definition of 'UK relevant' includes:
- SUSARs originating in the UK.
- SUSARs originating outside the UK where the sponsor has an ongoing trial in the UK involving the same medicinal product.

Urgent Safety Measures: An urgent safety measure is a procedure not defined by the protocol that is put in place prior to authorisation by the sponsor, MHRA or REC in order to protect clinical trial participants from any immediate hazard to their health and safety. During the course of a clinical trial involving an IMP, new safety information in the form of a Serious Adverse Event or information received from an external source may necessitate an immediate change in the study procedures or a temporary halt to the study in order to protect clinical trial subjects from any immediate hazard to their health and safety. If time does not allow for an amendment to be authorised by the Sponsor, MHRA, and REC, this change in procedure can be implemented as an urgent safety measure, by the Investigator, in accordance with the process put in place by the MHRA, and as detailed in this SOP.

Valid report must contain: For all events:

- Public database number
- Study number
- Unique study identifier
- Identifiable reporter
- At least one (legible) event
- A causality assessment or confirmation that the event has been assessed by a site medically qualified team member and assessment is unknown
- For SUSARS - At least one suspect IMP

Please note, this SOP the CI is assumed to be the Sponsor medical assessor, in some cases this may not be the case in which case the medical assessor assumes all responsibilities allocated to the CI in this SOP.

Clinical Investigation Definitions

Adverse Device Effect (ADE): An adverse event which is related to the use of an investigational medical device. (ISO14155)

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. (ISO14155)

Anticipated serious adverse device effect (ASADE): An effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO14155)

Code break: Code break involves unblinding a participant so that the treatment allocation is made known, this can be single (just to research team) or double (to research team and participant) code breaks.

Day '0': The day the chief investigator first receives a report containing the minimum reporting criteria for an SAE or USADE.

Device Deficiency: An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors and labelling errors. (ISO14155)

Information Brochure: A compilation of the current clinical and non-clinical information on the investigational medical device relevant to the clinical investigation. (ISO14155)

Investigational Medical Device: The medical device being assessed for safety or performance in a clinical investigation.

Safety Events**- for purpose of this SOP this represents** SAEs, SARs, SUSARs, SADEs, ASADEs, USADEs, device deficiencies, and AESI

Serious Adverse Event (SAE): An adverse event that:

Led to death; or

Led to a serious deterioration in the health of the participant that resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalisation, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
- led to foetal distress, foetal death or a congenital abnormality or birth defect. (ISO14155)

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO14155)

Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO14155)