**Reference Safety Information (RSI) and the Assessment of Expectedness of Serious Adverse Reactions (SARs) in Clinical Trials of Investigational Medicinal Products (CTIMPs)**

The RSI should be a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to clinical trial participants, and do not require expedited reporting to the national competent authorities.

The RSI forms part of the clinical trial authorisation (CTA) and should be clearly defined in the study protocol. This should include a list of all observed related adverse reactions, serious and non-serious, including a description of the nature of events, severity, or grade as well as their frequency. Only the RSI approved by a national competent authority can be implemented during the study. The RSI approved with the clinical trial authorisation (CTA) can only be changed via submission of a substantial amendment.

**RSI Submissions**

The RSI can be submitted in the following formats:

For IMPs without Marketing Authorisation (MA) in the European Union (EU), the RSI should be a clearly specific and separated in a section within the Investigator’s Brochure (IB).

For IMPs with an MA in the EU, the RSI should be the section 4.8. ‘Undesirable Effects’ of the appropriate Summary of Product Characteristics (SmPC).

For IMPs with an MA in several EU Member States concerned with different SmPCs, Sponsor should justify its selection of the most appropriate to use as source for the RSI.

**RSI Changes**

Changes to RSI can be made that include new or removed expected adverse events, or newly released IB/SmPC with no new adverse events listed or removed. These changes can impact your study DSUR: Please refer to the TASC SOP on *Preparing and Submitting Development Safety Update Reports (DSUR) for Clinical Trials of Investigational Medicinal Products (CTIMP)*.

**When new events are listed or removed**

A substantial amendment must be sent to the MHRA and the RSI cannot be implemented until approval has been received. If this change is issued mid DSUR period, it will have an impact on the DSUR line listing.

**No new adverse events listed or removed**

If the IB/SmPC has been updated but no changes have been made to the RSI, an assessment needs to be made and documented on the Trial Master File.

Note: An amendment can also be submitted stating the new RSI will only be implemented at the end of the current DSUR period.

If changes have been made and are significant and/or are relevant to the study or patient population, the Investigator must risk assess how those changes affect the RSI. The outcome can be:

**To continue using the old version of the RSI**

The Investigator has to document the risk assessment for all the changes of the RSI and this document has to be reviewed and approved by an independent specialist clinician.

**To change the RSI**

This requires the submission of a substantial amendment. The implementation of the new RSI will start only after approval by the competent authority and will be simultaneous with the start of a new reporting period of the DSUR (if this implies that for a period after approval the old version will still be in use, this has to be documented and stated in the amendment request).

Sponsor will control and track the change process which can demonstrate when the RSI was approved by the national competent authority and implemented by those making the expectedness assessment.

**Expectedness Assessment**

**For the purpose of Serious Adverse Reactions** (**SARs) Expectedness Assessment**

Sponsor should use the RSI version contained in the SmPC or IB which has been approved at the time of the event. This will determine whether an event should be classified as a SUSAR and require expedited reporting. Please refer to the TASC SOP on *Identifying, Recording and Reporting Adverse Events for Clinical Trials of Investigational Medicinal Products (CTIMPs*).

Sponsor is responsible for reviewing and assessing Expectedness (when applicable) of all reported SAEs and SARs on the Tayside Pharmacovigilance System.

For a reaction to be categorised as expected the reaction must be clearly listed in the RSI or clearly defined in the current approved version of the protocol.

Adverse Reactions may be classed as either:

**Expected**: the AR is consistent with the information on adverse effects of the study drug listed in the RSI. An expected AR must be an event previously observed and documented.

**Unexpected**: the AR is not consistent with the information on adverse effects of the study drug listed in the RSI. (An AR may be also described as ‘unexpected’ if it has occurred with greater frequency or severity that might otherwise have been expected.)

The RSI can change during the course of the trial. Therefore, it is essential to ensure the correct approved version is being used when making Expectedness assessment.