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Title	**Sponsor Review of Expectedness for Serious Adverse Reactions: CTIMPs (Including ATMPs)**		

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SOP category	NHS GG&C Sponsor Pharmacovigilance

Staff category

Staff Category	**R**	**A**	**C**	**I**
R&I Research Governance Manager		X		
R&I Pharmacovigilance	X			
Lead Clinical Trial Monitor	X			
R&I Innovation Lead			X	
Sponsor Research Co-Coordinators			X	
R&I Pharmacy			X	
Chief Investigator			X	
Project Managers				X
Industry Collaboration Project Manager				X
R&I Monitoring				X
Principal Investigator				X

1. Scope

This procedure applies to NHSGGC staff with responsibility for assessing the expectedness of serious adverse events in Clinical Trials of Investigational Medicinal Products (CTIMPs) including phase I and first in human trials. For the purposes of this SOP CTIMPs may involve conventional investigational medicinal products (IMP(s)) and/or advanced therapeutic medicinal products (ATMP(s)). Studies may involve a combination of devices and IMP/ATMPs and where this is the case this SOP is not applicable for device related events. This SOP also applies to Chief investigators, and other clinicians delegated this responsibility, who may be employed by organisations other than NHS Greater Glasgow and Clyde.

2. Purpose

The purpose of this SOP is to describe the processes for determining the expectedness of serious adverse events assessed by the local investigator as causally related to an IMP i.e. serious adverse reactions (SARs).

3. Procedures

3.1. Background

One of the principle objectives of pharmacovigilance is to assess serious adverse events occurring within a CTIMP to determine whether those events highlighted by the site investigators have a causative relationship to the IMP(s) utilised within the trial and for Sponsor (PV manager and or CI)to determine if those events are expected for that IMP. Where events are not expected it is referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR). The Sponsor has a legal responsibility to inform the competent authority, and other investigators taking part in the trial of any events meeting SUSAR criteria that have been reported. Given the importance of pharmacovigilance in monitoring the safety of IMPs utilised in clinical trials there are multiple guidelines, regulations, and information provided by the competent authority or other regulatory bodies that apply to reviewing the expectedness of serious adverse reactions.

The most important document used in determining the expectedness of a serious adverse reaction for each IMP is the reference safety information (RSI) and this is submitted to the MHRA for approval. Each IMP will require it's RSI to be submitted for approval, including RSIs for placebos where an active product is utilised.

For most trials a section of the SmPC or IB is used as the RSI for each IMP under investigation. For IBs this is generally section 6, and an IB should contain a subsection specifically titled Reference Safety Information. For SmPCs section 4.8 titled undesirable effects is used as the RSI, or may be used to inform the RSI, see SOP 55.005 for further details.

For an event to be listed in an RSI it must have been observed within any participant taking the IMP in question. Generally, this is not dependent on participant population but reflects use of the product to date within any CTIMPs. On occasion listings may be split into sub categories of medical conditions – this is particularly seen for drugs used in oncology repurposed for use in other medical conditions.

There are differences in how guidance regarding the assignment of expectedness applies to studies depending on the use of IBs, SmPCs or a mixture of the two and these differences will be covered in detail later in this SOP.

While causality is a clinical decision that must be assigned by a clinician (ideally the clinician responsible for the care of the participant), taking into account all known information pertaining to the event and the experience of the investigator, expectedness is purely based on the reference safety information and does not take into account other factors*. As such, expectedness can be assigned by any appropriately trained Sponsor representative as well as clinical members of staff. Sponsor representatives authorised to review expectedness are the PV and safety manager, clinical trial pharmacists, the lead monitor or the research governance manager.

*The RSI may list reactions that are only considered expected in participants with certain medical conditions or who are taking certain medications.

3.2. Regulations Regarding Expectedness in Clinical Trials

The principle documentation relating to determination of expectedness is guidance published by the clinical trial facilitation group in 2017. This acts in combination with The Medicines for Human Use (Clinical Trials) Regulations 2004, The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, and ICH GCP R3. Clarifying the MHRAs perspective are 3 separate blog posts (Reference Safety Information for Clinical Trials – MHRA Inspectorate, Reference Safety Information II – MHRA Inspectorate, Reference Safety Information (RSI) for Clinical Trials- Part III – MHRA Inspectorate) providing a set of general rules to be used when carrying out a review of expectedness.

3.3. Assessment of Causality

The responsibility for assigning causality is with a delegated, medically qualified, local investigator with responsibility for the participant. Causality will be reviewed by the Sponsor during the assessment of expectedness. The Sponsor may query the assignment of causality with the local trial team if they believe there to be alternative explanations for the serious adverse event and determine if there is more information that led the local investigator to their conclusion. **NOTE: The Sponsor cannot downgrade causality assessments**, only query or upgrade. The local investigator assessment is final for causality, even where there are discussions with the Sponsor around the causal relationship. If the event requires reporting as a SUSAR reports may state that the local investigator and Sponsor do not agree on the relationship between the event and the IMP.

3.4. Expectedness for IMPs with an IB as the RSI

3.4.1. Where is the RSI in an IB?

The RSI can generally be found in section 6 of an IB, more specifically the section "Effects in Humans or Summary of Data and Guidance for the Investigator, but must always be labelled Reference Safety Information.

3.4.2. Specificity: IB

Events may become unexpected due to the specificity of a reaction. In an IB the terms listed must match the preferred term of a previously reported reaction. For example an IB may list lower respiratory tract infection, in which case an upper respiratory tract infection would be considered unexpected and vice versa. If the IB had stated respiratory tract infection both could be considered expected. The specific type of infection must be listed for it to be considered expected, even where a drug is immunosuppressive, for example, not all infections can be considered expected unless listed.

Further examples:

Listed SAR in RSI	**'Suspected' SAR in SAE form that would be considered unexpected**
Acute renal failure	Interstitial nephritis
Cerebral vascular accident	Cerebral thromboembolism
Exfoliative dermatitis	Stevens-Johnson Syndrome
Supraventricular Cardiac Arrhythmia	Atrial fibrillation

As a general rule synonyms (i.e. MedDRA lower level terms under an umbrella preferred term) may be considered expected. For example the preferred term "Atrial Fibrillation" has the following as synonyms i.e. LLTs: AF, AFib, Arrhythmia absoluta, Asymptomatic atrial fibrillation, Atrial fibrillation aggravated, Atrial fibrillation and flutter, Atrial fibrillation paroxysmal, Atrial fibrillation with aberrancy, Atrial fibrillation with rapid ventricular response, Atrial fibrillation with slow ventricular response, Atrial flutter/ fibrillation, Auricular fibrillation, Bradyarrhythmia absoluta, Chronic atrial fibrillation, Fibrillation atrial aggravated, Fibrillation paroxysmal atrial, Flutter/fib, Intermittent atrial fibrillation, Lone atrial fibrillation, Nonvalvular atrial fibrillation, Paroxysmal atrial fibrillation, Permanent atrial fibrillation, Persistent atrial fibrillation, Recurrent atrial fibrillation, Recurrent symptomatic atrial fibrillation, Tachyarrhythmia absoluta.

3.4.3. Severity: IB

Events may become unexpected due a reaction being of a greater severity than expected. For IBs events must meet the regulatory definition of serious to be included in the listings and therefore of particular note are life threatening and fatal events. Events that are not fatal or life threatening can be considered expected unless the reported event is of greater severity than expected.

3.4.3.1. Life threatening events

In general life threatening cannot be considered expected for IMPs. Life threatening events may be considered expected only if this is explicitly stated within the RSI. For IMPs with a risk-benefit ratio sufficient to consider life threatening events expected this must be detailed within the trial protocol along with justification.

3.4.3.2. Fatal events

Fatal events can never be considered expected for trials utilising an IB as the RSI and where the IMP does not have a marketing authorisation within the UK. Such events should automatically be upgraded to SUSAR status by the reviewer.

3.4.3.3. Other events of greater severity than listed

There may be events reported that are of greater severity than expected for example:

- Exfoliative dermatitis is listed within the RSI section of the IB and the event reported is Stevens Johnson Syndrome. While the two terms are related Steven Johnsons syndrome is of greater clinical significance and likely to be life threatening or fatal or require urgent intervention to prevent it from becoming so.

- Hepatitis is listed within the RSI section of the IB and the event reported is fulminant hepatitis. Hepatitis is a chronic condition, while fulminant hepatitis is an acute and life threatening condition of rapid onset that is generally life threatening or fatal or requires urgent intervention to prevent it from becoming so. Similar events would be hypertension/hypertensive crisis and sepsis/septic shock with the latter being unexpected due to severity in both cases.

- Transient increase in liver enzymes is listed and the event reported is persistently increase in liver enzymes. This would be considered unexpected due to the chronic nature of the event. While not fatal/life threatening the prolonged increase is of greater severity.

- Herpes zoster is listed and the event reported is multi derma herpes zoster. This would be considered unexpected as generally herpes zoster does not occur in multiple dermatomes and is limited to a localized rash.

As per the examples, most increases in severity would also be unexpected due to the event being fatal or life threatening or requiring urgent intervention. However, events may be more severe due to being more prolonged in nature, more widespread than anticipated, or other reasons.

3.5. Expectedness for IMPs with an SmPC as the RSI

3.5.1. Where is the section in the SmPC that informs the RSI?

The RSI is always contained within section 4.8 of the SmPC, Undesirable Effects. This section is more variable than the equivalent section in an IB, and the rules governing what can be listed are more flexible. One significant difference is the inclusion of adverse events within a SmPC. In addition there may be footnotes contained within section 4.8 that provide additional information relating to the expectedness of events for example, it may state that life threatening or fatal events have been reported, or may provide additional information relating to adverse reactions only considered expected for participants taking specific concomitant medications. Section 4.8 informs the RSI and is used to prepare an RSI summary document (Form 55.005B) as per SOP 55.005. Note: A specific version of the SmPC may also be submitted for approval directly in some circumstances.

3.5.2. Specificity: SmPCs

While generally the same rules used for IBs apply, the listings of adverse reactions within an SmPC may also be broader and less specific than those in an IB. This is particularly prevalent in SmPCs for older IMPs or drugs. Therefore, some degree of interpretation and decision making may be required when assigning expectedness.

As per SOP 55.005, trial specific RSIs will be created for each IMP utilising an SmPC and broader terms contained within section 4.8 will be expanded upon by the Sponsor following consultation with the CI (and clinical delegates where appropriate).

Where a reviewer believes an event to be expected it must be either explicitly listed within the RSI, synonymous with a listed term, or falls under a broader listed term expanded upon within the trial Specific RSI summary (Form 55.005B) for each IMP. The broad term itself, for example “Infection” cannot be considered expected.

3.5.3. Severity: SmPCs

Where SmPCs along with an RSI Summary (Form 55.005B) are used as the RSI then generally the RSI will state the expected severity of any events.

Similar rules to those detailed for IBs in section 5.3 will apply with the exception that fatal events may be considered expected for licensed IMPs with an MA in the UK if this is clearly documented in the RSI. The RSI summary and the protocol will state if any life threatening or fatal events can be considered expected.

Where CTCAE grades are used then these will be included within the RSI Summary. Where an event is reported with a CTCAE grade greater than the listed CTCAE grade the event will be considered unexpected

3.6. Expectedness in trials with multiple IMPs

Multiple IMPs can complicate the assignment of expectedness if given concomitantly. In addition IMPs may use a mixture of SmPCs and IBs as the RSI. Where this is the case, the relevant section for the respective type of RSI must be followed. Section 5 of this SOP is of particular importance when assessing expectedness of adverse reactions with a causal relationship to multiple IMPs, particularly where the IMPs have a disparate safety profile.

In some cases the RSI may pool terms from multiple SmPCs into one master document covering all IMPs. For example many oncology studies deliver IMPs concomitantly in a drug regimen and therefore it may be beneficial to use a trial specific RSI for that regimen rather than the individual IMPs.

3.7. Drug interactions and expectedness

There are several types of drug interaction that may be reported. The primary two are:

- Those where administration of one IMP, nIMP, or concomitant medication affects the absorption or metabolism of another IMP, nIMP or concomitant medication e.g. cytochrome p450 2d6, 3a4, 1a2 etc. Synergistic or antagonistic reactions are possible.
- Those that are additive in nature i.e. all or some IMP(s), nIMP(s), or other interventions all have the same listed adverse reaction

In general a drug interaction could result in:

- A listed event occurring at a greater severity than expected (due to additive or synergistic effects). This would be a SUSAR due to the increased severity.
- A new event not listed for any of the IMPs/NIMPs/interventions that occurs only when a specific combination of these is administered. This would be a SUSAR due to the reaction not being listed.
- A reduction in the efficacy of an IMP/nIMP/intervention due to antagonistic interaction. This is unlikely to be reported as an SAE, but this does not mean it cannot be one. For example in oncology trials a lack of efficacy of an IMP due to a drug interaction could result in rapid disease progression and this would be a SUSAR as it is unexpected.

Where a serious adverse reaction is assessed as being due to a drug interaction the principle questions are:

- Is the event listed for one or more of the IMPs/nIMPs/other interventions?
- If yes, is the severity of the SAR in line with the RSI for one or more of the IMPs/nIMPs/other interventions
- Is there any further reason as to why the reporter believes this to be an interaction?

If the serious adverse reaction is listed for one or more of the IMPs/nIMPs/other interventions at the severity listed then this is unlikely to be due to a drug interaction and this should be queried with the local investigator. In the event the local investigator believes the event be due to a drug interaction following discussion then it should be reported as a SUSAR.

3.8. Who can assign expectedness?

As stated in section 3.1, expectedness is not a clinical decision and therefore does not need to be assigned by a clinician. However, some degree of knowledge of medical terms and concepts is required when assessing events for expectedness.

For most trials both CI (and delegate) and Sponsor PV and Safety Manager (or delegate) review of expectedness is captured. In the first instance review by either the CI or Sponsor PV is sufficient for regulatory purposes, i.e. either party can "stop the clock" on the review process (see section 12). Review by both parties is required in a non-expedited manner.

Where the Sponsor PV and Safety Manager and the CI are not available, then the following may be approached for review:

- Clinicians within the TMG
- Clinical trial pharmacists
- Lead monitor
- Research governance manager

3.9. How is the assignment of expectedness captured?

The eCRF will capture the CI and/or Sponsor PV and Safety Manager assessments of expectedness within the relevant review section. The CI and/or Sponsor PV and Safety Manager will be asked for the expectedness of any SAE meeting SAR criteria i.e. the local investigator has indicated a suspected causal relationship between the event and the IMP(s) and their decision will be captured on the eCRF.

When expectedness is reviewed the assessor will be asked to state the version of the RSI used to assess the SAR. NOTE: This must be the version of the RSI approved at the time of the event.

Where review is carried out by a member of the trial team other than the Sponsor PV and Safety Manager or the CI (or other delegated clinician) then review by email is acceptable. The CI, Sponsor PV and Safety Manager, and the PV office should be copied into emails. The email should include the SAE ID, diagnosis, the opinion of the reviewer regarding expectedness including any justifications, and the version of the RSI used to assess expectedness.

3.10. What is the timeline for the review of expectedness?

The assessment of expectedness must take place within 7 days of the Sponsor becoming aware of a life threatening or fatal event or within 15 days of the Sponsor becoming aware of other events.

An event initially reported as unrelated to IMP may be upgraded to a related event in a subsequent follow up. In such a scenario the 7/15 timeframe described above would apply however, the event should be reported as soon as possible.

3.11. Disagreements in the assessment of expectedness

In the event the CI (or delegate) and the Sponsor PV and Safety Manager (or delegate) do not agree on the assessment of expectedness then it is important to reach consensus. In the event consensus cannot be reached then a third reviewer should be asked for their assessment to reach a majority. In these scenarios all correspondence relating to the decision must be documented and stored with the event.

4. Referenced documents

- SOP 55.005 Initial Review and Management of Updates to Reference Safety Information
- Form 55.005B RSI Summary
- CT3 Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use
- Clinical Trial Facilitation Group CTFG: Q&A document – Reference Safety Information 2017
- ICH Harmonised Guideline For Good Clinical Practice E6(R3)
- Reference Safety Information for Clinical Trials – MHRA Inspectorate - https://mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/
- Reference Safety Information II – MHRA Inspectorate - https://mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/
- Reference Safety Information (RSI) for Clinical Trials- Part III – MHRA Inspectorate) - https://mhrainspectorate.blog.gov.uk/2021/02/05/reference-safety-information-rsi-for-clinical-trials-part-iii/)

5. Related documents

- SOP 55.001 Pharmacovigilance in Clinical Trials of Investigational Medicinal Products (Glasgow Clinical Trials Unit)
- UK SI 2004/1031 The Medicines for Human Use (Clinical Trials) Regulations 2004
- Directive 2001/20/EC Clinical Trials Directive

6. Document history

Version	Date	Description	Retrospective Implementation
1.0	19/08/2026	First Release	No