Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Reference Safety Information

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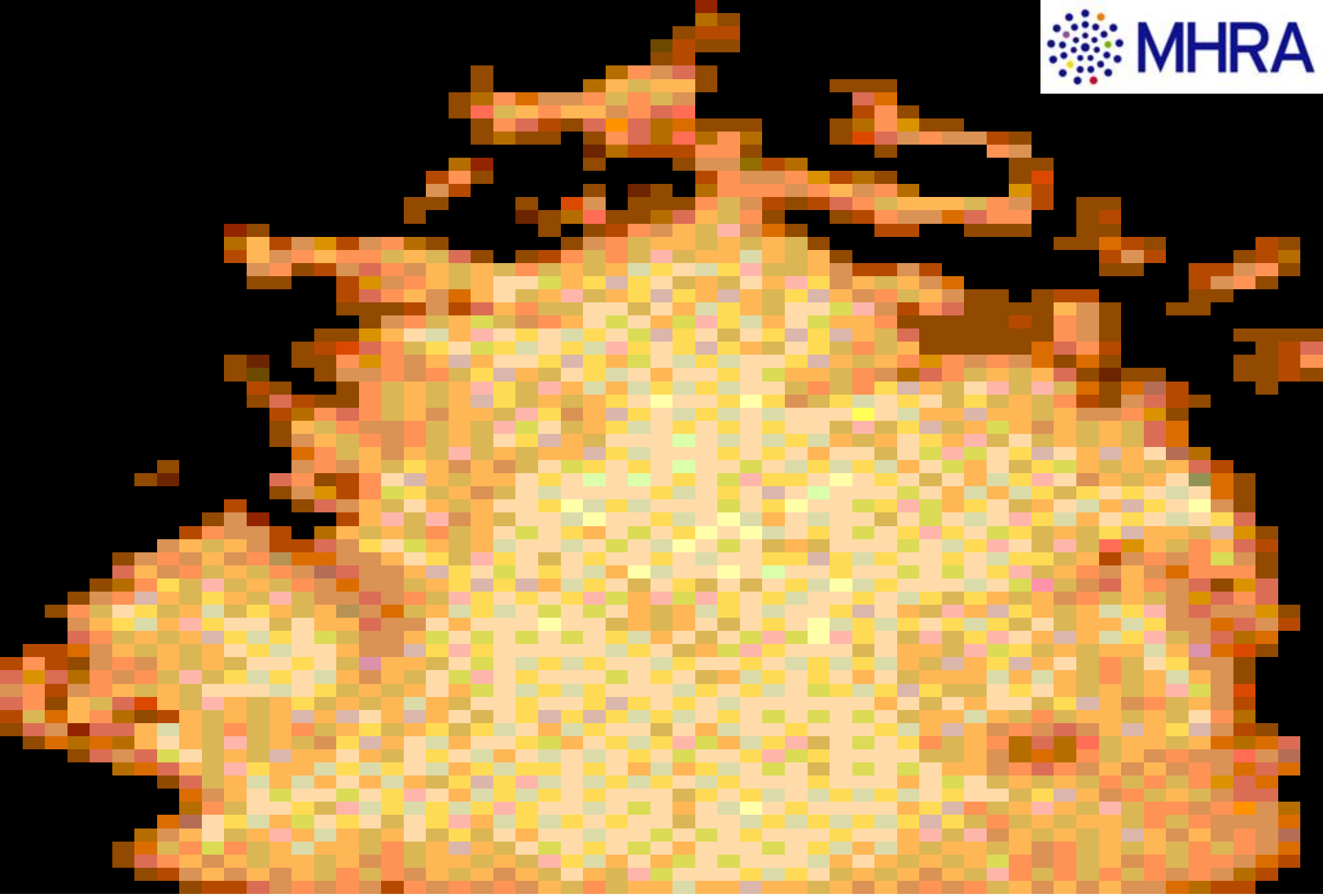
What is Reference Safety Information (RSI)

RSI should be a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP).

One single definitive list or document that determines which Serious Adverse Reactions (SARs) require expedited reporting and which are exempt



Hot Topic

- Major or Critical findings being given at majority of inspections
- Issues across commercial and non-commercial organisations
- Critical finding at my last 2 inspections

Who is Responsible?

Ultimately the sponsor

33.—(1) A sponsor shall ensure that all relevant information about a suspected unexpected serious adverse reaction which occurs during the course of a clinical trial in the United Kingdom and is fatal or life- threatening is—

(a)recorded; and

(b)reported as soon as possible to—

(i)the licensing authority,

(ii)the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted, and

(iii)the relevant ethics committee, – ***UK Statutory Instrument 2004/1031 (as amended)***

32.—(1) An investigator shall report any serious adverse event which occurs in a subject at a trial site at which he is responsible for the conduct of a clinical trial immediately to the sponsor. – UK Statutory Instrument 2004/1031 (as amended)

14. The investigator's responsibilities entail:

— reporting of Serious Adverse Events (SAEs) to the sponsor (see section 4), - ***Communication from the Commission ('CT-3')***

What the Guidance States

CT3 EC Guidance 2011/C 172/01

- The expectedness of an adverse reaction is determined by the sponsor in the reference safety information ('RSI')

- If the RSI is contained in the IB, the IB should contain a clearly-identified section to this effect. This section should include information on the frequency and nature of the adverse reactions

- If the IMP has a marketing authorisation in several Member States concerned with different SmPCs, the sponsor should select the most appropriate SmPC, with reference to subject safety, as RSI

- The RSI may change during the conduct of a clinical trial. This is typically a substantial amendment

- For the purpose of SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR applies

Issues Include But Not Limited to….

- No awareness of RSI
- RSI not clearly defined
- No control over the RSI
- Incorrect RSI being used to assess expectedness of SARs
- RSI changed without a substantial amendment being submitted
- New RSI implemented before the substantial amendment is approved
- Same event being assessed as both expected and unexpected in single DSUR period
- SUSARs being downgraded based on new RSI
- UK relevant SARs being assessed against RSI from a different region
- Potential increase in occurrence of expected events not captured

Case Study

All issues seen at one organisation

- Implementation of RSI changes before amendments have been approved
- Actual RSI used by case processers separate document with additional terms to that sent to MHRA
- Latest versions of SmPCs being used as comparator RSI not version sent to MHRA
- Separate measure of suitability for SUSAR submission to REC compared to MHRA (large number of SUSARs not sent to REC)
- Use of RSI from other regions not approved by MHRA

End Result

- Unreported SUSARs
- SUSARs incorrectly downgraded
- Substantial amendments not submitted for approval
- DSUR line listings incorrect
- Line listings provided to investigators incorrect

Critical finding – return visit to complete inspection

Patient Safety Impact

The regulator (MHRA) has not had the opportunity to assess new information that may impact on the risk benefit ratio of your trial and to determine if as a result your IMP and its dosing regimen are still appropriate for your trial population.

MHRA GCP Inspectorate Actions

- Working with GPvP Inspectorate and MHRA Clinical Trials Unit to ensure consistency in advice, findings and expectations
- Raising issue today for onward dissemination to stakeholders
- Plan to include it as a topic at future MHRA Symposia
- RSI blog

Key RSI Characteristics?

Identifiable

Approved

Consistent

Thoughts……