From SAE to SUSAR: Safety mailings for clinical trials

Sarahann Simpson
Cluster Safety Lead, Australia/South Asia

Pfizer
WORLDWIDE SAFETY & REGULATORY
Worldwide Research & Development

Disclaimer

The views expressed are my own personal views and not those of Pfizer. Information presented was correct at the time of presentation.

Overview – answering your questions

- Safety mailings
  - What are they?
  - What is their purpose?
  - Why do I get them?
  - What do they tell me?
  - Why do they matter?
  - What should I do with them?
  - What are the issues?
  - Will they change?

What are safety mailings?

- SUSARs (**S**uspected **U**nexpected **S**erious **A**dverse **R**eactions)
- CTSURs (**C**linical **T**rial Safety **U**pdate **R**eports aka periodic line listings
- SSC (**S**pecial **S**afety **C**oncerns)
- Originate from
  - SAEs at sites (including yours – please respond to queries asap)
  - Preclinical studies
  - Study data review and analysis

What is their purpose?

- Protect patient safety
- Inform investigators of new developments
- Compliance
- Study integrity

Why do I get them?

- Variously required by
  - Legislation / regulatory guidance across jurisdictions
  - GCP
  - Sponsor SOPs
  - Study contract
  - NHMRC Position Statement
  - Professional ethical obligation

Regulatory framework for safety mailings: SUSARs

- USA
  - **The sponsor reports SUSARs to the FDA and all participating investigators (US and non-US sites) in IND studies within 7-15 days.** 21 CFR 312.32(c)(1)(i)
- EU
  - **Individual SUSARs not routinely required.** Directive 2001/20/EC. Apr2001 Article 17 - the sponsor shall also inform all investigators [of SUSARs]... CT-3(2011/C 172/01) Jun2011, section 7.10 whenever practicable the information on SUSARs should be aggregated in a line listing
- Australia
  - **Individual SUSARs not routinely required.** NHMRC AHEC Position Statement May 2009 – sponsor to send individual SUSARs only if HREC or sponsor consider it necessary given the nature of the study.
- Company SOP
  - **minimum requirement, based on US requirements,** i.e. expedite to PI individual SUSARs, assessed as related to IMP by company and others via 6 monthly line listing (unless local law more stringent).

Regulatory framework for safety mailings: Periodic reports

- US
  - **21 CFR 312.55** has 'periodic' reporting requirements of new observations to investigators (21CFR 312.33 requires annual IND reports)
- EU
  - **Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01) Jun2011– 7.10** whenever practicable the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP.
- Australia
  - **NHMRC AHEC Position Statement May 2009 –**Periodic reports as required for submission to ECs (at least 6 monthly and annual; EU format acceptable).
- Company SOP
  - Distribute line listings to investigators for all ongoing studies, usually 6 monthly (incl. brief comment on the impact on benefit-risk)

Regulatory framework for safety mailings: Special safety concerns

- USA
  - **21 CFR 312.50 -** Sponsors are responsible for ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug
  - **21 CFR 312.32** as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting

- EU
  - **CT-3(2011/C 172/01) Jun2011, section 7.11.4** Sponsor informs national competent authorities and the Ethics Committee of safety issues which might materially alter the current risk-benefit assessment of the IMP

- Australia
  - **NHMRC AHEC Position Statement May 2009** – In a prompt manner, sponsors must communicate to investigators information which could adversely affect the safety of subjects, materially impact the continued ethical acceptability of the trial or that requires (or indicates the need for) a change to the trial protocol including changed safety monitoring

- Company SOP
  - Consistent requirement across jurisdictions - notify special safety concerns promptly / no later than 15 days from decision date

GCP - sponsor

- Development of SOPs for the conduct of clinical trials per GCP
  - Incl. SOPs on safety mailings
  - Must satisfy the most conservative international regulations
- Obligation to notify of safety issues that may impact
  - study conduct
  - rights, safety of study participants

GCP - investigator

- Adequate time, resources
  - also applies to time, resources (incl staff who understand study obligations) to handle safety mailings

Contractual obligations - sponsor

5. SPONSOR OBLIGATIONS AND RESPONSIBILITIES

5.4 The Sponsor will monitor the application of the Investigational Product in other places (both within and outside Australia) and advise the Institution, through the Principal Investigator, and TGA of the cessation elsewhere of any relevant trial, or the withdrawal of the Investigational Product from any other market for safety reasons.

5.5 The Sponsor will notify the Institution of any Adverse Events (including Serious Adverse Events) that occur during the course of the Study (either at the Study Site or other study sites, including overseas sites) which may require alteration of the conduct of the Study, or which may affect the rights, interests, safety or well-being of Study Participants.

Contractual obligations - investigator

3. PRINCIPAL INVESTIGATOR

3.3 Obligations and responsibilities

(1) thoroughly familiarises himself or herself with the appropriate use of the Investigational Product(s), as described in the Protocol, Investigator's Brochure, information relating to the Investigational Product and any other information sources provided by the Sponsor;

(10) notifies the Sponsor, institution and the reviewing HREC of any AE (incl.SAEs) that occur during the course of the study in accordance with the Protocol and relevant ethical guidelines and regulatory guidelines & in the case of the Institution and the Reviewing HREC with their policies and procedures

What do they tell me?

- New safety information
  - Not listed in the IB
  - Individual SUSARs (company causality assessment =yes)
    - contains all the case information to date incl
      - patient, report source, Tx, Hx, study meds, con meds
      - Dechallenge/rechallenge
      - consolidated narrative, summary of updates and investigator causality assessment
      - Company comment wrt causality and impact on risk/benefit balance incl. undertaking to notify identified safety concerns
  - Periodic line listing has all SUSARs (incl. where company causality = no)
  - SSC
    - not necessarily arising from individual SUSAR
    - may impact study conduct

Why they matter

- Essential to ensure
  - safety of trial subjects
  - HCP knowledge of IMP
  - May affect study conduct
  - Regulatory compliance

What should I do with them?

- Read and understand potential impact to your patients
- Forward to EC in accordance with local requirements
- File in SMF

What are the issues?

- Volume of SUSARs
- individual SUSARs not routinely required by ECs in AUS
- Sponsor technology
- Misunderstanding of responsibilities
- Lack time
- Lack of resources
- Inability to delegate task

Will they change?

- Possible influences
  - NHMRC consultation outcome
  - Regulation changes
  - Sponsor company interpretation of regulations esp. US regulations
  - TGA pharmacovigilance inspections from 2015

Summary

- International regulations and ethical frameworks
  - protect patient safety
  - ensure scientific and ethical integrity of studies
  - require safety mailings
  - dictate sponsor processes
  - Apply to handling of safety mailings at site
- Compliance is essential

Thank you for your attention – questions?