Interventional Clinical Trials
Pharmacovigilance

GPvP Symposium, 14 March 2014
Catharine Raitt, GCP / GPvP Inspector
Overview

1. Refresher and tips:
   – Key legislation and guidance
   – Case processing considerations
   – Expedited reporting
   – DSURs

2. Reference safety information (RSI): CTFG guidance

3. RSI and investigator’s brochures:
   what might GPvP inspectors look at?

4. Forward look: new Clinical Trials Regulation
Refresher and tips
Key legislation and guidance

European Directives:
• 2001/20/EC – Clinical Trials Directive
• 2005/28/EC – GCP Directive

UK Clinical Trials Regulations:
• Statutory Instrument 2004/1031 (as amended)
  Primarily Part 5 – Pharmacovigilance

Guidance:
• ‘CT-3’ (2011/C 172/01): “Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use”
• ICH E2F: Guideline on DSURs
SAE case processing: some considerations

Expectedness assessments

Consistency

RSI - “moment of occurrence”

Unblinding

SUSARs

7/15 day reporting

Follow up

Timeliness

Completeness
DSURs: Multiple parties

• Where more than one sponsor is running trials of the same IMP, the parties should arrange to prepare a single DSUR if possible. For example:
  – co-development or licensing relationship
  – development programme involving collaboration with public or private institutions.

• When a single DSUR cannot be arranged, multiple sponsors can prepare separate DSURs. The rationale should be provided in the report.
Please include:

- A cover letter (including any justification for the approach taken).
- A specific point of contact for any queries.
DSURs: Sections that may be shared with the PSUR

- Worldwide Marketing Approval Status
- Actions taken in the reporting interval for safety reasons
- Cumulative subject exposure in clinical trials
- Cumulative patient exposure from marketing experience
- Significant findings from clinical trials during the reporting period
- Non-clinical data
- Literature
- Lack of efficacy
- Late-breaking information
- Conclusion and actions

Inspectors may check for consistency between DSURs and PSURs, where applicable.
Reference Safety Information: Clinical Trials Facilitation Group Guidance (2013)
Clinical Trials Facilitation Group (CTFG):
- Representatives from NCAs, EC and EMA.
- Aims include: harmonising processes, practices and assessment relating to clinical trials mainly in the fields of clinical trial applications, amendments and safety procedures.

Guidance on clinical trials safety:
- DSUR Q+As
- Reference safety information (RSI)
  http://www.hma.eu/78.html
CTFG Guidance – RSI (1)

General points

• The RSI should be within the investigator’s brochure (IB) or SmPC.
• The cover letter for the clinical trial authorisation application should state where the RSI is located. (Consistent with CT-3: 7.2.3.2 Reference safety information.)
If the RSI is within the IB, the RSI should be:

- A clearly identified separate section.
- A list of expected adverse reactions (e.g. table format): nature, severity, frequency.

- For ongoing trials, if the above has not yet been implemented, it should be done at the next (regular) IB update.
- If different indications are being investigated, separate tables of expected adverse reactions by indication might be applicable.
- If the IB (rather than the SmPC) is used as the RSI for IMPs with a marketing authorisation, any differences between the list of expected adverse reactions in the IB and the SmPC should be highlighted and justified.
If the RSI is within the SmPC:

- The list of expected adverse reactions is in Section 4.8 (Undesirable Effects).
- If the IMP has marketing authorisations in several Member States concerned with different SmPCs, the sponsor should justify its selection of the most appropriate SmPC as the RSI (with reference to subject safety).
Changes to the RSI during a trial:

• Any change to the RSI is considered a substantial amendment and it requires to be justified with supportive data.

• It is recommended to update the RSI, if necessary, in alignment with the annual period for a DSUR. The DSUR can act in part as justification for the RSI changes.

• If the RSI is updated prior to the end of the reporting period of the DSUR, a detailed justification by data is expected.
Investigator’s brochures:
What might GPvP inspectors look at?

- Has the RSI section been clearly identified?
- Is the RSI in the IB consistent with section 4.8 of the SmPC? If there are differences, is there data to support this?
- When safety information is updated in the SmPC, has the IB been updated (as appropriate) and vice versa? What is the process for this?
- Where changes have been proposed to the RSI in the IB, has a substantial amendment been submitted?
- Has the IB been reviewed on an annual basis?
Investigator’s brochures: What might GPvP inspectors look at?

- What mechanisms are in place to ensure that:
  - if a substantial amendment is required, the updated IB is not used before MHRA approval?
  - updated IBs are promptly circulated to concerned investigators and to MAH/contractor staff who are involved in managing the trial and in the assessment of expectedness?

- If the IB has been updated with details of recently completed non-clinical and clinical studies, have the results been included in PSURs/RMP updates where appropriate (and vice versa)?
Forward look: new Clinical Trials Regulation
EU legislative process
Timelines

- Agreed text endorsed by Member States on 20 December 2013.
- We expect the Regulation to be adopted formally by the European Parliament in early April and quickly after by the Council of Ministers after which it will be published.
- It is expected to come into effect in 2016.
  - It won’t come into force until 6 months after the IT is deemed functional.
What does it look like? A taster…

- ‘Regulation’.
- Requirement for trials to be registered in a public registry (EudraCT, clinicaltrials.gov, ISRCTN).
- Efficiencies in authorisation process: EU portal, joint assessment.
- Concept of ‘low-intervention clinical trials’.
- Much of what was in CT-3 is in the Annex to the Regulation.
What does it look like?

Safety

- **RSI:** Proposed text largely reflects current requirements (CT-3, CTFG guidance).

- **Safety reporting:**
  - Database for SUSAR and annual reporting by the sponsor to EMA (module of EudraVigilance).
  - Standard web-based form for SUSAR reporting.
  - Timelines for SUSAR reporting to EudraVigilance remain unchanged (7/15 days).
What does it look like?

Safety

Other reporting obligations (sponsor):

• Unexpected events that affect the benefit/risk balance of the clinical trial, but are not SUSARs - within 15 days via EU Portal.

• Serious breaches and urgent safety measures - within 7 days via EU Portal.
New CT Regulation

• Just a taster…
• More information will be available in due course:
  – Published text
  – Guidance
  – UK legislation to cover national aspects (e.g. consent, enforcement).
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