Overview of Adverse Reaction Reporting Requirements in Clinical Trials

IMB Clinical Trials Seminar, 19th June 2012

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Introduction

- Legislation
- Definitions
- Assessing adverse events/reactions – causality & expectedness
- SAE/SAR/SUSAR reporting requirements
- Methods for reporting to the IMB
- Eudravigilance
- Methods for reporting to Eudravigilance
Legislation

• Directive 2001/20/EC
• S.I. No. 190 of 2004

Guidance documents

• Eudralex Volume 10 Clinical Trial Guidelines - Chapter II
  *Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use*

• *Guide to Clinical Trial Applications* (IMB website)
What is an adverse event (AE)?

‘Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment’.

→ May be serious or non-serious and may/may not be related to investigational product(s)
What is a Serious Adverse Event (SAE)?

‘Any untoward medical occurrence or effect that at any dose results in:
  • death,
  • is life-threatening,
  • requires hospitalisation or prolongation of existing hospitalisation,
  • results in persistent or significant disability or incapacity,
  • or is a congenital anomaly or birth defect’.

→ is serious per criteria and may/may not be related to investigational product(s)

**NB:** Important medical events which jeopardise the subject or may require an intervention to prevent one of the serious criteria listed above should also be considered serious
What is a Serious Adverse Reaction (SAR)?

All untoward and unintended responses to an investigational medicinal product, related to any dose administered

→ Is serious per criteria, expected per the Investigator’s Brochure/SmPC and is related to investigational product(s)
What is a SUSAR?

‘A suspected, unexpected serious adverse reaction’.

→ Is serious, is unexpected/not listed in the Investigator’s Brochure/SmPC and is related to investigational product(s)
Who assesses causality and how?

- **Causality assessment** must be made by the Investigator.

- Made using knowledge of biological, pharmacological properties of the IMP/comparator, clinical and scientific judgement.

- Investigator must report all SAEs to the Sponsor within 24 hours.

- Causality assessment cannot be downgraded by the Sponsor.
Who assesses expectedness and how?

- **Expectedness assessment** must be made by the **Sponsor**
- Expectedness assessment is made using the reference safety information – applicable version at time of the reaction

Reference safety information → Investigator Brochure or SmPC

- Expectedness should be determined from the perspective of reactions previously reported – unexpected unless documented in the RSI

**NB:** Reports which add significant information on the specificity, increase in occurrence or severity of a known, documented serious adverse reaction constitute unexpected events
SUSAR

Investigator  →  Sponsor  →  CA, EV, EC, Inv

24 h  →  7/15 days

CA – Competent Authority
EV - Eudravigilance
EC – Ethics Committees
Inv - Investigators
When should I unblind?

- SUSARs **must** be unblinded prior to submission per guidance
- Waivers on unblinding - needs to be proposed and agreed at authorisation stage of application – DSMB recommended

**Points to consider**
- Defined process for unblinding to be in place prior to commencing trial
- Access to unblinding codes
- Maintaining blind for relevant personnel
Overview of Reporting

Event/reaction noted by investigator at site

Submitted to Sponsor for assessment

SAE
SAR
DSUR
IMB
EV
Ethics Committees
All other investigators
DSUR
What type of report must be submitted to the IMB and Eudravigilance by the Sponsor?

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Points to consider before submission

- Do I have the minimum criteria for a valid report (reporter, subject, drug & reaction)?
- Have I unblinded the report?
- Have I provided the EudraCT number and IMB CT number?
Timelines for reporting SUSARs to IMB and EV by Sponsor

- **All SUSARs**
  - **Fatal and life-threatening SUSARs**
    - 7 calendar days from first notification to Sponsor
    - A further 8 days for completed report
  - **All other SUSARs**
    - 15 Calendar days from first notification to Sponsor
How does the Sponsor submit SUSARs to the IMB?

Electronic reporting of SUSARs is mandatory per Directive 2001/20/EC

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GUIDE TO ELECTRONIC TRANSMISSION OF ICSRs AND SUSARs ASSOCIATED WITH THE USE OF HUMAN MEDICINES

22/06/2012
What is the Eudravigilance database?

- EMA’s centralised adverse reaction database (Dec 2001)
- Is maintained by the EMA

- The EV Post Authorisation Module (EVPM) – Individual Case Safety Reports (ICSRs)

- The EV Clinical Trial Module (EVCTM) – SUSARs
  

Points to consider

- Registration with Eudravigilance required prior to study commencement
- Prior training & testing required before access is granted to production phase
- ICH E2B (R2) compliant pharmacovigilance system in place
I do not have access to a compliant PhV system. Are there alternatives routes for electronically submitting my SUSAR reports and meeting reporting requirements?

**EVWEB** – Web interface for secure transmission of SUSARs

**Points to consider**
- More manual procedure than E2B compliant EV submission
- Also requires registration with EMA and training

Is there any support for submission of SUSARs to EVCTM?

- Provided for small, non commercial, investigator led trials
- Prior arrangement and agreement by e-mail (imbpharmacovigilance@imb.ie)
- Trial by trial basis

Points to consider
- Shorter timeline for reporting to IMB
- IMB will only facilitate onward reporting of National SUSARs
- Intended for exceptional circumstances and specific needs
- Not an indefinite solution
Is there a specific IMB template SAE form available?

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SERIOUS ADVERSE EVENT FORM FOR INVESTIGATOR-LED TRIALS

<table>
<thead>
<tr>
<th>IMB.CT number:</th>
<th>Study protocol number:</th>
</tr>
</thead>
</table>

IMB reference no. (follow up reports only): 

- [ ] Initial Report
- [ ] Follow up to the report of: 

<table>
<thead>
<tr>
<th>Date of this report:</th>
</tr>
</thead>
</table>

1. **PATIENT INFORMATION**

<table>
<thead>
<tr>
<th>Patient initials</th>
<th>Date of birth</th>
<th>Age</th>
<th>Sex</th>
<th>Weight</th>
<th>Is the patient pregnant?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>Yes No</td>
</tr>
</tbody>
</table>

2. **DESCRIPTION OF THE SERIOUS ADVERSE EVENT**

Category of event (tick all that apply):

- [ ] 
- [ ] 
- [ ] 
- [ ] 
- [ ]
Submission of other reports?

- SAEs - DSUR
- SARs - DSUR
- Line listings (quarterly/6 monthly) - for Ethics Committees – not routinely required by the IMB
Further Information

Where can I get further information and access online forms?
IMB: Guide to Clinical Trial Applications

IMB: SAE form
http://www.imb.ie/EN/Medicines/Clinical-Trials/Serious-Adverse-Event form.aspx

IMB: Guide to Electronic Transmission of ICSRs and SUSARs
Thank you