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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



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Legislation and Guidance Documents

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)



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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)



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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



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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)



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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)



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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



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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



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SUSAR

Investigator



24 h

Sponsor



7/15 days

CA, EV
EC , Inv

CA – Competent Authority
EV - Eudravigilance
EC – Ethics Committees
Inv - Investigators



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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

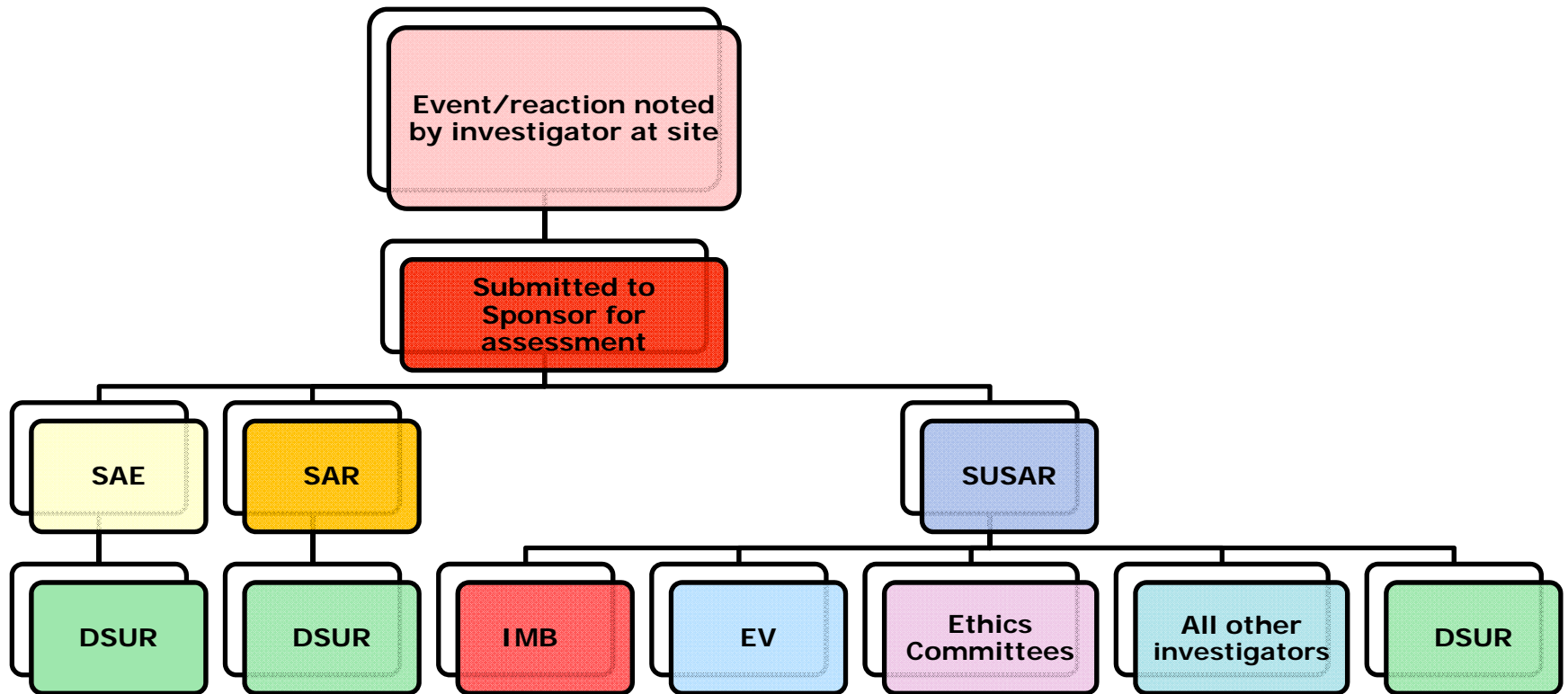
Points to consider

- ❖ Defined process for unblinding to be in place prior to commencing trial
- ❖ Access to unblinding codes
- ❖ Maintaining blind for relevant personnel



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Overview of Reporting



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What type of report must be submitted to the IMB and Eudravigilance by the Sponsor?

Suspected Unexpected Serious Adverse Reactions (SUSARs)

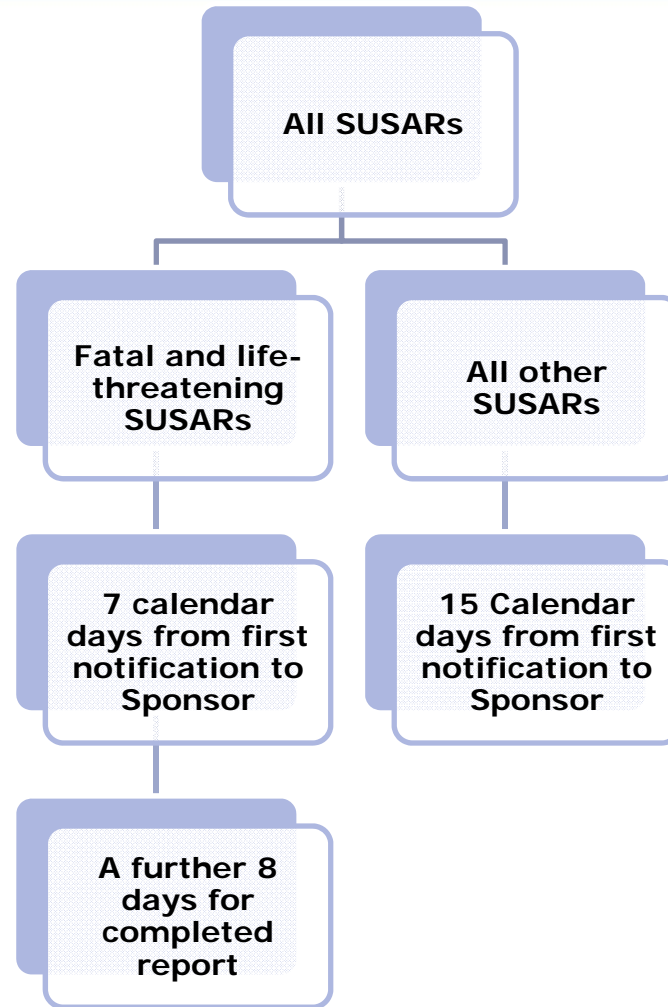
Points to consider before submission

- ❖ 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?



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Timelines for reporting SUSARs to IMB and EV by Sponsor



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How does the Sponsor submit SUSARs to the IMB?

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

| | |
|---|--|
|  | IRISH MEDICINES BOARD GUIDE TO ELECTRONIC TRANSMISSION OF ICSR _s AND SUSAR _s ASSOCIATED WITH THE USE OF HUMAN MEDICINES |
| | |



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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
<http://eudravigilance.ema.europa.eu/highres.htm>

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



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Methods for reporting to EVCTM by the Sponsor

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

<http://eudravigilance.ema.europa.eu/human/evweb01.asp>



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Exceptional Circumstances

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



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Is there a specific IMB template SAE form available?

| | |
|---|---|
|  | IRISH MEDICINES BOARD SERIOUS ADVERSE EVENT FORM FOR INVESTIGATOR-LED TRIALS |
|---|---|

| | |
|---|---|
| IMB CT number: <input type="text"/> | Study protocol number: <input type="text"/> |
| IMB reference no. (follow up reports only): <input type="text"/> | |
| <input type="checkbox"/> Initial Report | Date of this report: <input type="text"/> |
| <input type="checkbox"/> Follow up to the report of: <input type="text"/> | |

| 1. PATIENT INFORMATION | | | | | |
|------------------------|----------------------|----------------------|---|----------------------|--|
| Patient initials | Date of birth | Age | Sex | Weight | Is the patient pregnant? |
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="checkbox"/> M <input type="checkbox"/> F | <input type="text"/> | <input type="checkbox"/> Yes <input type="checkbox"/> No |

| 2. DESCRIPTION OF THE SERIOUS ADVERSE EVENT |
|---|
| Category of event (<i>tick all that apply</i>): <input type="checkbox"/> ... <input type="checkbox"/> ... <input type="checkbox"/> ... |



Processing Other Reports

Submission of other reports?

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



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Further Information

Where can I get further information and access online forms?

IMB: Guide to Clinical Trial Applications

<http://www.imb.ie/EN/Publications/Publications/Guide-to-Clinical-Trial-Applications.aspx?page=1>

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

<http://www.imb.ie/EN/Publications/Publications/Guide-to-Electronic-Transmission-of-ICSRs-and-SUSARs-associated-with-the-use-of-Human-Medicines.aspx?page=1&year=0&categoryid=36&letter=&q=>



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Thank you

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