IRISH MEDICINES BOARD

Overview of Adverse Reaction Reporting Requirements in Clinical Trials

IMB Clinical Trials Seminar, 19th June 2012

Clare Brennan PhD

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

IRISH MEDICINES BOARD

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)

IRISH MEDICINES BOARD

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)

IRISH MEDICINES BOARD

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 <u>serious per criteria</u> and may/may not be related to investigational product(s)

NB: <u>Important medical events</u> which jeopardise the subject or may require an intervention to prevent one of the serious criteria listed above should also be considered <u>serious</u>

IRISH MEDICINES BOARD

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)

IRISH MEDICINES BOARD

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)

IRISH MEDICINES BOARD

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

IRISH MEDICINES BOARD

Who assesses expectedness and how?

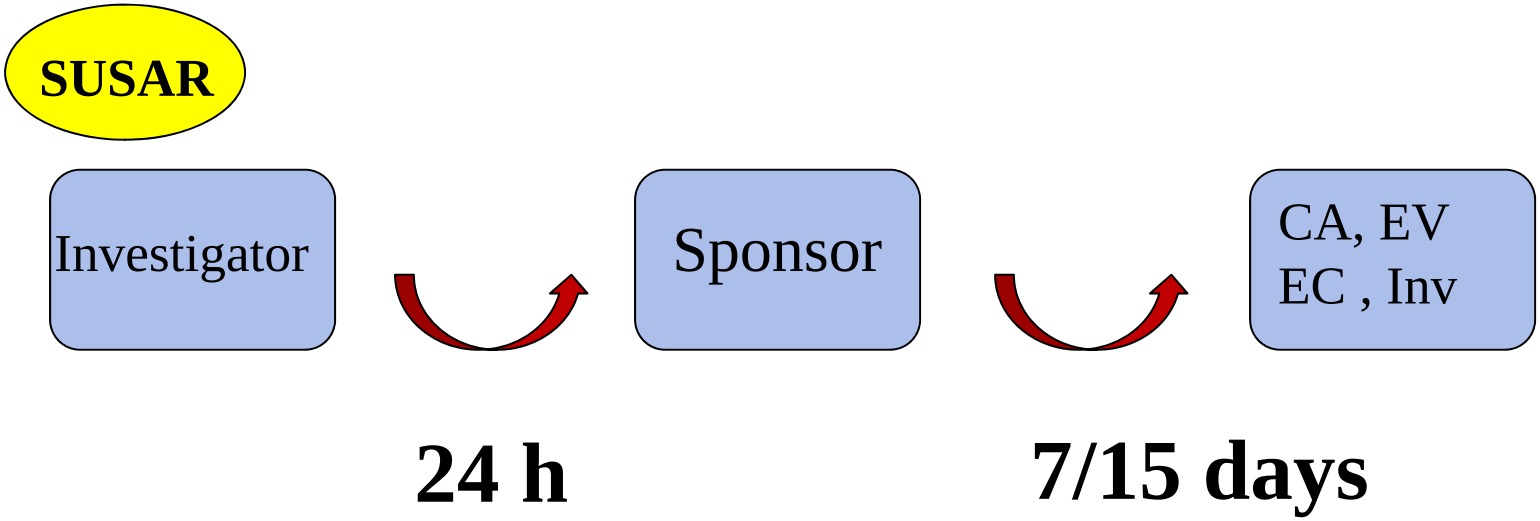
- Expectedness assessment must be made by the Sponsor
- Expectedness assessment is made using the reference safety information – applicable version at time of the reaction

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

IRISH MEDICINES BOARD



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

IRISH MEDICINES BOARD

When should I unblind?

- SUSARs must be unblinded prior to submission per guidance

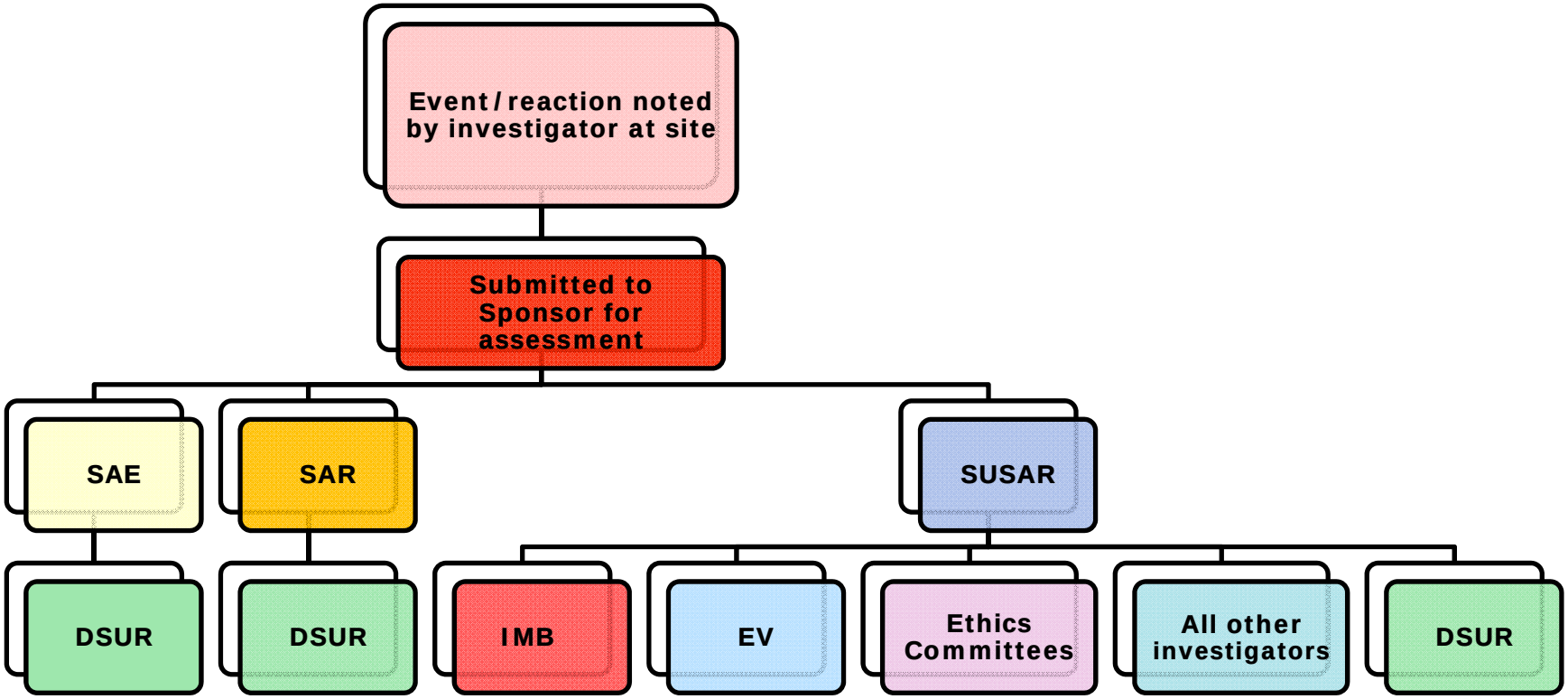
- Waivers on unblinding - needs to be proposed and agreed at authorisation stage of application – DSMB recommended

Points to consider

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

IRISH MEDICINES BOARD

Overview of Reporting



IRISH MEDICINES BOARD

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

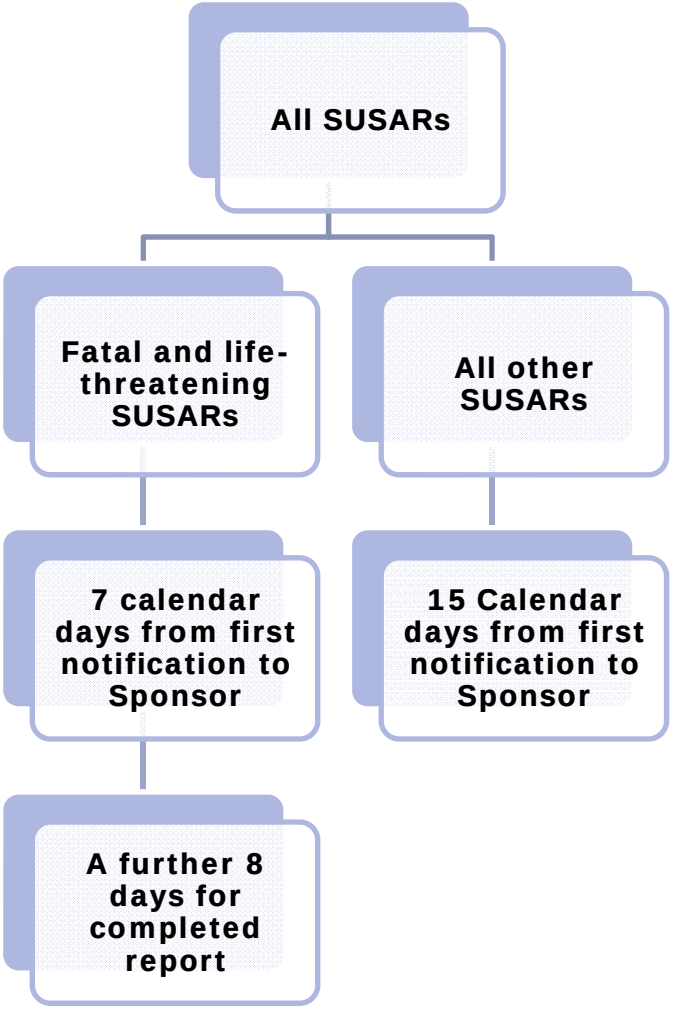
Suspected Unexpected Serious Adverse Reactions (SUSARs)

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?

IRISH MEDICINES BOARD

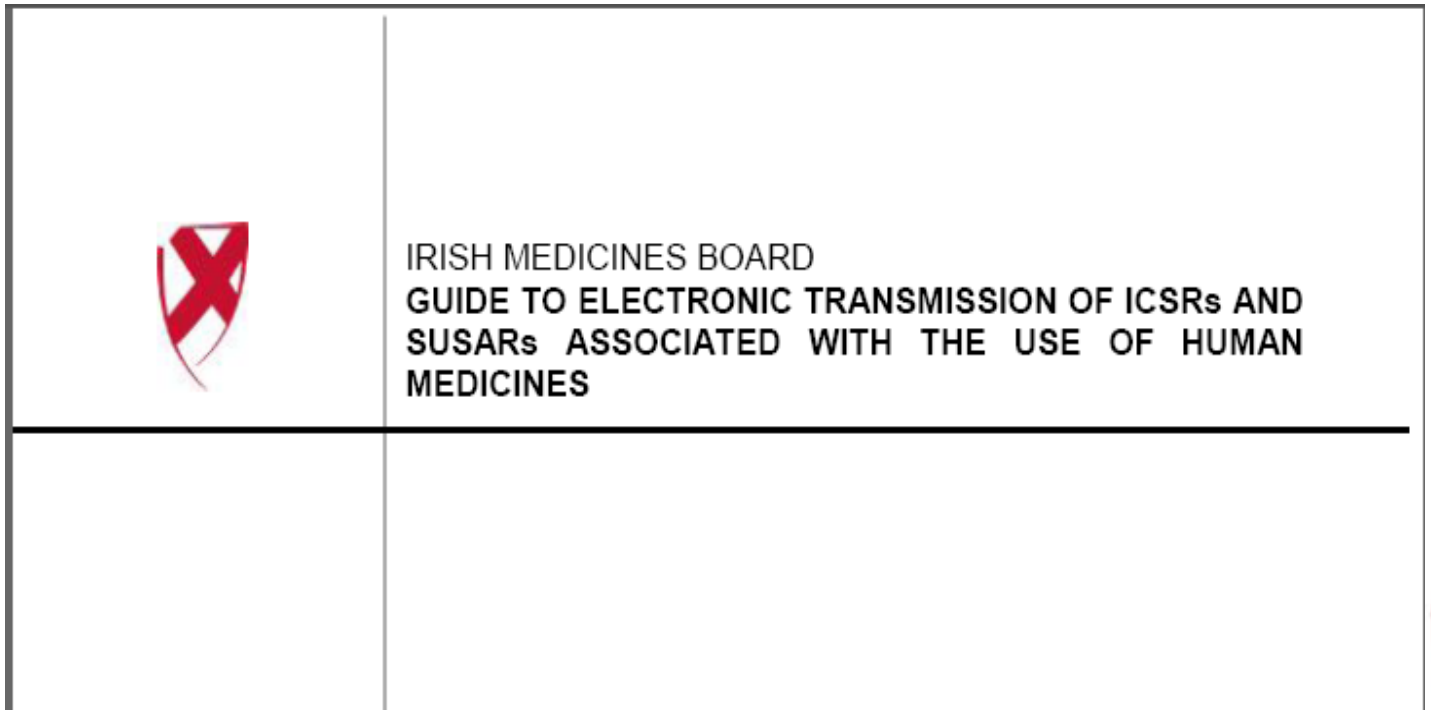
Timelines for reporting SUSARs to IMB and EV by Sponsor



IRISH MEDICINES BOARD

How does the Sponsor submit SUSARs to the IMB?

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



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

IRISH MEDICINES BOARD

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

IRISH MEDICINES BOARD

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

IRISH MEDICINES BOARD

Is there a specific IMB template SAE form available?

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

IMB CT number: Study protocol number:

IMB reference no. (follow up reports only):

☐ Initial Report Date of this report:
☐ Follow up to the report of:

1. PATIENT INFORMATION					
Patient initials	Date of birth	Age	Sex	Weight	Is the patient pregnant?
			☐ M ☐ F		☐ Yes ☐ No

2. DESCRIPTION OF THE SERIOUS ADVERSE EVENT

Category of event (*tick all that apply*):

IRISH MEDICINES BOARD

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

IRISH MEDICINES BOARD

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=

IRISH MEDICINES BOARD

Thank you

?

IRISH MEDICINES BOARD