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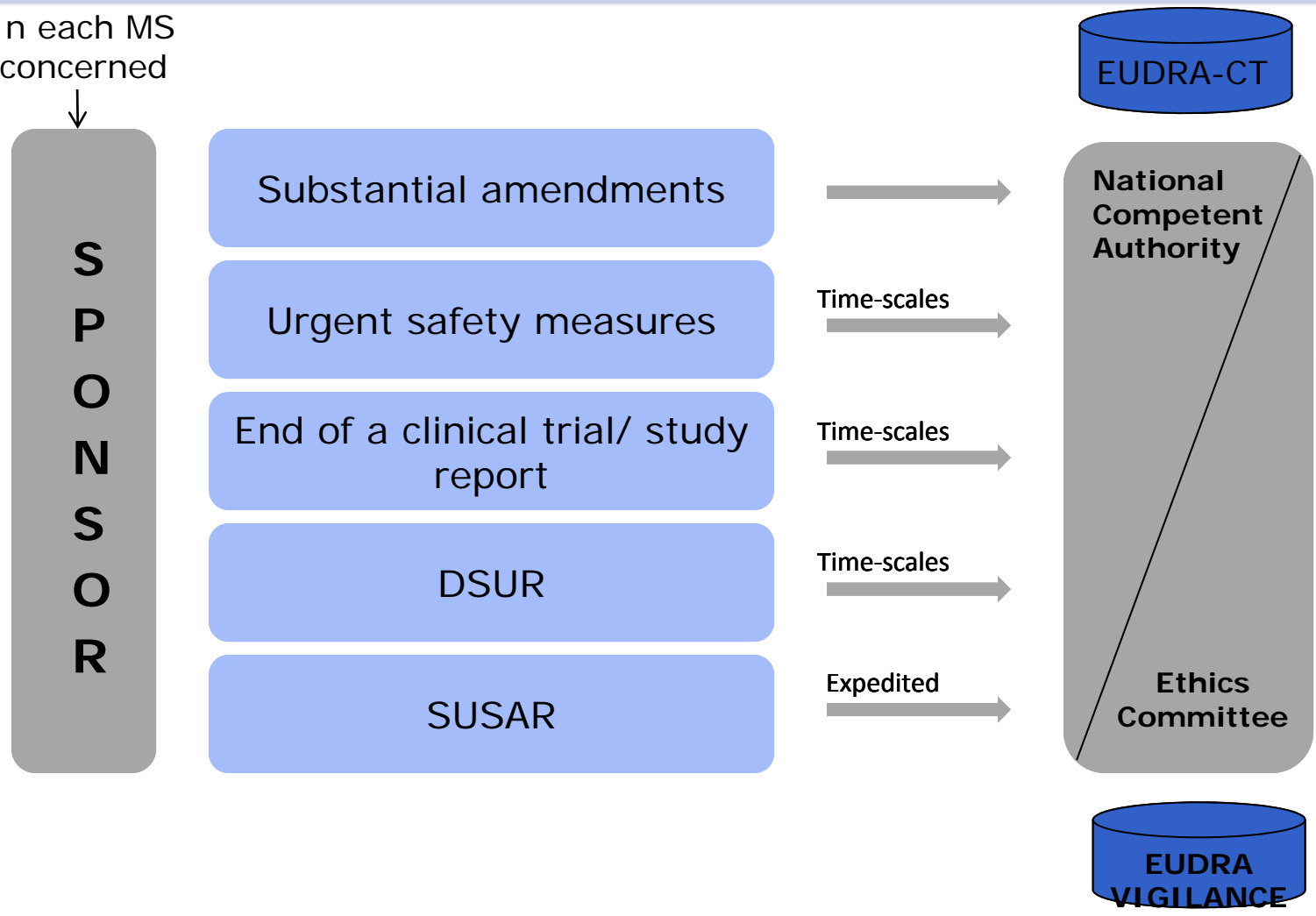
Life cycle of a clinical trial

IMB Clinical Trial Seminar June 19th

Dr. Agnieszka Przybyszewska, MD, MSc, PhD, PGDipPharmMed

Life cycle of a clinical trial

In each MS concerned



Life cycle of clinical trial

- [CT1 guideline](#) - Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments & the declaration of the end of the trial
- [E2F guideline](#) - Note for guidance on development safety update reports



<http://ec.europa.eu/health/documents/eudralex/vol-10/>



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Amendments

Amendments

Change to the documentation submitted to & approved by the National Competent Authority or Ethics committee

- Protocol
- Investigator's Brochure
- IMPD



Substantial



Non-Substantial



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When is an amendment substantial?



If likely to have a significant impact on: the safety or physical or mental integrity of the clinical trial participants, or the scientific value of the trial

- **Look for examples – CT1 guideline**
- Ask the IMB (clinical.trials@imb.ie)
- Submit an amendment as substantial



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What am I required to do about a substantial amendment?



Substantial amendments must be submitted to the Competent authority or/and Ethics committee **prior to the implementation**

Submit:

- Covering letter with the EudraCT number, the IMB CT number, the protocol number(s) affected by the amendment and the trial title
- EU Substantial Amendment Notification Form
- Amended documents with justification
- New version of documents
- Amended EU Application form (if required)



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If required, submit an amended EU Application Form



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Important!

Some amendments are substantial for Ethics Committees but non-substantial for the IMB

Examples:

- amendments relating to the clinical trial site or investigators
- amendment to the consent form & patient information leaflet



When is an amendment non-substantial?



Look for examples – CT1 guidelines

Examples:

- additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis
- minor clarifications to the protocol
- correction of typographical errors



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What am I required to do about non-substantial amendments?



Non-substantial amendments do not have to be notified to the IMB, however they

- **must be recorded** &
- submitted with a subsequent substantial amendment notification



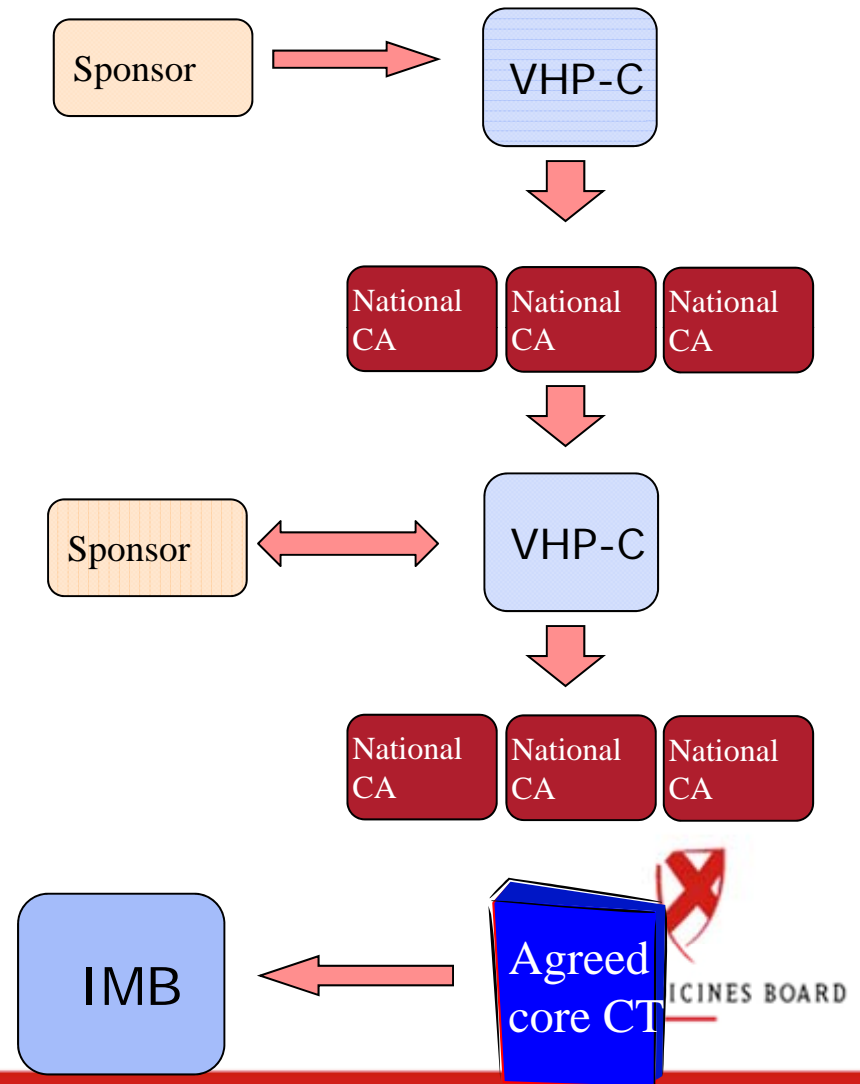
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Voluntary Harmonisation Procedure (VHP) – Amendments

Amendments

of studies assessed through VHP procedure can be assessed through VHP as well.

 VHP Coordinator:
VHP-CTFG@VHP-CTFG.eu



Annual update to the investigator's brochure

- In accordance with the legislation, the investigator's brochure is required to be validated and updated at least once a year.
- Revisions to the investigator's brochure can be substantial or non-substantial.



Urgent safety measures

Urgent safety measures may be taken **without prior** notification to the National competent authority/Ethics committee

Examples:

- for reasons of safety of the clinical trial participants, a trial is temporarily halted
- additional monitoring measures are set up



Urgent safety measures

Implement changes

Immediately  ↓

Send urgent safety measures notification (fax or e-mail)



Substantial amendment:

- protocol changes
- temporary halt of a trial

15 days



Declaration of the End of Trial if trial is stopped



SUSAR

Temporary halt of a trial

A temporary halt can be:

- part of an urgent safety measure
implementation → notification
- a substantial amendment
notification → implementation


The **restart of the trial** should be treated as a substantial amendment providing evidence that it is safe to restart the trial



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Declaration of the end of the clinical trial



- **Within 90 days** of the end of a clinical trial the sponsor shall notify the competent authorities of the Member State or Member States concerned & the Ethics Committee that the clinical trial has ended
- **In the case of early termination**, the sponsor must notify the end of the trial **within 15 days** 
- End of the trial is not defined in Directive 2001/20/EC. The definition of the end of the trial should be provided in the protocol



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Clinical trial summary report

- The sponsor should provide this summary report within **one year** of the end of the complete trial for non-paediatric clinical trials
- For paediatric clinical trials – **6 months**

EU Clinical
Trials
Register

In the future the results of clinical trials will be publically available on the EU Clinical Trials Register



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The Development Safety Update Report

- **Clinical trials Directive 2001/20/EC:**

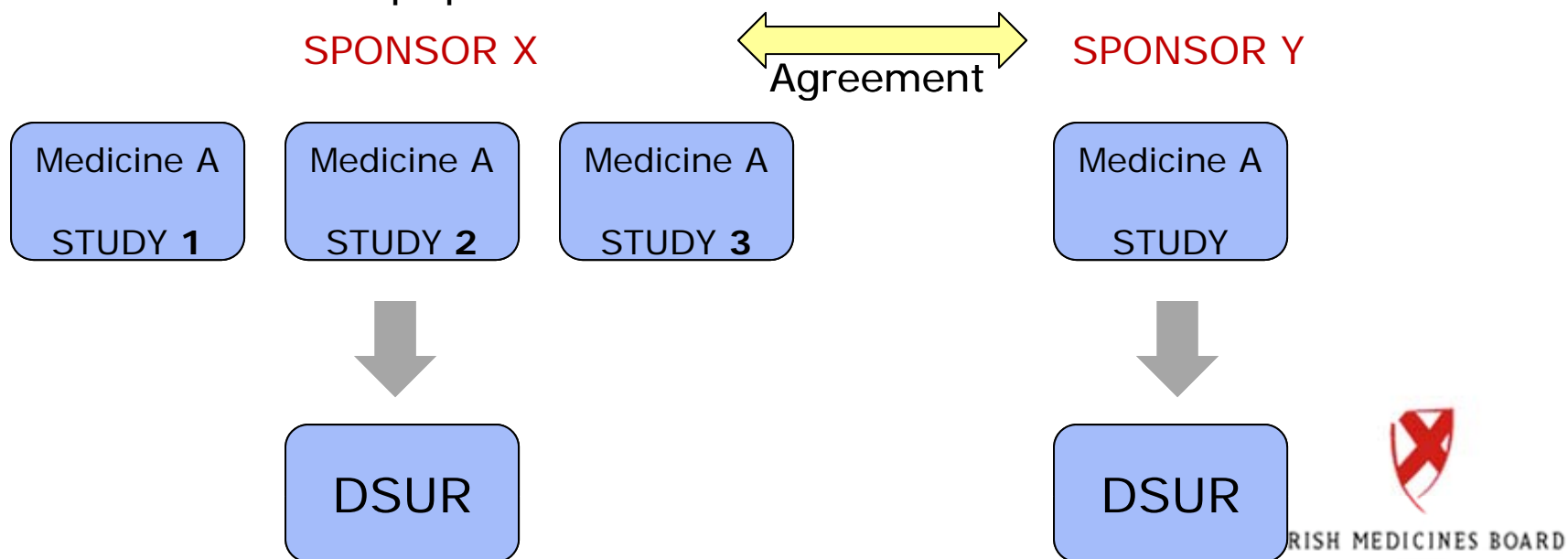
Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted & the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period & a report of the subjects safety

- From September 2011 – Annual Safety Report should be in Development Safety Update Report format - [E2F guideline](#)



The Development Safety Update Report

- **Single DSUR for an Active Substance**
- A single DSUR including safety data from all clinical trials for:
 - all indications
 - all dosage forms
 - all intended populations



When to **start** submitting a DSUR?

- A DSUR should be prepared **after the first authorisation** of a clinical trial.
- A copy of the DSUR should be submitted to each concerned Member State (MS) **if a clinical trial is authorised in this MS.**

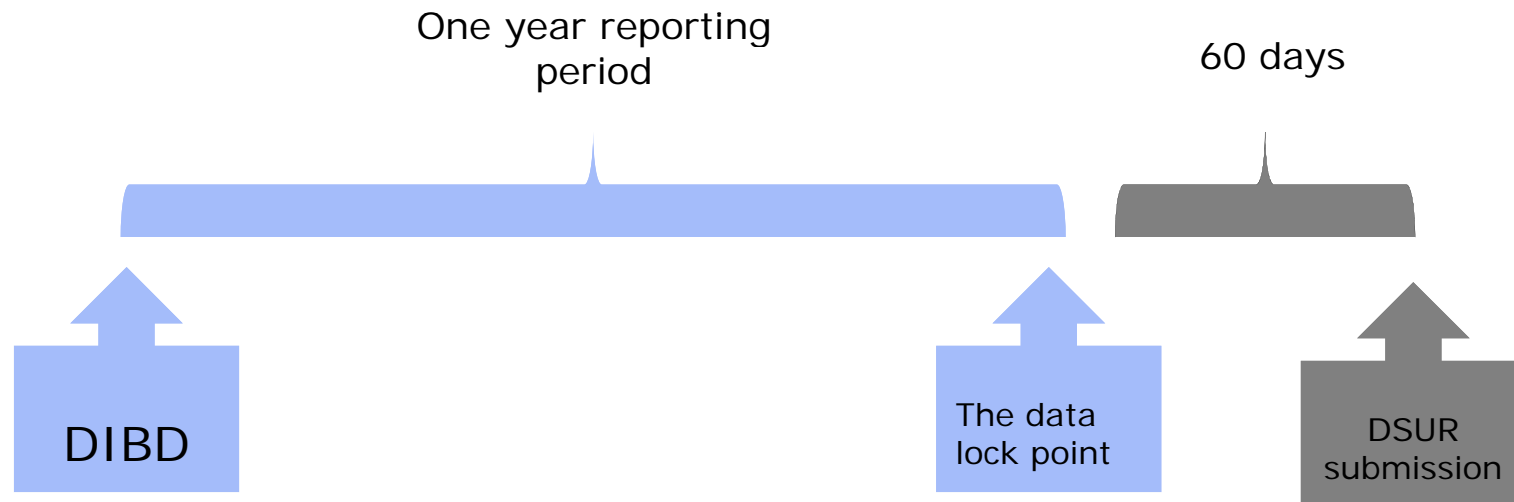


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Periodicity & DSUR Data lock point

DSUR needs to be submitted once a year

The "Development International Birth Date" (**DIBD**) is the date of the first authorisation of a clinical trial in any country worldwide



For authorised products "International Birth Date" (**IBD**) can be used - (<http://www.hma.eu>)

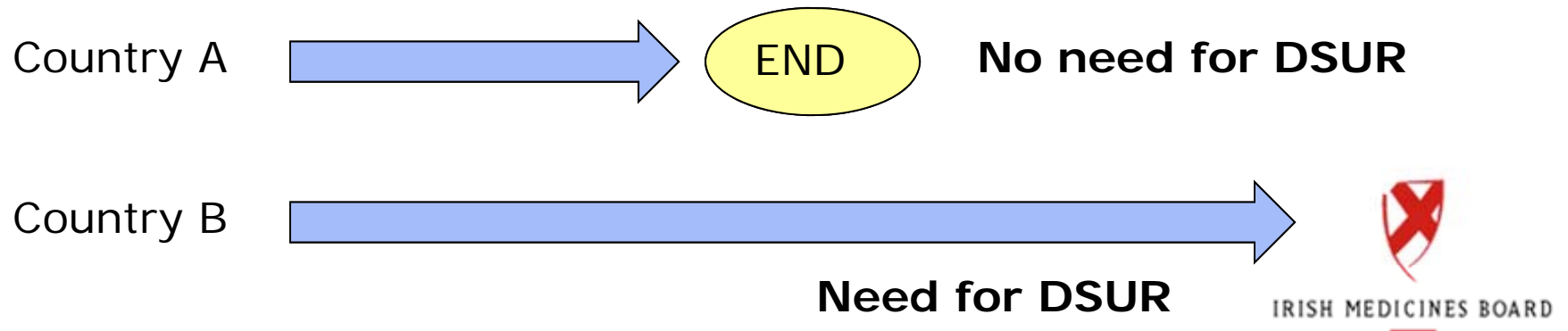


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When to **stop** submitting a DSUR?

- DSUR should only be submitted to the concerned MS(s) on which's territory the clinical trial has not ended yet.

Multinational Study (A+B)



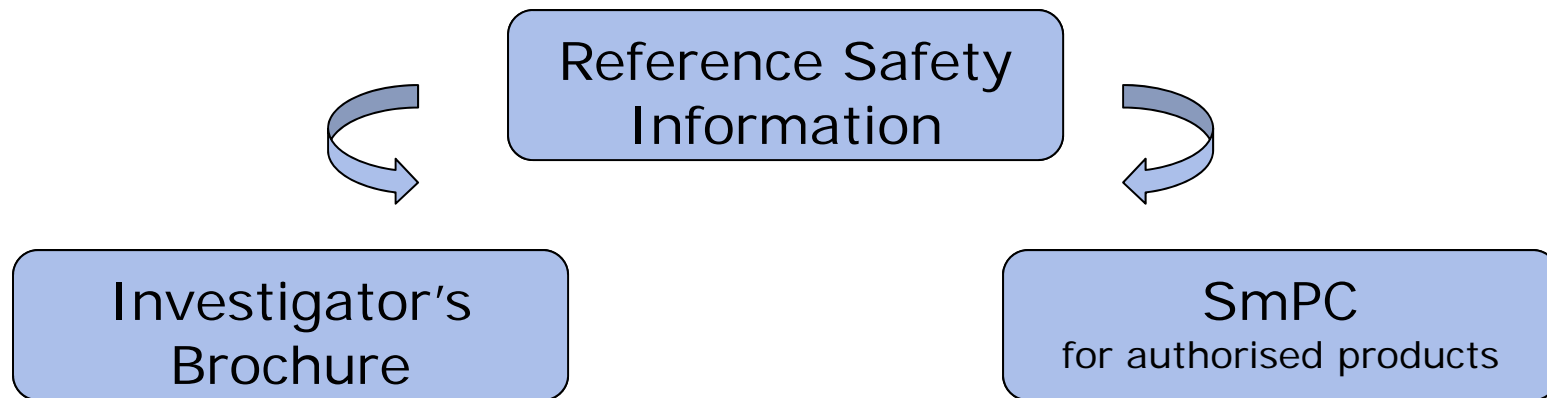
Format of the Development Safety Update Report

1. Executive Summary
 1. Introduction
 2. Worldwide marketing approval status
 3. Actions taken in the reporting period for safety reasons
 4. Changes to RSI
 5. Inventory of clinical trials ongoing and completed during the reporting period
 6. Estimated cumulative exposure
 7. Data in Line Listings and Summary Tabulations
 8. Significant findings from clinical trials during the reporting period
 9. Relevant findings from non-interventional studies
 10. Other Clinical Trial / Study Safety Information
 11. Safety findings from marketing experiences
 12. Non-clinical data
 13. Literature
 14. Other DSUR
 15. Lack of Efficacy
 16. Region Specific information
 17. Late-breaking information
 18. Overall safety evaluation
 19. Summary of important risks
 20. Conclusions
- Appendices



Reference Safety Information

- Information on the **Reference Safety Information** used for DSUR should be provided.



- Reference Safety Information is used to assess **expectedness**



Requirements for an academic sponsor.



I am an academic sponsor. Some information about the IMP is only held by the company. How I can meet the requirements ?

For IMPs with **the marketing authorisation**, simplified document based on the headings of the guidance could be accepted. **Only relevant & available information needs to be filled in for the DSUR.**



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Development Safety Update Report

Useful information:

- 'model DSURs' is available on the ICH website
(<http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>)
- Q&A document is published by the CTFG on the HMA website
(http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2011_12_22_Q___A_DSUR.pdf)



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Revision of the Clinical Trials Directive 2001/20/EC

- Revision of the CT Directive is ongoing
- The proposed Regulation will be presented by the **European Commission** to the European Parliament and the Council after August 2012



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Revision of the Clinical Trials Directive 2001/20/EC

The Clinical Trials Directive 2001/20/EC will be replaced by the **Clinical Trials Regulation**.

- Implementation of Directive



- Implementation of Regulation



Revision of the Clinical Trials Directive 2001/20/EC

Expected changes:

- Single submission with a subsequent “coordinated assessment procedure”
- Risk-based approach to clinical trials (less requirements, faster review process for “low risk” clinical trials)



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The IMB Clinical Trial Seminar June 19th



Any questions?



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