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Pharmacovigilance Requirements

Sinead Curran, QRAM

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Objectives

- Role of Pharmacovigilance (PV) in protection of public health
- Overview of legislation and guidance relevant to PV in the context of HPRA regulated IMP trials
- Focus the key requirements
- Provide sponsor considerations

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What is PV?

'Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem' (WHO, The importance of PV: safety monitoring of medicinal products)

Underlying objectives in EU medicines legislation:

- contributes to the protection of patients' and public health.
- preventing harm from adverse reactions in humans
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products.

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Why is PV important?

- 5% of all hospital admissions are due to an Adverse Reaction (AR)

- 5% of all hospital patients suffer an AR

- ARs are the 5th most common cause of hospital death.

- It is estimated that 197,000 deaths per year in the EU are caused by ARs

Source: Annex 2 of the Report on the impact assessment of strengthening and rationalising EU Pharmacovigilance COMMISSION OF THE EUROPEAN COMMUNITIES Sept 2008

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European Medicines Agency website; www.ema.europa.eu

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Medicines to be withdrawn due to serious allergic reactions and limited evidence of benefit ... Read more

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Measures include close monitoring and use of antibiotics to prevent pneumonia ... Read more

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More frequent MRI scans should be considered for patients at higher risk ... Read more

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Use to be avoided in patients at greatest risk and doses to be kept low ... Read more

27/02/2015 **Ambroxol and bromhexine expectorants: safety information to be updated**

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Animal health professionals

Pharmaceutical industry

Media professionals

Product emergency HOTLINE (Outside working hours)

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Pharmacovigilance legislation

PRIME Priority medicines

Clinical data publication

Data submission for medicines (Art.57)

Online side effects reports

FAQs about the Agency

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EMA reviews cancer medicine Zydelig

Press release

11/03/2016

EMA reviews cancer medicine Zydelig

Review follows concerns over serious adverse events in ongoing clinical trials

The European Medicines Agency (EMA) has, at the request of the European Commission, started a review of the cancer medicine Zydelig (idelalisib), which is authorised in the EU to treat two types of rare blood cancers called chronic lymphocytic leukaemia and follicular lymphoma (one of a group of cancers called non-Hodgkin lymphoma).

The review has been started because an increased rate of serious adverse events including deaths, mostly due to infections, was seen in three clinical trials[1] investigating the medicine in combination with other cancer medicines. The clinical trials involved patients with chronic lymphocytic leukaemia and indolent non-Hodgkin lymphoma. However, the study in chronic lymphocytic leukaemia investigated combinations of medicines that are currently not approved and the studies in non-Hodgkin lymphoma included patients with disease characteristics different from those covered by the currently approved indications.

Investigators of all clinical trials involving Zydelig are currently being informed of the actions to be taken in relation to the conduct of ongoing studies.

EMA will now review the data from these studies to assess whether the findings have any consequences for the authorised uses of Zydelig. In the meantime, patients starting or on treatment with Zydelig should be carefully monitored for signs of

Related information

- Zydelig: EPAR
- Zydelig: Article 20 procedures
- Zydelig: Pending EC decision

Contact point:

Monika Benstetter
Tel. +44 (0)20 3660 8427
E-mail: press@ema.europa.eu
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Clinical Trials and PV

- ICH GCP E6, Principle 2.2
- Before a trial is initiated, foreseeable risks and inconveniences should be weighted against the anticipated benefit for the individual trial subject and society.
- A trial should be initiated and continued only if the anticipated benefits justify the risks.

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EU: CT & GCP Directives

ICH Efficacy Guidelines

EU: Eudralex Volume 10 CT Guidelines (CT-3)

National: S.I no. 190 of 2004 (as amended)

ICH E6: GCP

ICH E2F: DSURs

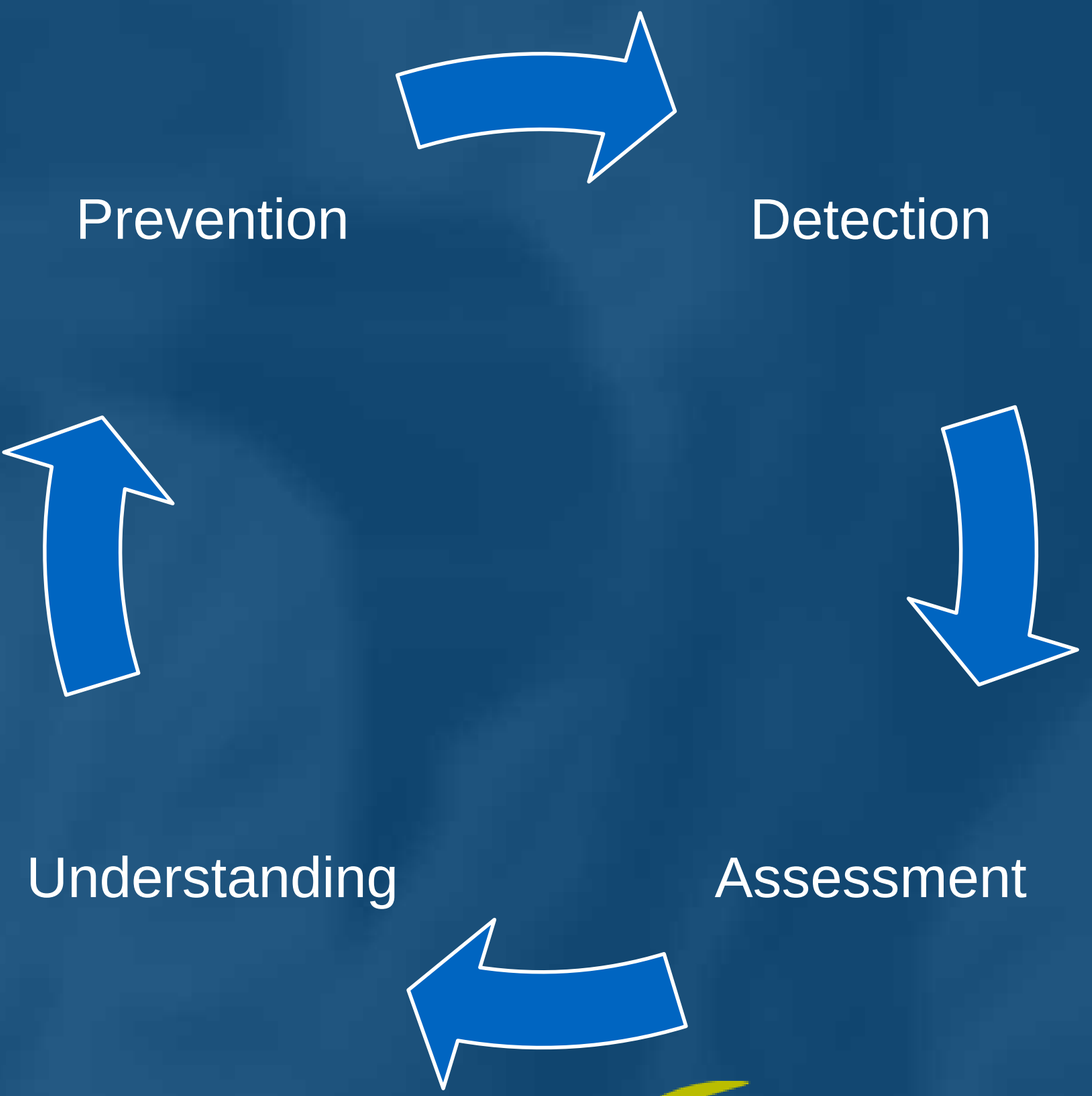
ICH E2A: Safety Data mgt.

Eudravigilance

HPRA Guide to Clinical Trial Applications

What is PV? ….in context of a Clinical Trial

‘Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem’



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Detection of AE: Definitions

- Provided for in legislation and included in protocol
- 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.
- Adverse Reaction (AR): reasonable possibility of causal relationship between the event and IMP
- Serious Adverse Event (SAE); meet serious criteria including, death, life-threatening, (prolongation) hospitalisation, disability/incapacity, congenital anomaly/birth defect, any other important medical event

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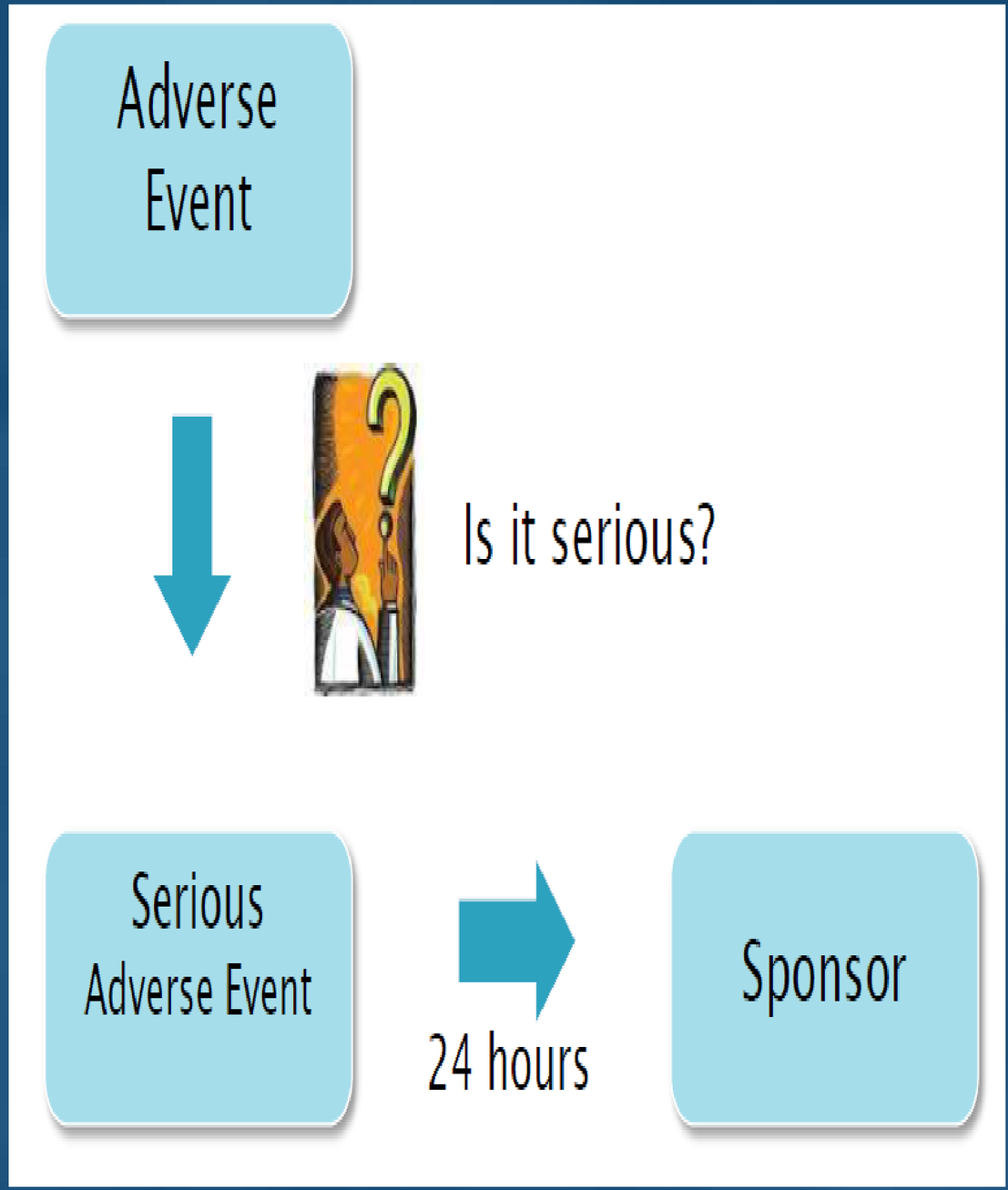
Detection of AEs: Collection

- Specified in Protocol/Study procedures
- Subject monitoring activities relative to risks: e.g. frequency of subject visits, lab/clinical assessments etc.
- Process for collecting, recording and reporting AEs onward to the sponsor, including timelines.
- SAEs:
  - Subject to immediate reporting from Investigator to Sponsor
  - Except those identified in protocol as not required



Sponsor Considerations: Detection

- ✓ Assessment to determine level of subject monitoring appropriate for the trial population, relative to the anticipated risks
- ✓ Ensure clear definitions/procedures provided for in the protocol, including any exemptions
- ✓ Study team training
- ✓ Monitor for compliance with procedures
- ✓ Reporting tools available for investigators e.g. SAE form for immediate reports
- ✓ Reporting system: e.g. email, phone, fax
- ✓ Process for receiving reports, with appropriate resource and back up

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Assessment

- Range of attributes for each (S)AE must be assessed.
- SAEs: Key attributes are causality and expectedness.
- Other attributes include severity, coding to MedDRA, checking for duplicates and evaluating the completeness of information etc..
- Assessment process determines if a case requires regulatory reporting (e.g. SUSAR)

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Assessment: Causality

- Assessment to determine if there is a reasonable possibility of causal relationship between event and the IMP
- Assessment made by the investigator. Should not be downgraded by the sponsor.
- The assessment is made on the basis that there are facts or arguments to suggest a causal relationship.
- The assessment may change as information on a case evolves over time.
- Output of Assessment:
  - AEs may be classified as Adverse Reactions (ARs)
  - SAEs may be classified as Serious Adverse Reactions (SARs)

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Assessment: Expectedness

- All SARs must be assessed as expected or unexpected
- Assessment is made based on the trial Reference Safety Information (IB, SmPC)
- Unexpected reaction: the nature or severity of which is not consistent with the applicable Reference Safety Information
- Regulatory assessment: based on what events are listed as having been previously observed, and not on the basis of what might be anticipated

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Assessment: Expectedness

- Determined by Sponsor, after receiving immediate report from Investigator
- Non commercial studies: Investigator may perform expectedness assessment, but difficult to ensure uniformity, and therefore must be monitored closely
- **Output of assessment:** SARs may be assessed as SUSARs

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SUSAR Reporting

- SUSAR - Suspected Unexpected Serious Adverse Reaction
- Subject to regulatory reporting requirements – ‘expedited reporting’
- SUSARs must be submitted electronically to Competent Authority and/or to Eudravigilance (EV) database (EMA).
- Reports must also be made to trial investigators and EC
- Timelines - Fatal/Life threatening: 7 days. All others: 15 days
- HPRA may agree, by prior arrangement, to submit reports to EV on behalf of sponsors.

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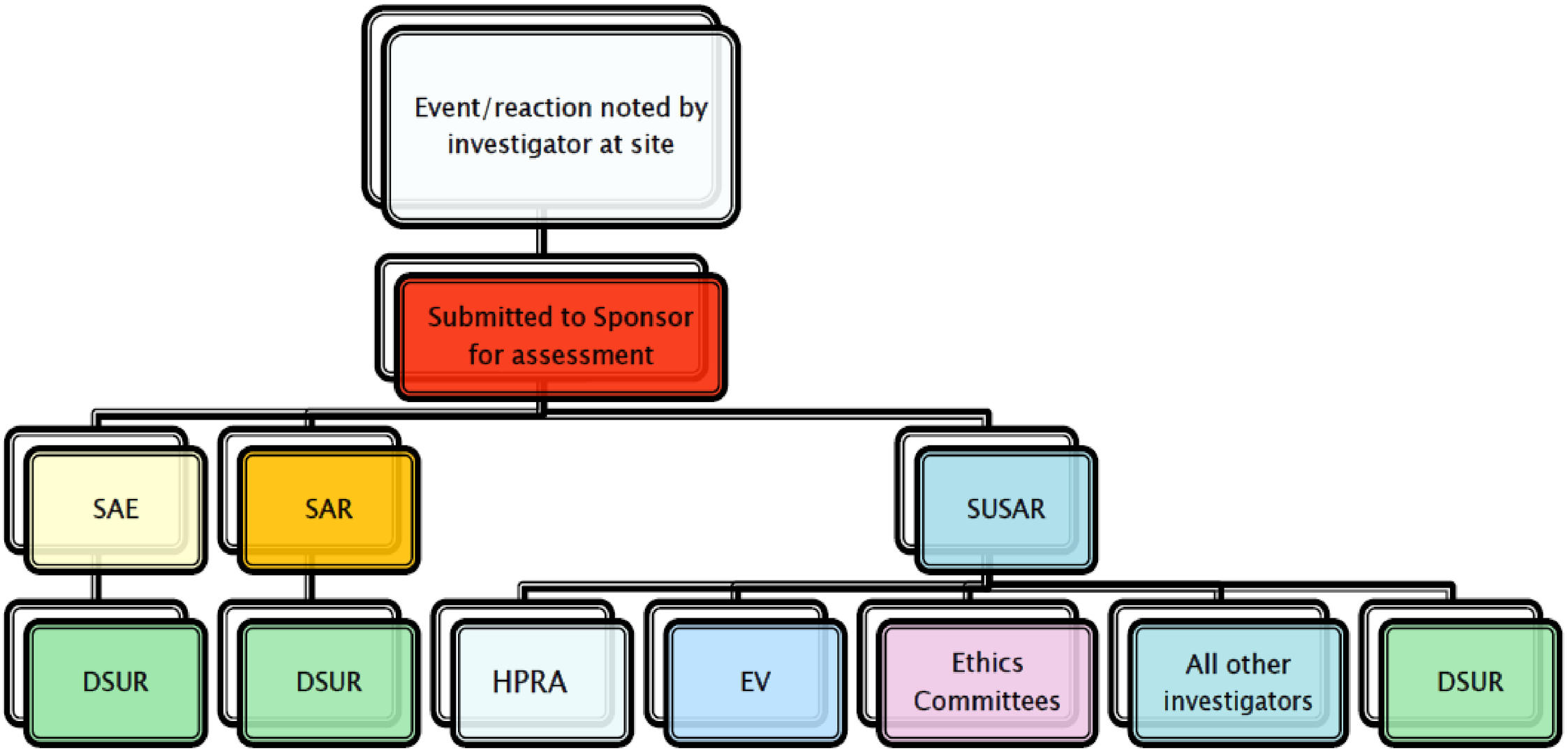
Summary of Assessment/Reporting Process



Sponsor Considerations: Assessment

- ✓ Considerable communication, data management, technical and clinical process

- ✓ Systems and procedures at every stage of assessment:
  - ✓ On receipt of a case: duplicate and validation check
  - ✓ Expectedness assessment by trained personnel, using the correct RSI for trial
  - ✓ Technical coding of event terms to MedDRA
  - ✓ Consider completeness of information and follow-up, as appropriate
  - ✓ Criteria for case classification (SAR, SUSAR)
  - ✓ Procedures for regulatory reporting to HPRA
  - ✓ Regulatory unblinding procedure, if relevant
  - ✓ Process for maintaining detailed records, including case files and safety database
  - ✓ Defined data entry instructions for personal
  - ✓ Monitoring for compliance with reporting timelines
  - ✓ Etc…

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Understanding the evolving safety profile

- Does the evolving safety profile indicate a change in the initial risk assessment?
- Typically (outside of formal interim analysis):
  - Qualitative assessment using sound clinical judgement
  - Bradford Hill criteria – basis for causation assessment and understanding safety information as it evolves during a trial
  - Due account for control of bias, as needed

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Not expected for ongoing safety monitoring in CT

- Application of complex statistical quantitative methods

4.4. The chi-square (χ^2) statistics

The Chi-square is a statistic, which is traditionally used in disproportionality analyses. In certain standard queries of the EudraVigilance Data Analysis System, the Chi-square is used as an alternative measure of association between the medicinal product P and the adverse event R based on the following calculation:

$$\chi^2 = (AD - BC)^2 (A + B + C + D) / [(A + B)(C + D)(A + C)(B + D)]$$

The PRR is computed as follows[3]:

$$PRR = \frac{A/(A+B)}{C/(C+D)}$$

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Understanding the evolving safety profile

- Continuously weigh anticipated benefits and risks of the clinical trial, which includes ongoing safety evaluation of IMPs
- Requires a multifaceted approach
- ICH E2F, DSUR:
  - Periodic analysis of safety information is crucial to the ongoing assessment of risk to trial subjects
  - Must ‘not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected
  - Other ‘signal management process/data safety monitoring activities’ required

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DSUR

- Relevant guideline: ICH E2F, defines content, reporting timelines
- A comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:
  - (1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;
  - (2) describing new safety issues that could have an impact on the protection of clinical trial subjects;
  - (3) summarising the current understanding and management of identified and potential risks; and
  - (4) providing an update on the status of the clinical investigation/development programme and study results

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Signal Management Process

What is a signal?

“Information that arises from one or multiple sources (incl. observations and experiments), which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action”

Practical Aspects of Signal Detection in Pharmacovigilance Report of CIOMS Working Group VIII, Geneva 2010,

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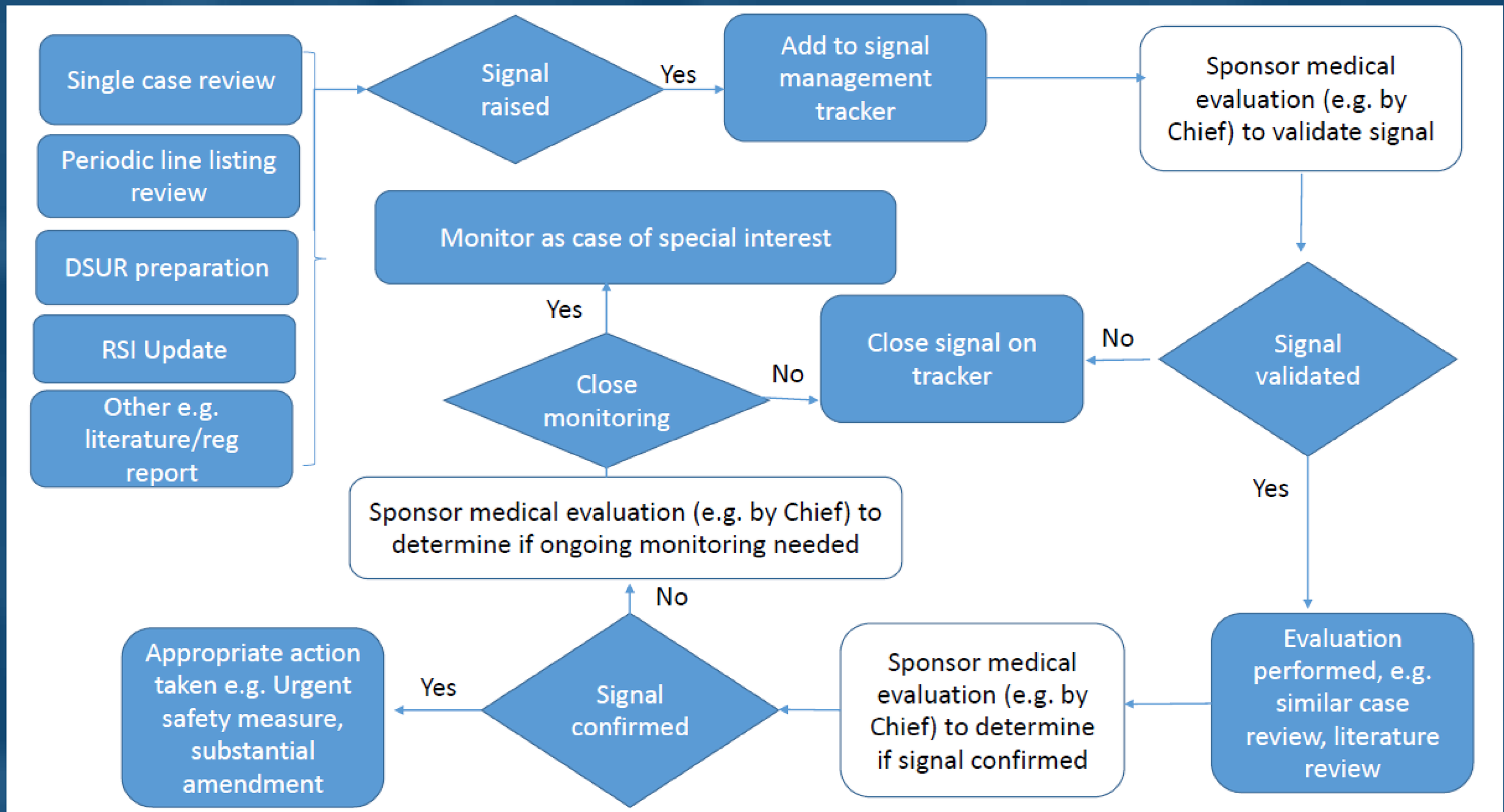
Signal Management Process



Data Monitoring Committee

- Formalised approach to ongoing risk/benefit monitoring in a trial, typically with broader remit than safety alone

- Sponsor must decide when it is appropriate to use a DMC and the type e.g. Independent for blinded randomised trial, internal safety committee for a Phase I dose escalation study

- IDMC: Charter, Inclusion of IDMC reports as part of Data Management Plan, Method for documenting and communicating DSMB recommendation

- Similar principles should be applied for internal safety monitoring committees

- EMA Guidance on DMCs (Doc. Ref. EMEA/CHMP/EWP/5872/03):
  - Groups overlook clinical trial conduct (including safety, quality, integrity)
  - Assess the need for a DMC
  - Responsibilities of a DMC/Establishing a DMC
  - Working Procedures

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Sponsor Considerations: Understanding

- ✓ DSUR:
  - ✓ Adherence to reporting timeline
  - ✓ Format/content complies with requirements
  - ✓ Data are complied in an accurate/complete manner (QC checks), including information on safety amendments, updates to RSI, SAEs, SARs.
  - ✓ Review by sponsors medical expert, typically the Chief Investigator
  - ✓ Care taken in case of unblinded information, to control for bias

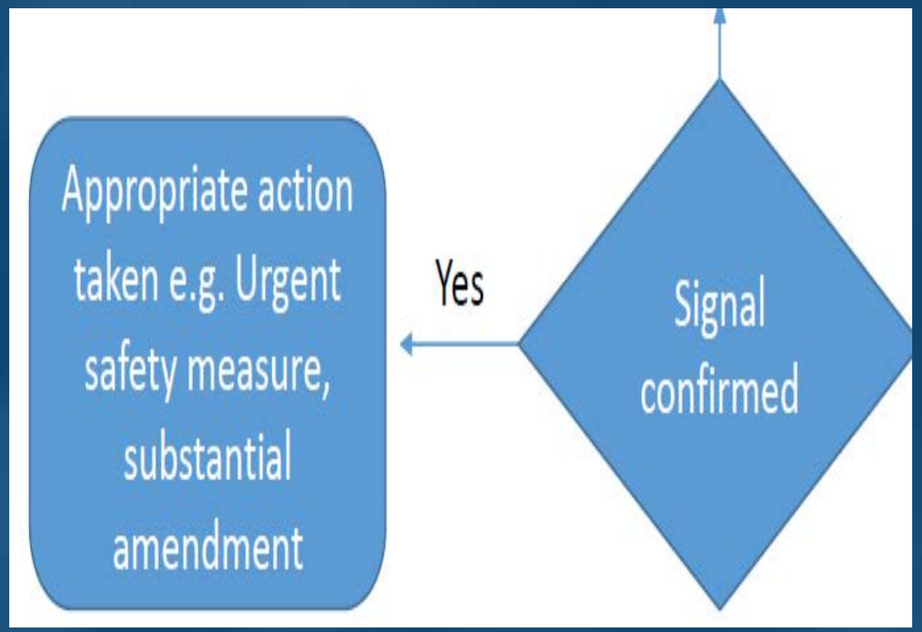
- ✓ Ongoing safety monitoring and signal management, based on appropriate risk assessment and is suitable to the nature and design of the trial

Prevention

- Level of subject monitoring in a trial should be proportionate to the risk

- Trial continued on if the anticipated benefit continues to justify the risk

- If new/potential risk evolves, the sponsor should take appropriate action



- May require an amendment to protocol, patient information sheet for example (substantial amendment)

- Appropriate regulatory procedure followed: Substantial Amendment, Urgent Safety Measure, Suspension/Hold on the trial

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Recommended reading

- CT-3: http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

- ICH E2F: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf

- National Institute for Health Policy for Data and Safety Monitoring: https://grants.nih.gov/grants/guide/notice-files/not98-084.html

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Thank you

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