Pharmacovigilance and Safety Reporting

26th August 2015

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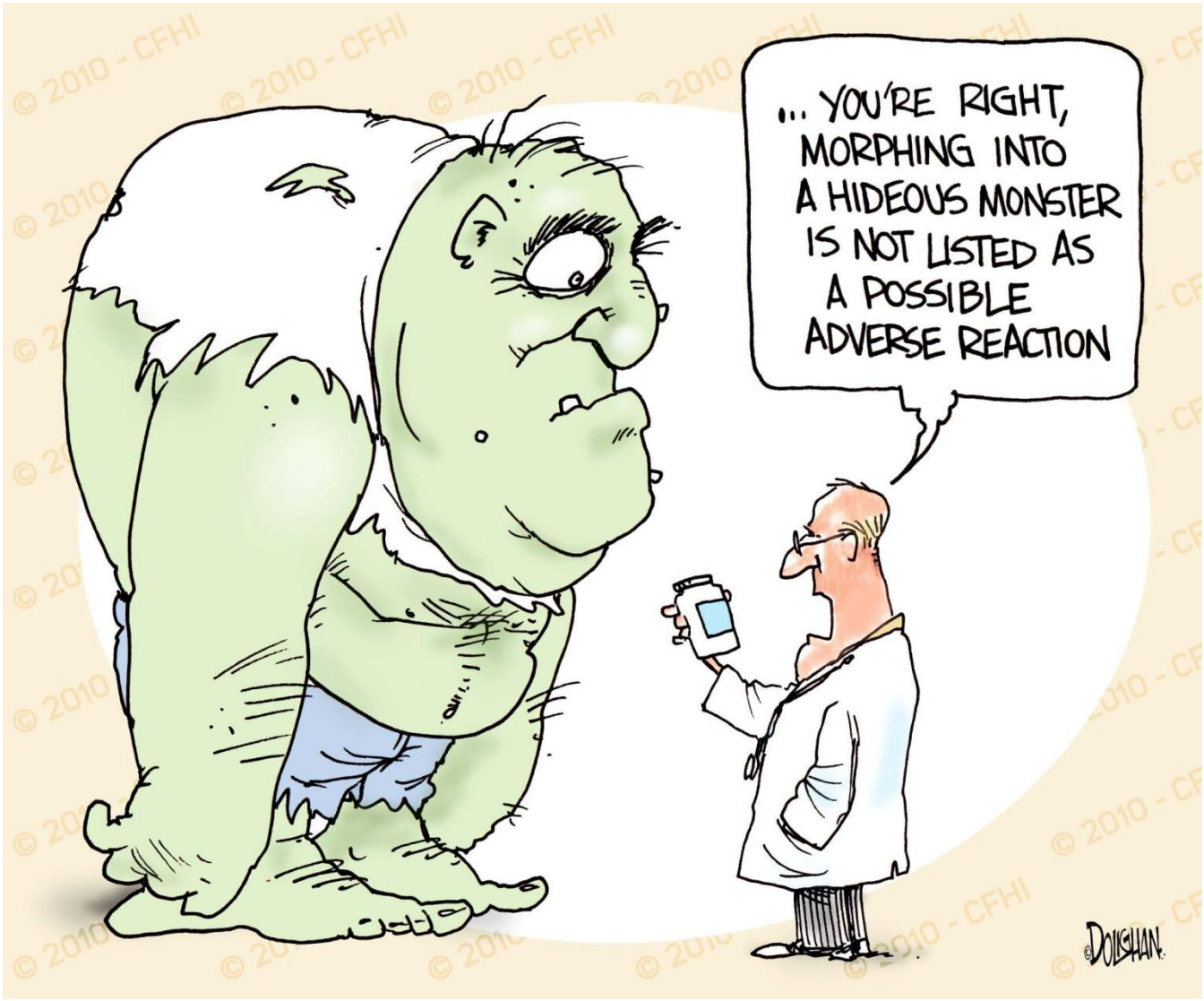
Tales of the Unexpected



What we will cover in today's session

1. PV: What is it, why do we do it, when did it all begin
2. Definitions
3. Adverse event reporting: Assessment and categorisation
4. Risk Assessment
5. Expedited reports and Aggregate reports/ DSUR
6. Odd points

Section 1

PV: What, why, when

What is Pharmacovigilance?

- **Pharmacovigilance** (**PV** or **PhV**), also known as **Drug Safety**, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products

pharmakon (Greek for drug)

vigilare (Latin for to keep watch)

Why do we collect safety data in trials?

- Compulsory: Regulatory requirement/ embedded in law
- Good quality safety data improves the accuracy of prescribing information
- The UK data contributes significantly to drug safety all over the world

To foster the rational and safe use of medicines, worldwide

By what methods?

- Pre-marketing/Trial Phase:
  - SAE reports to PV department
  - Annual reports (DSUR/IND Annual Report)
- Post-marketing/Approved Drug Phase:
  - Spontaneous reports (yellow card)
  - Reports (PSUR/PADER)

Regulatory reports are of 2 types:

1. Expedited
2. Aggregate

When did regulatory efforts on drug safety data collection begin?

- Thalidomide (1957 to 1961) was the trigger (FDA submission Sep 1960)
- Horrific birth abnormalities were not reported as no such system existed at the time
- It took several years before there was awareness of what was happening
- In 1962, the US enacted legislation (Kefauver- Harris Amendment) requiring tests for safety during pregnancy. The amendment also mandated that pharmaceutical manufacturers having an NDA must report adverse events to the FDA.

History of PV 1

1962: Thalidomide legislation

1968: World Health Organization Pilot Project

started to pool adverse drug reactions from multiple countries

1997: ICH E2B adopted

Electronic reporting standard agreed worldwide

1999: Revised MedWatch, draft MedDRA

MedWatch is the form used to report adverse events to FDA (FDA 3500A/CIOMS)

1999: Institute of Medicine – report on errors and risk issues

Introduction of risk management concepts

History of PV 2

2001: Post marketing safety reporting guidelines

FDA Guidance on how to report adverse events in post marketing phase

2002: PDUFA III

Prescription Drug User Fees Acts allowed FDA to charge fees

Allowed FDA to monitor risk post approval, requires companies to monitor risks 2 yrs post approval

2003: The “Tome”

94 pages of proposed rules on adverse event reporting

Pre-marketing section finalised in 2010

History of PV 3

2004: Draft risk management guidelines

2005: Final risk management guidelines

Specifies how to perform signal detection, risk assessment and risk mitigation

2007: FDA Amendment Act

2008: Volume 9A in EU

2010: New IND Reporting Rule

2010: European PV legislation passed

History of PV 4

2011: Volume 10 (Eudravigilance)

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') , (2011/C 172/01)

2012: European PV legislation effective (UK SI 2012 No 1916)

2014: MHRA Good Pharmacovigilance Practice for Medicines (Dec 14)

Several drugs with safety concerns in the last decade

- Eg. Seroxat, Vioxx, Celebrex

- “We recommend that more research be undertaken into the adverse effects of drugs, both during drug development and medicines licensing” Health Committee Report 22Mar2005

Objectives of Pharmacovigilance

- Detect serious risk during a clinical trial
- Communicate risk to patients
- Provide adequate information to Investigators
- Assess risk for risk benefit equation

The safety of a drug

- ..... is not necessarily about being on average worse than the gold standard drug
- A single event in a small database can constitute a major concern (seizure, sudden death)
- A drug may be withdrawn due to 2 or 3 serious events occurring in the marketing phase

The likelihood of observing adverse reactions in a clinical trial of 2,000 patients

# Patients	ADR Threshold	Sample ADR	Probability
2,000	1 / 500	Lymphoma from azathioprine	0.98
2,000	1 / 1,000	Eye damage from practolol	0.86
2,000	1 / 5,000	MI in older women from OCP	0.33
2,000	1 / 10,000	Anaphylaxis from penicillin	0.18
2,000	1 / 50,000	Aplastic anemia from chloramphenicol	0.04

Unlikely to be seen in clinical trial phase

Nomifensine/Merital

- First used as an anti depressant in Germany in 1976, in the UK in 1977 and in the US in 1985
- From 1978 to 1985 approx 200,000 prescriptions written each year
- 4 reports of haemolytic anaemia received by manufacturer between 1978-1979
- Case report published 1979
- 3 more cases in UK 1981-1982
- 1981 – label changed to indicate rare cases of haemolytic anaemia
- UK fatalities first reported in 1985
- June 1985 incidence of haemolytic anaemia stated as 1 in 20,000
- Nov 1985 incidence stated as 1 in 4,000
- Drug withdrawn Jan 1986 worldwide

- 10 million patients exposed, 11 deaths
- 2 drug related deaths failed to be reported to the FDA
- Criminal charges brought, fines were the maximum allowed by law

Take home message: Why we need to be concerned about rare events

- If your trial identifies a rare serious adverse drug reaction then this data is extremely important in a global context and it must be communicated quickly to the regulatory authority concerned - so that the information can be shared globally in a standardised format
- Every day more patients are put at risk, so speed is essential

Investigator Responsibilities (ICH GCP 4.11.1)

- Reporting of SAEs to sponsor
- Reporting of certain non-serious adverse events and/or lab abnormalities

Investigator shall report SAEs “immediately” to the sponsor except for those that the protocol or IB identifies as not requiring this.

Reports should be made in a short timeframe and under no circumstances should this exceed 24 hrs following knowledge of the SAE.

Immediate report shall be followed up by detailed, written reports.

Subjects identified by study code number ONLY.

Sponsor Responsibilities

- Recording of AEs/Keeping detailed records
- Reporting of SUSARs to the MHRA and ethics committee
- Informing the Investigators
- Annual safety reporting to the MHRA and ethics committee

Sponsor responsibilities may be delegated!

Section 2

Definitions

Adverse Event ICH GCP 1.2 Definition

- Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
- An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product

Serious Adverse Event ICH GCP 1.50 Definition

- Any untoward medical occurrence that at any dose:

Results in Death

Is Life-threatening

Requires In Patient Hospitalisation

or Prolongation of Existing Hospitalisation

Results in Persistent or Significant Disability/Incapacity

Is a Congenital Anomaly/Birth Defect

Is an Important Medical Event

Some debatable concepts

- Life threatening – subjective, “immediate risk”
- Requires hospitalisation – there are some grey areas here
- Serious/Important without requiring hospitalisation
- The concept of a “significant” disability

Life threatening

- At immediate risk of death
  - Pulmonary embolism
  - GI haemorrhage
  - Stroke (Haemorrhagic)

NOT:
If worsened would have been life threatening

Important Medical Events

Important medical events may not be immediately life-threatening or result in death or hospitalisation

but may jeopardise the subject's safety or may require intervention to prevent a Serious Adverse Event e.g., increased serum creatinine levels, anaphylaxis treated with epipen

Non-Reportable Serious Adverse Events

- Hospitalisations described in the Protocol e.g., for drug administration or protocol required tests.
- Hospitalisations for social reasons in the absence of an AE e.g., subject with Alzheimer's Disease admitted to hospital in order to give caregiver relief.
- Surgery/Procedure planned prior to trial entry (record in CRF at screening visit)

Protocol Defines

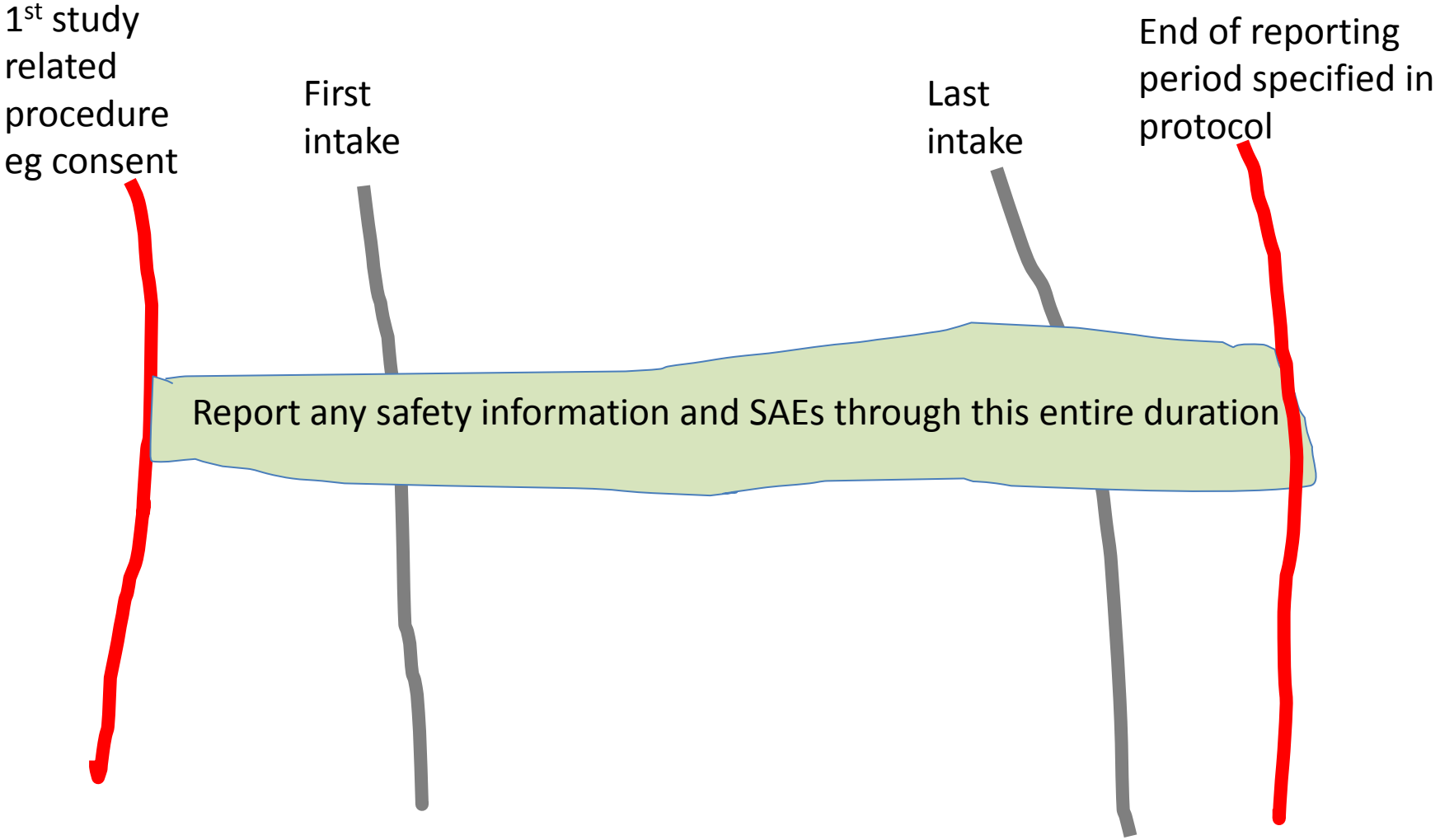
- Accident and Emergency visit – subject treated and released
- Subject held 24 hrs for observation and not admitted
- Procedure performed in hospital on an out-patient basis (if stay <24 hrs)
- Treatment at centres not associated with a hospital, usually for minor surgical procedures, e.g., chiropody, laser eye surgery

Protocol Defines

Section 3

Adverse event reporting: Assessment and categorisation

AE/SAE Reporting period in a trial



End of Trial has occurred: SAE Reporting in this period?

- No obligation to actively monitor subjects for SAEs after trial participation has ended.
- However, if made aware of SAEs after trial end, then these should also be reported to sponsor.

- Collecting AEs/SAEs from the First Trial Related Procedure Means:
  - AEs could occur when no medicinal product has been taken
  - More conservative than ICH definition during pre-randomisation phase of trial
- **Rationale: Conservative approach to patient safety.**
- Allows us to consider: Do trial related procedures affect patient's safety?
- Are we giving the study subject full and complete information?

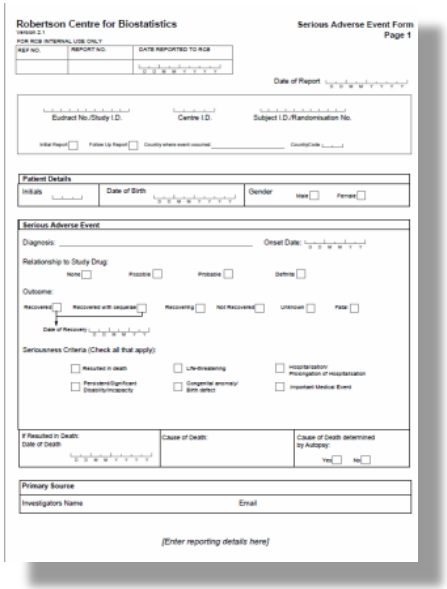
How do I report an SAE?

Comply with Sponsor's reporting requirements.

Phone/Email

Electronically

Fax



How to report a SAE for a trial sponsored by NHS Tayside/University of Dundee

- Use the form on the TASC website
- Follow the exact instructions in your protocol

- Consider if the SAE is reportable or not before preparing the form!

Pharmacovigilance in Tayside

Contact:
Pharmacovigilance Section
Tayside Medical Science Centre (TASC)
Level 3, Residency Block
Ninewells Hospital & Medical School
Dundee

pharmacovigilance.tayside@nhs.net
Tel: 01382 383455

Further Information: http://www.tasc-research.org.uk

- TASC Pharmacovigilance Policy
- TASC SOP11 Identifying, recording and reporting AEs for CTIMPs (includes all forms)

Minimum essential elements for completion of SAE Report according to Guidance

The SAE Report form shall include, as a minimum, the following essential elements:

- EudraCT number
- Sponsor study number
- Coded Subject ID
- 1 identifiable reporter
- One Suspected event
- One suspect IMP
- Causality assessment
- Sender's case report unique identifier
- Receipt date of initial information (Day 0)
- Receipt date of most recent information
- Worldwide unique case identification number
- Sender identifier

**If relatedness and expectedness have not yet been assessed by a medically qualified practitioner the initial report should be sent within one working day anyway. A follow up signed copy with the assessment outcomes should be sent as soon as possible.

Does this apply to the drug in the trial only? - No

Includes

- Comparator drugs or drugs studied in combination
- Placebo
- Repackaged drugs

Excludes

- Allowed or required concomitant medications

Adverse events of special interest

- Some trial protocols ask for AEs of special interest to be reported via the SAE reporting pathway or an alternative pathway
- These are usually events considered to be of particular concern to the sponsor, for which they wish to have immediate notification

Completing the SAE form requires some decisions

- Severity
- Causality
- Expectedness

Assignment of Intensity/Severity

- Mild
- Moderate
- Severe

The event may be of minor significance but may be severe eg headache/migraine

Do not confuse severity with seriousness

Intensity	Characteristic	Intervention
Mild	Awareness of sign, symptom or event	Tolerated; no or minimal intervention
Moderate	Discomfort enough to cause interference with usual activity	May warrant intervention
Severe	Incapacitating with inability to do usual activities or significantly affects clinical status	Warrants intervention

Assignment of Causality

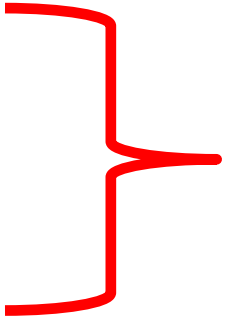
- Relationship to study medication:

None

Possibly

Probably

Definitely



Related

Who assigns causality?

- **PI only**

- Possibly related is not the default answer if you aren't sure
- Seek support if you find it difficult to decide

Definitely Related

- Event or lab test abnormality with plausible temporal relationship to drug exposure
- Cannot be explained by disease or con meds
- Response to withdrawal plausible (ie event lessens)
- Objective and specific medical disorder
- **Positive rechallenge** = Proof

Probably Related

- Event or lab test abnormality with reasonable temporal relationship to drug exposure
- Unlikely to be attributed to disease or other con meds
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possibly Related

- Event or lab test abnormality with reasonable time relationship to drug intake
- Could also be explained by disease or other con meds
- Information on drug withdrawal may be lacking or unclear

Not Related

- Event or lab test abnormality with a temporal relationship to drug exposure that makes a relationship to drug improbable (but not impossible)
- Disease or other con meds provide plausible explanations

Consider

- If the study drug may have changed the pharmacology of con meds by metabolic interaction

- Scenario where study drug is possibly related but suspect drug for the reaction seen is a con med

Assignment of Expectedness

Definition of Unexpected ICH GCP 1.60

- **An adverse event, the nature or severity of which is not consistent with the applicable product information i.e. 'expected' ADR**
- E.g., Investigator's Brochure for an unapproved investigational product Or, package insert/summary of product characteristics (SmPC) for an approved product

This is frequently interpreted INCORRECTLY as "we expected this person to have this medical issue" or "this medical issue was a surprise from the researcher's point of view"

Expected	Unexpected
Previously observed and documented	Not previously observed and documented
	Anticipated by pharmacological properties but not yet observed

Re-Phrase the Question

- Expected/Unexpected?

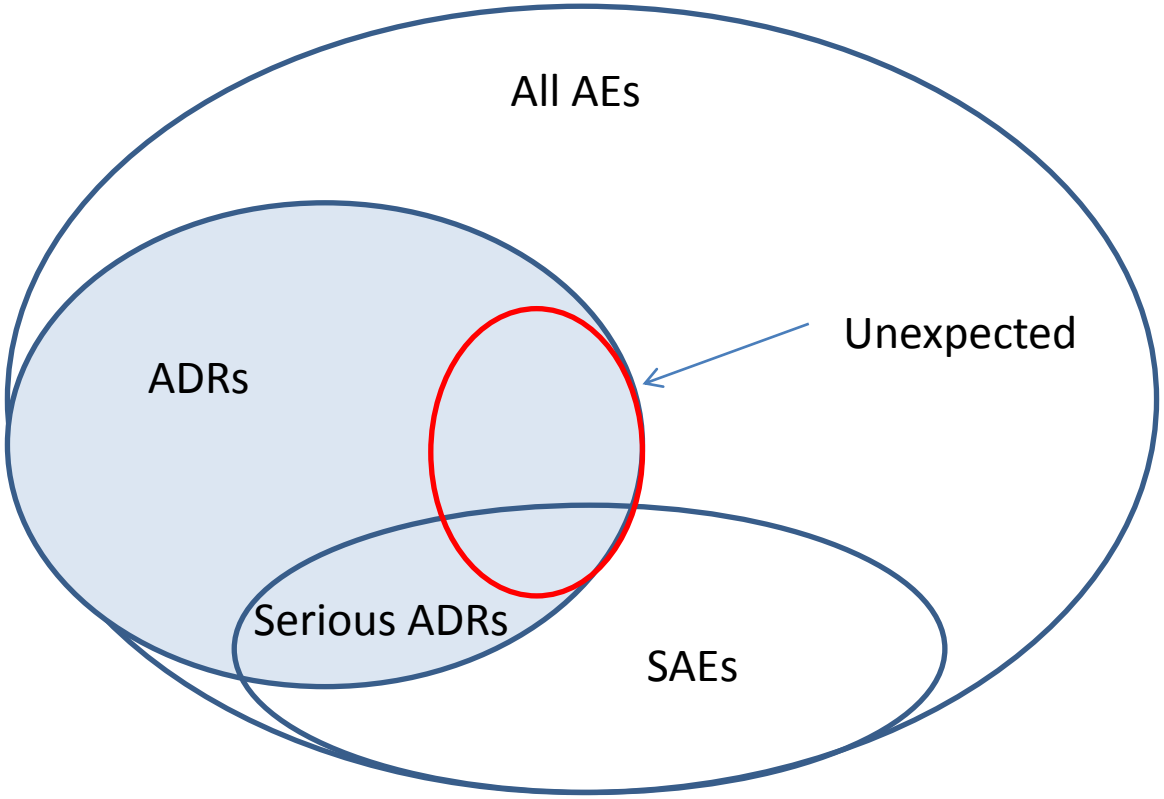
The real question being asked here is “Is this event described in the reference safety information ie. The IB or SmPC?”

Even if described as a rare event, it is expected

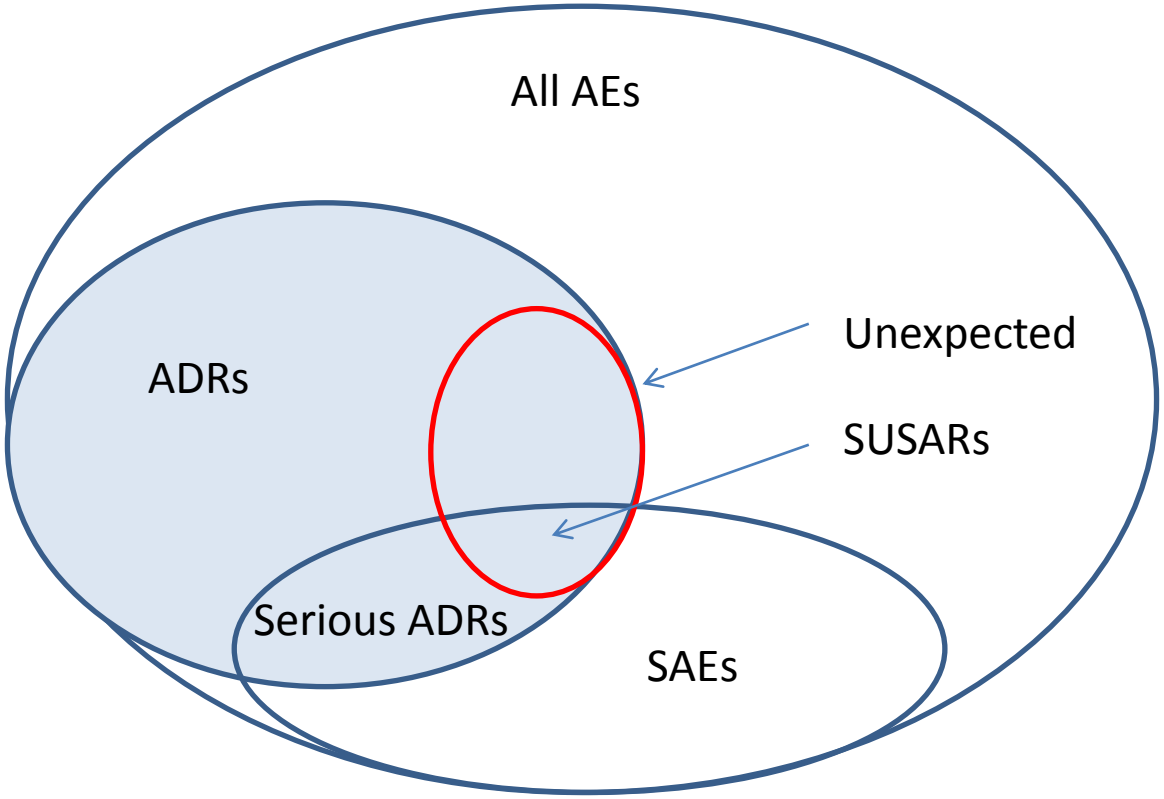
Why do we need all this information?

- To categorise your serious adverse event so we can decide what to do next

Categorising Adverse Events



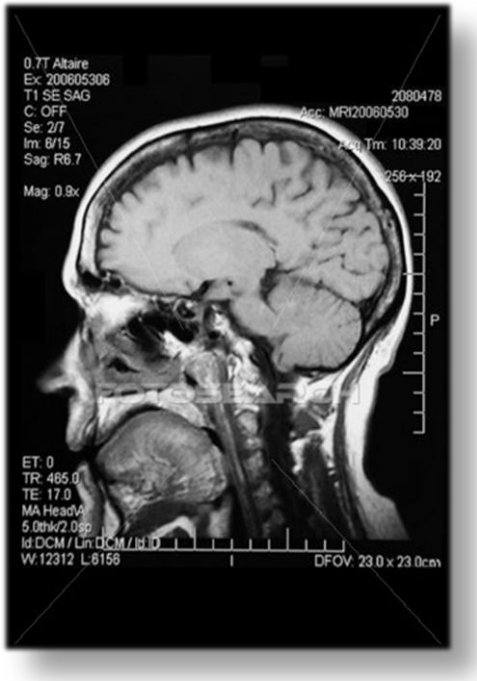
Categorising Adverse Events



SUSAR

Suspected Unexpected Serious Adverse Reaction

- Adverse Event
- Considered serious
- Reasonable causal relationship
- Unexpected according to the Reference Safety Information for the study drug



Recording & Reporting for Investigators

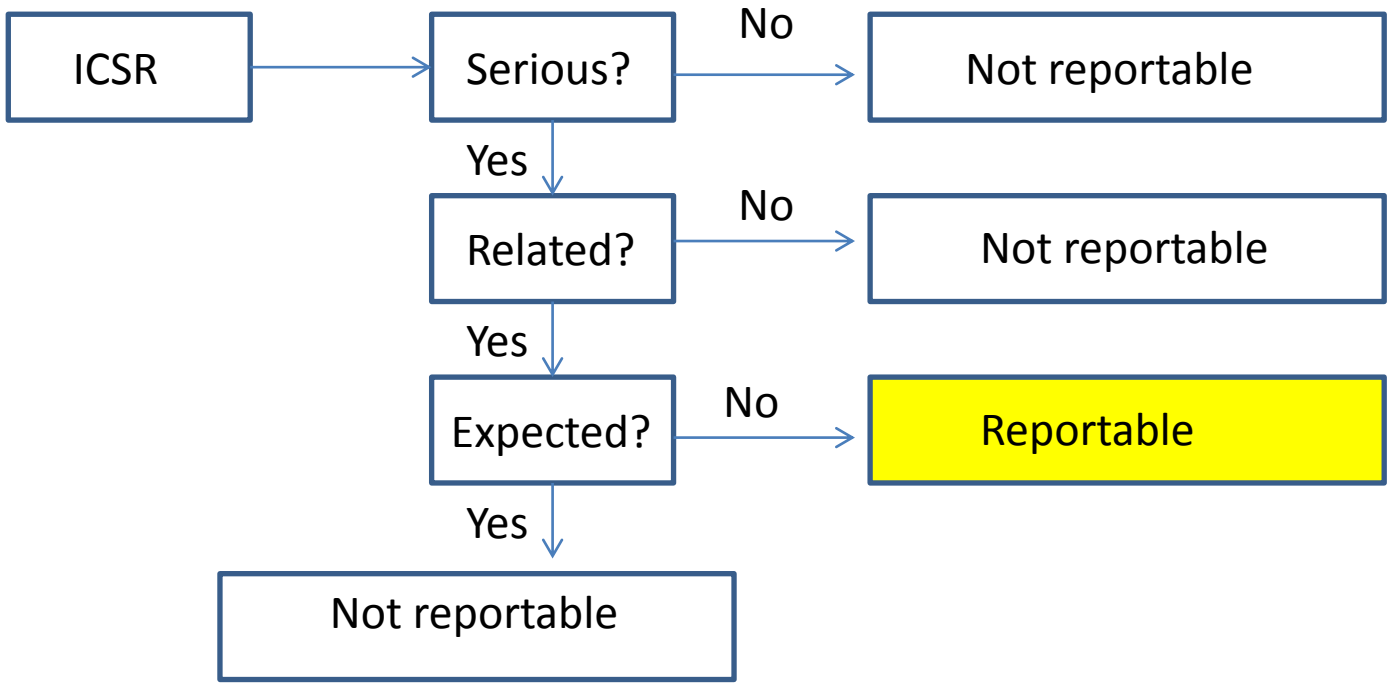
AE or AR

- Record in Case Report Form & patient record

SAE, SAR, SUSAR

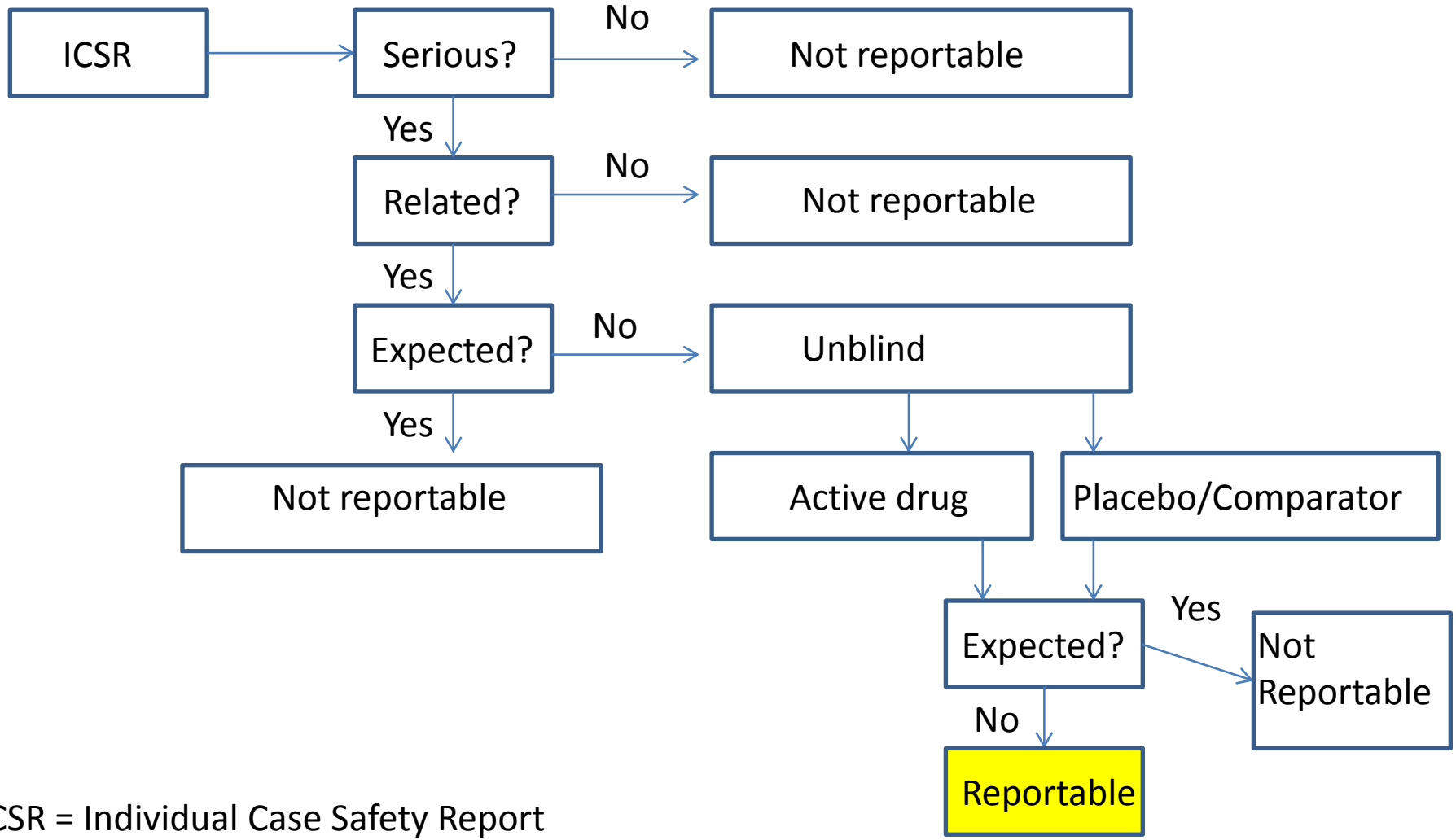
- Record and report to sponsor immediately ≤ 24 hrs
- Participants should be identified by unique codes
- Details including: outcome, nature, dates.

Assessing Reportability in Trials



ICSR = Individual Case Safety Report

Assessing Reportability in Blinded Trials



ICSR = Individual Case Safety Report

The Role of Unblinding for Safety Purposes

- Investigator led unblinding:
  - For immediate treatment of adverse event
  - Rarely required, usually drug withdrawal sufficient
  - With caution, may compromise data

- PV unblinding for reporting
  - Confined to PV department
  - Not a safety monitoring tool

- Unblinding for DSMB review:
  - Confined to DSMB members (not otherwise involved with trial conduct or sponsor)
  - For safety monitoring purposes

- Unblinding for a Safety Concern:
  - “All involved, all informed”

Following up SAEs

- All SAEs must be followed up to resolution
- This means if the outcome is unknown, not recovered or recovering you should file a follow up SAE report in due course to inform PV that the study subject is recovered or recovered with sequelae, including date of recovery
- Recovery is usually interpreted as discharge from hospital

Section 4

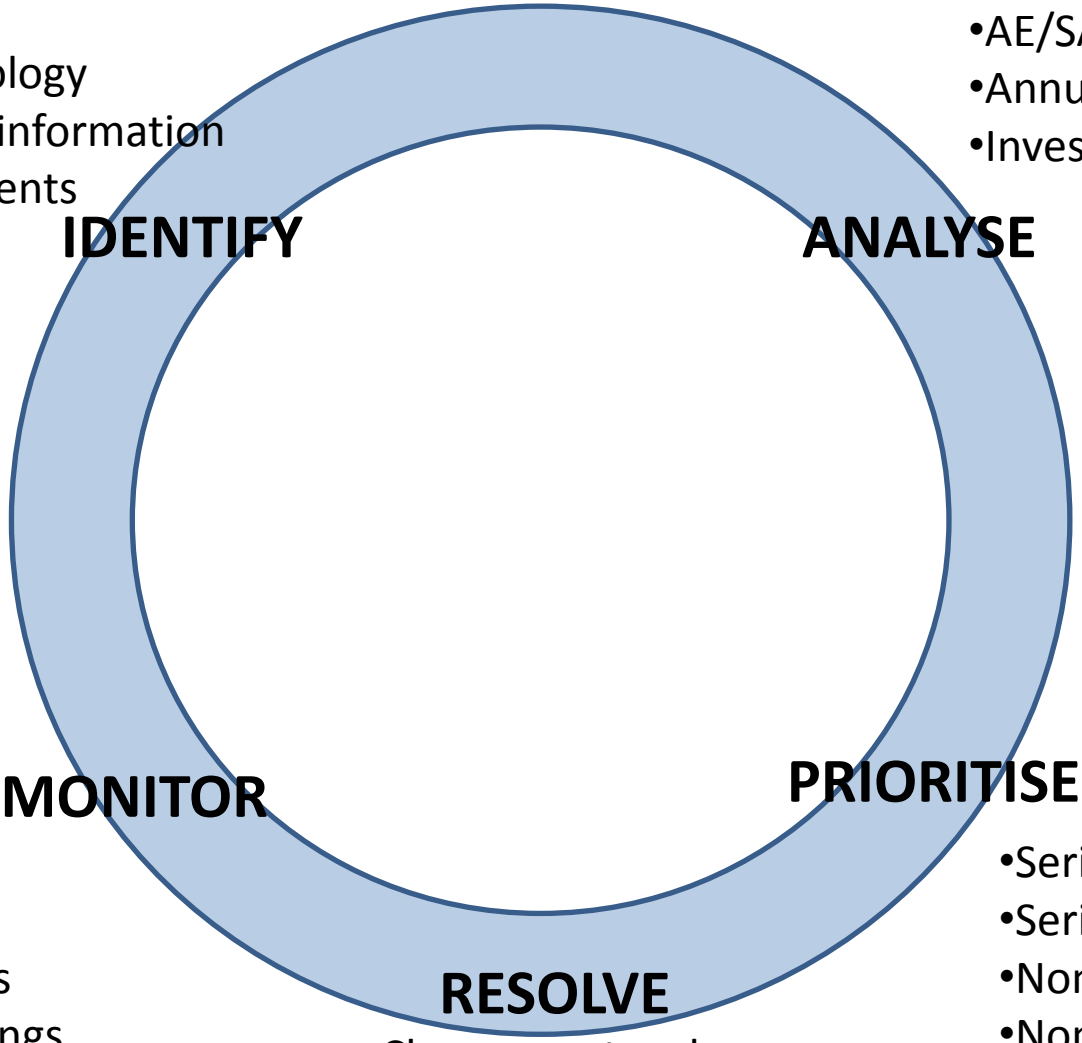
Risk Assessment

Risk assessment programme

- The sponsor and study team should continuously weigh the benefits and risks of the trial, which includes ongoing safety assessment of IMPs

- The study team should ensure the subjects are being given complete, up to date and thorough information regarding the risks of participation in a study

Risk Assessment



- Toxicology
- Clinical pharmacology
- Reference safety information
- Other adverse events

- AE/SAE listings
- Annual reports
- Investigator's brochure

- Serious unexpected
- Serious expected
- Non serious unexpected
- Non serious expected

- Change protocol
- Change informed consent/PIS
- Halt study

- Monitor
- Audit
- Annual reviews
- Sponsor meetings
- Study meetings

Pre-marketing versus Post marketing

PRE-MARKETING

- Before licensing
- Investigational Medicinal Product
- Little known about the drug – patients are more at risk
- Patient selection is restricted by the protocol
- Information available from all patients as all treated subjects in trials
- Audit of data collection in place

MARKETING APPROVAL IN PLACE

- Post licensing
- Approved Medicinal Product
- Full registration package of data available and reviewed by regulatory authority
- Patient selection is unrestricted
- No information available from most patients
- Spontaneous reporting eg via yellow card scheme

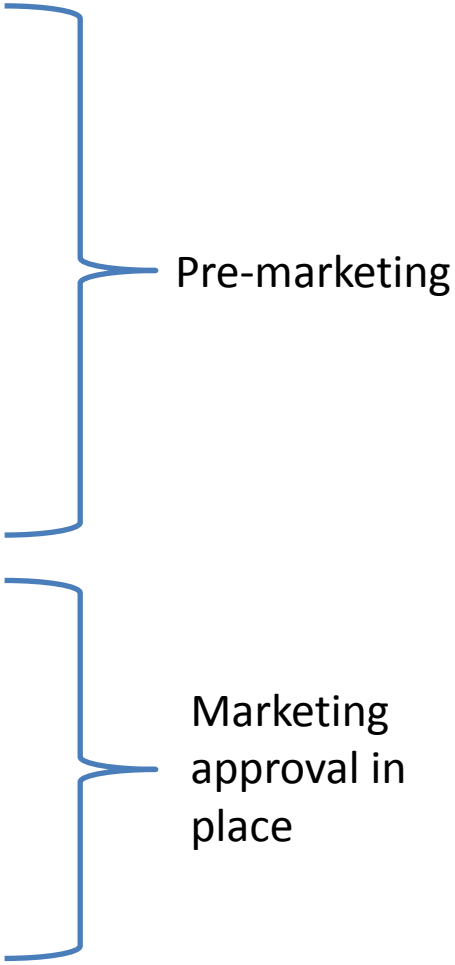
Resolving Risk

PROTOCOL
- Change the inclusion/exclusion criteria
- Change the dose of the drug
- Instigate additional patient monitoring

INVESTIGATOR'S BROCHURE
- Update AEs
- Add flags to identify events which may be drug related
- Include warnings for special populations

SAFETY INFORMATION
- Update SmPC/Prescribing information

APPROVED DRUG LABEL
- Change the label – eg. warnings and contraventions
- Change the approved for use population characteristics



Section 5

Expedited Reports and Aggregate Reports/DSURs

Expedited Reports (SUSARs)

- Submitted by TASC PV Department
- After unblinding if relevant

Reporting Timelines

- SUSARs that are fatal or life-threatening
  - As soon as possible and no later than 7 days of first knowledge by sponsor
  - Relevant follow-up within a further 8 days
- Other SUSARs
  - As soon as possible within a maximum of 15 days of first knowledge by sponsor

Report to: MHRA, ethics, other Investigators

Day 0 = Information received by sponsor

Causality changes

- Reporting required for events
  - With reasonable possibility of causal relationship (Decided by reporting Investigator)
  - Serious (Decided by reporting Investigator)
  - Unexpected (Decided by sponsor using the RSI)

If the reporting Investigator has not expressed an opinion on causality, sponsor should consult and encourage an opinion to be expressed. Sponsor should never downgrade the opinion but may upgrade it, in which case both opinions should be provided with the report

We Do NOT report

- Adverse reactions relating NOT to IMP but to non-IMP and without interaction with IMP
- SUSARs raised from other trials for which the sponsor is not connected
- Adverse reactions that occur in a country where a MA is present but where the product is IMP in other countries

Reporting of a SUSAR

- Member state (MHRA): via EVCTM/ESUSAR
- Ethics committee of the country where the SUSAR occurred
- ALL Investigators irrespective of location

Annual Safety Report/Development Safety Update Report (DSUR)

- The Annual Safety Report must be submitted for all trials where regulatory authorisation has been granted, whether or not the trial has started or there have been any SARs or SUSARs
- Must be submitted to the MHRA and REC
- Once a year throughout the clinical trial until End of Trial is declared
- If the trial is short term (i.e. less than 6 months), the Annual Safety Report is due within 90 days of the end of the trial, together with the notification of end of trial

DSUR Time

- First CTA Approval anniversary date plus 60 days
- Every year
- Until the End of Trial Declaration has been submitted

How are DSURs developed?

- Interactive process between TASC and the study team

DSUR Contents

- Analysis of the subjects' safety in the clinical trial
- A line listing of all SARs (including all SUSARs) occurred in the trial, including also SARs from third countries
- An aggregate summary tabulation of SARs that occurred in the trial
- RSI at the start of the reporting period is declared.
- Significant changes to the RSI are declared in the report.

The document template follows regulatory requirements

- The DSUR is an ideal opportunity to think about risk benefit.
- If there are RSI changes noted, should study subjects be informed via the PIS?

Section 6

Odd Points

Reference of Expectedness

- Reference safety information (RSI) can change during the conduct of a study eg IB update.
- Change in the RSI may alter whether an event is a SUSAR and the applicable RSI to be taken is that available at the time of occurrence of the SUSAR.
- What this means: An event which is a SUSAR in the early part of a trial may not qualify as a SUSAR a few months later, if the RSI has changed

SAE Reporting for Non-CTIMPs

- An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

Related – that is, it resulted from administration of any of the research procedures, and

Unexpected – that is, the type of event is <u>not listed in the protocol</u> as an expected occurrence.

How to Report SAEs for Non-CTIMPs

SAE

Within 15 days of becoming aware

SAE report form for non-CTIMPs, available from NRES website.

Send to main REC

Reconciliation of PV and AE clinical trial databases

- A PV database is a “real time” data collection
- The Clinical Trial AE log is the final conclusive data for the study

- The databases do not need to match
- The purpose of the reconciliation is to make sure that PV reporting has not missed anything

Common audit/inspection findings in PV for trials

- Failure to submit or late expedited safety reports
- Failure to submit or late periodic safety update reports (DSURs)
- Failure to follow up SAEs to resolution
- Lack of or inadequately written SOPs
- Failure to describe risks in the PIS/ICF

- Thank you for listening