

SAFETY PRACTICES AND REPORTING IN CLINICAL RESEARCH

Acknowledgement

*Acknowledgment to Ms Chun Geok Ying
for preparation of the core contents of
this presentation*

Outline

- Why is safety practices important?
- What is safety monitoring?
- Safety Reporting
 - What is safety reporting?
 - What are the requirements of report?
 - Define and categorisation of AEs based on causality, seriousness and relatedness

WHY IS IT IMPORTANT

BBC NEWS

Two drug trial men critically ill

Before any new medicine can be given to patients, detailed information about how it works and how safe it is must be collected.

Clinical trials are the key to getting that data - and without volunteers to take part in the trials, there would be no new treatments for serious diseases such as cancer, multiple sclerosis and arthritis.

But one disastrous drug trial at a London hospital in 2006 threatened to derail that system.

In what became known as the Elephant Man trial, **six healthy young men were treated for organ failure** after experiencing a serious reaction within hours of taking the drug TGN1412 in a clinical trial.

After they were all admitted to intensive care, two became critically ill, the worst affected lost his fingers and toes, and all the men were subsequently told they would be likely to develop cancers or auto-immune diseases as a result of their exposure to the drug.

In follow-up interviews, **the men described feeling like their brains were "on fire" and their "eyeballs were going to pop out"**.

BBC NEWS [Watch One-Minute World News](#)

Last Updated: Monday, 12 December 2005, 15:52 GMT

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Woman died on cannabis drug trial

A woman developed mental health problems and later died after taking part in trials of a cannabis-based drug, an inquest has heard.



Diabetic Rene Anderson, aged 69 from Sheffield, was taken to hospital after starting to take Sativex to see if it would relieve pain she was suffering.

Sativex is made from the cannabis plant

She died in March 2004 from acute kidney failure.

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WHY IS IT IMPORTANT

- **Rights, SAFETY and Well-being of trial subjects are protected (ICH GCP E6: 2.3)**
- Safety of human subject should prevail over interest of science and society (ICH GCP 2.3)
- ICH GCP 4.11 on safety reporting states that
 - “All Serious adverse events (SAE) should be **reported immediately** to sponsor except for those SAEs that the protocol or other document identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects’ names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement related to the reporting of unexpected serious adverse drug reactions to the **regulatory authorities** and the **IRB/IEC**.”
- In Investigator Initiated research (IIR):
 - investigators are also sponsor and plays both sponsors and investigator’s role
 - Also known as **sponsor-investigator**

Safety Practices: Roles & Responsibilities of Investigator

Investigator assures subject safety and data integrity by:

Conducts study as per protocol

Adhere to inclusion & exclusion criteria

Continued adherence to protocol throughout study duration

Monitor subject status eg: wellbeing, minimise risk, toxicity management etc

Monitor study and safety database

Safety Practices and Monitoring

- Study design that complies with Good Clinical Practice
- Have a plan for safety monitoring during protocol development phase
 - Have a data safety monitoring board (DSMB)/data management centers (DMC) :
 - Comprise of staff (who are familiar with study product and procedure) independent of the study
 - to ensure continued vigilance in safety → useful for large, multicentre, randomised control trials
 - Trend analysis
 - Training plans for staffs involved in research
 - QC/QA in place to ensure protocol is adhered to
 - Monitor and review Safety reports and follow up plans
 - Have rescue therapy
- Risk management plan

Safety Practices and Monitoring

- Safety monitoring and pharmacovigilance is a dynamic process to:
 - protect trial volunteers from harm
 - Gain understanding of safety profile of drug during drug development phase
- Ensure timely detection of adverse events because:
 - Safety data influence clinical care of subjects
 - For drug already in market: data may affect clinical use of the investigational product
- Challenges:
 - requires coordination between observant investigators,
 - analysis by investigator,
 - prompt reporting to regulators, ethics committee (EC).

How to report?

SAE REPORTING

- Use of **CIOMS I** form: enables standardization of reporting process , and data entry quality and completeness: → allowing possible evaluation
 - Ability to assess, analyse and act on safety issues are dependent on reporting quality
- Complete SAE report should include:
 - Subject identifier
 - Study details: ie: product name, study design
 - Narrative (temporal info on date of event onset, start/stop date of investigational product
 - Past medical history
 - Lab information, test, procedures
 - Concomitant medication
 - SAE outcome; biopsy results (if applicable)
 - causality

Adverse event

Serious

Not Serious

Serious
Adverse
Event

Adverse
Event(AE)

Related to
IP

Not related
to IP

Related to
IP

Not related
to IP

Serious
Adverse
Reaction
(SAR)

Serious
Adverse
Event
(SAE)

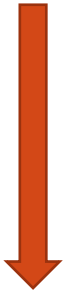
Adverse
Reaction
(AR)

Adverse
Event
(AE)

Serious?



Related?



Expected?

Expected

Serious Adverse Reaction

Unexpected

Suspected Unexpected Serious
Adverse Reaction (SUSAR)

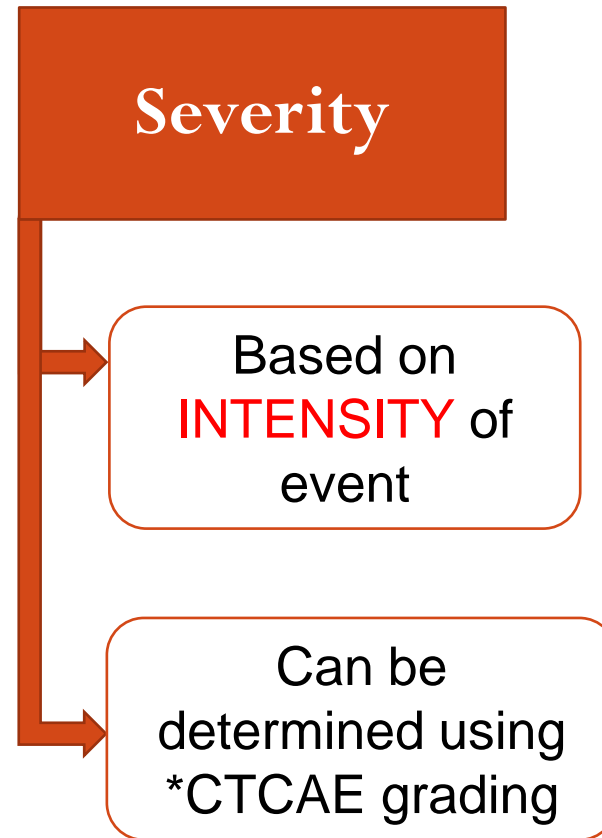
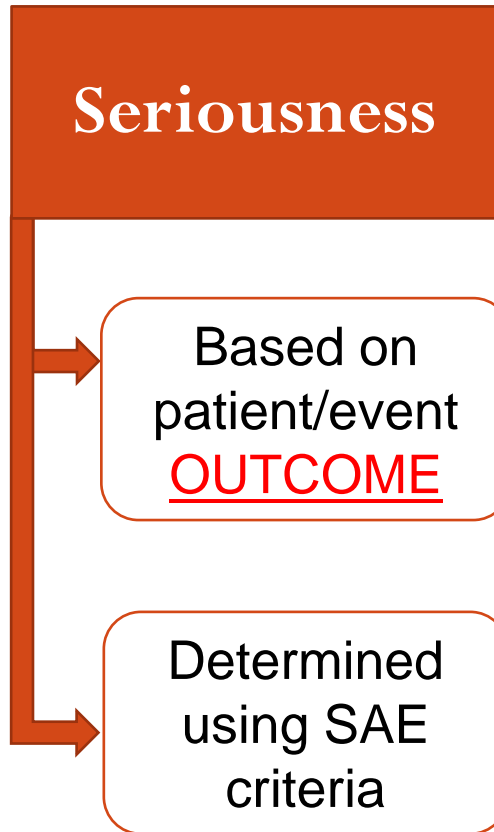
Definitions

- 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**
 - Ie: can be an abnormal lab finding, symptom/dx temporarily associated with use of an IP, whether or not related to the IP
- Adverse reaction
 - Any **untoward and unintended responses to an IP** related to any dose administered
 - Ie: AEs that have reasonable causal relationship to a medicinal product
- Assessment done based on medical judgement
 - Assessment of seriousness
 - Assessment of causality/relatedness
 - Assessment of expectedness

Definition of Seriousness

- **SAE/SAR/SUSAR:**
 - Results in death
 - Is life threatening (subject was at risk of death at the time of event)
 - Requires hospitalisation or prolongation of existing hospitalisation
 - Results in persistent/significant disability/incapacity
 - Consists of a congenital anomaly/birth defect

Seriousness is different from Severity



Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: life threatening/disabling
Grade 5: Death related AE

*CTCAE: Common Terminology Criteria of Adverse Event

Causality and Relatedness

- Categories:

| Relatedness ratings | Definition |
|---------------------|--|
| Unrelated | An adverse event which is <u>NOT</u> related to use of investigational product (IP) |
| Possible | An adverse event, which <u>MIGHT</u> be due to the use of IP. An alternative explanation is <u>INCONCLUSIVE</u> . The relationship in time is reasonable and therefore causal relationship cannot be <u>EXCLUDED</u> |
| Probable | An adverse event which <u>MIGHT</u> be due to the IP. The relationship in time is suggestive (confirmed by <u>DECHALLENGE</u>). An alternative explanation is <u>LESS</u> likely, eg: concomitant drugs/disease |
| Very Likely | An adverse event, which is listed as a <u>POSSIBLE</u> adverse reaction and cannot be reasonably explained by an alternative explanation. |

Determination of Causality

- Standard determinations include:
 - Is there [Drug Exposure] and [Temporal Association] ?
 - Is there [Dechallenge/Rechallenge] or [Dose Adjustments] ?
 - Any known association per [Investigator's Brochure] or [Package Insert] ?
 - Any other possible [Etiology] ?

Examples of Reasonable Possibility

- Individual occurrence
 - **Single** occurrence of an event that is **uncommon** but known to be **strongly associated** with drug Exposure
 - Eg: anaphylaxis; hepatic injury; stevens- Johnson syndrome
- **Aggregate** analysis/specific events
 - Analysis of events, observed in a research indicates those events occur **more frequently** in drug treatment group than control group,
 - Events **common in study population** independent of drug therapy
 - Known consequences of underlying disease
 - Eg: acute MI in long duration trial with an elderly population with heart problems

Expectedness

- Based on
 - **nature** ,
 - **severity and**
 - **frequency**
- **Not consistent** with application product information
 - ie: Trial products: not in IB
 - Registered product: not in package insert/SPC
- May be unexpected if **CHANGES** occur in:
 - **rate**;
 - **severity**; or
 - **duration of event**

Narrative

- Comprehensive, stand-alone “medical story”
 - Written in logical time sequence
 - Include key information from supplementary records
 - Include relevant autopsy or post-mortem findings
- Summarize all relevant clinical and related information including:
 - Study subject characteristics
 - Medical history
 - Clinical course of the event and therapy details
 - Diagnosis (workup, relevant tests/procedures, lab results)
 - Other information that supports or refutes an AE

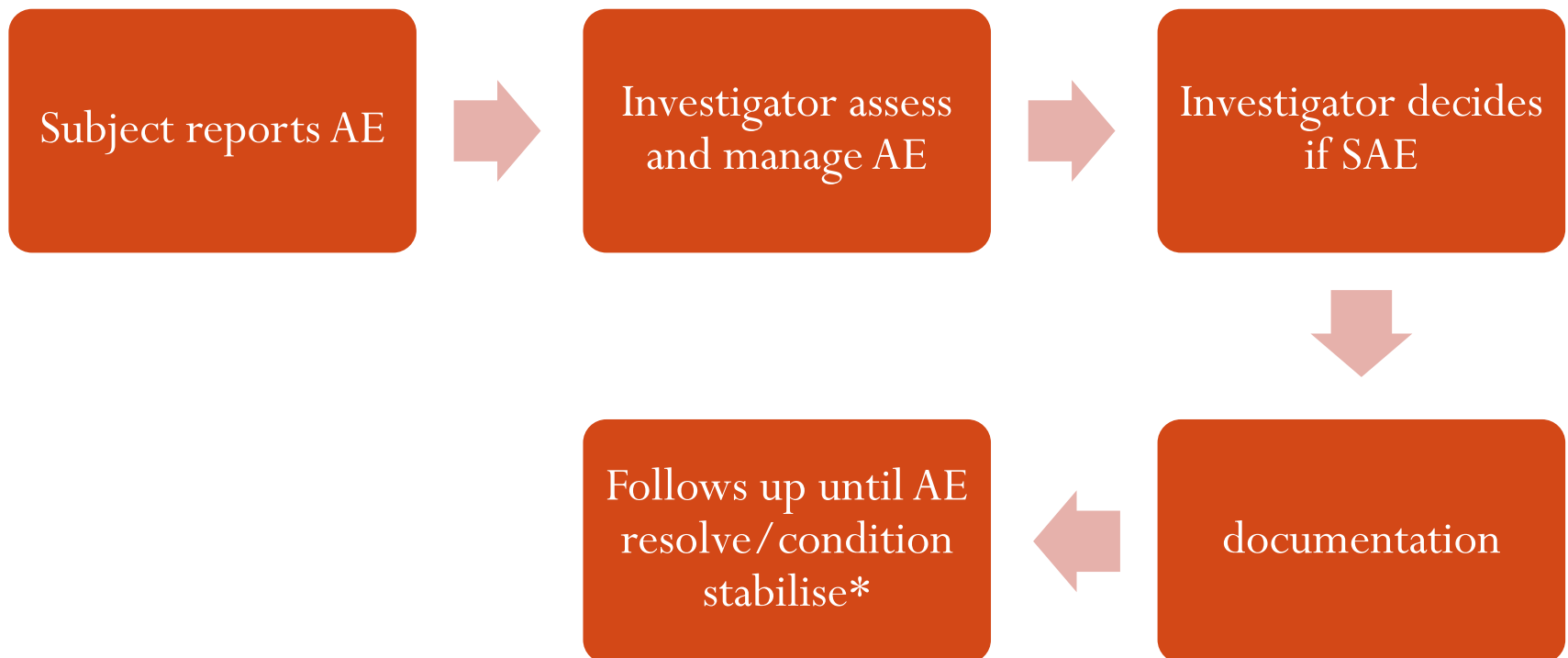
Action taken with IP after AE

- **Subject**
 - Study product: drug withdrawn, dose reduced/increased/not changed, unknown, NA
 - Study participation: continue/withdraw
- **Study:**
 - Study product: per site, per study?
- **Study status:** safety pause, clinical hold, early termination?
- **Outcome of reaction/event** at time of last observation
 - Recovered/resolved; recovering/resolving; not recovered/resolved; recovered with sequelae; fatal; unknown
- **Outcome of subject** in study:
 - Remains in study, withdrawn; lost to follow up; death

Roles and responsibilities of Investigators

c.f. protocol specification of SAE:

- Criteria
- Timeframe
- Reporting form



* At minimum, patient followed until end of study

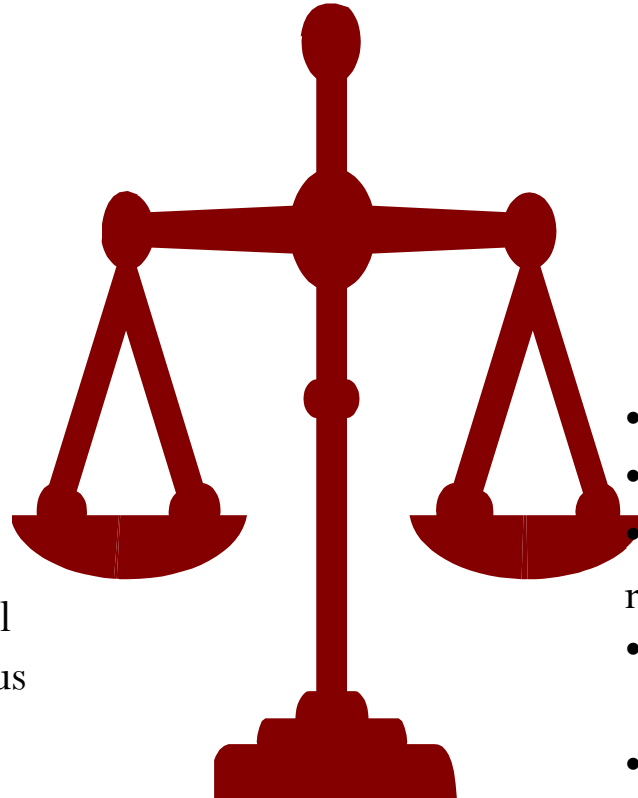
Safety Reporting

- Documents in Case report form
- Involves Reporting of adverse events to: Regulators, other investigators, MREC, patients (re-consent)
- If **SUSAR**: reported as fast as possible to National Pharmaceutical Control Bureau and Ethics Committee but not later than
 - **7 calendar** days if **life threatening/ fatal**
 - **15 calendar** days if not life threatening/fatal
- When does the clock start?
 - Day 1 is the day of **sponsor-investigator has knowledge** that SAE qualifies as a SUSAR, ie:
 - A suspected IP
 - An identifiable subject
 - AE assessed as serious & unexpected and there is a reasonable causal relationship
 - Identifiable reporting source
 - Clock stops on the day **regulators receive report**

Investigators balance both roles

Clinical Role: Subject OK?

- Subject in jeopardy?
- Provide appropriate Management
- Provide appropriate referral
- Follow up with subject status



Research Role: study / data OK?

- Identify AE
- Immediate notification required?
- Documents AE. Follow until resolution/stable and updates record
- Determine if AE meets criteria for SAE
- Adhere to reporting requirements
- Adhere to toxicity management as specified
- Adhere to stopping rules

Rescue therapy

- If treatment does not work → What do we do?
 - Do we withdraw the patient or continue on trial?
 - Is it safe to continue on trial?
 - If withdrawn, do we restart subject on standard treatment?
- Any rescue plan/management in case of any adverse events?
 - Especially important in certain interventional studies involving high risk patients
 - Eg: in oncology trials, we may provide premedication to prevent common side effects of chemotherapy
- If there is run in phase → any risk if subjects are withdrawn from standard therapy temporarily?

Current issues with safety reports



Journal of Clinical Epidemiology 64 (2011) 124–135

**Journal of
Clinical
Epidemiology**

SYSTEMATIC REVIEWS

The **quality** of safety reporting in trials is still **suboptimal**:
Survey of major general medical journals

Anna-Bettina Haidich*, Charis Birtsou, Theodore Dardavessis, Ilias Tirodimos,
Malamatenia Arvanitidou

Department of Hygiene and Epidemiology, School of Medicine, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

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- ▶ Poor reporting quality: lacking in detail
- ▶ Underreporting
- ▶ Recognition of SAE due to difficulty in causality assessment

CASE STUDIES

CASE 1^a

- An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. Data stored on a laptop without encryption and laptop was stolen from the investigator's car on the way home from work
- Is this an Serious Adverse event?
- What are the risks?

Case 2^a

- A phase 3, double blind RCT comparing relative safety and efficacy of a new chemotherapy agent combined with current standard chemo regimen, versus placebo combined with current standard chemo regimen, for management of multiple myeloma
- In this study, a subject develops neutropenia and sepsis → subsequently multi organ failure and dies
- Is this an SAE?
- Is this a SUSAR?
- Why?

Case 3^a

- The 3rd subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to standard treatment, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent
- The known risk profile of the new oral agent prior to this includes mild elevation of serum liver enzymes in 10% of subjects receiving the agents in the previous clinical trials, but reports of clinically significant liver disease. MREC approved protocol and consent form states mild liver injury as a risk of the trial.
- Is this an SAE?
- Is this a SUSAR?
- Why ?

Case 4^a

- Subjects with coronary artery disease presenting with unstable angina are enrolled in a trial evaluating safety and efficacy of a new investigational vascular stent. Prior animal and human studies anticipated that up to 5% subjects receiving the stent will require emergency CABG surgery due to acute blockage of the stent that is unresponsive to non-surgical interventions.
- After first 20 subjects, interim analysis done by DSMB and notes that 10 subjects needed to undergo emergency CABG → greatly higher than expected rate. Sponsors immediately report to investigator.
- Is this an SAE?
- SUSAR?
- Why?

Thank You

References

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