
A Rational and Risk based Approach to Documenting, Reporting & Evaluating Safety

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Key Concepts

- A clinical trials program should be configured to progressively reduce uncertainty about the balance of benefits and risks in clinically defined populations
- Once adequate certainty on risk or benefit is reached, the value of incremental efforts diminish rapidly
- Non-value added efforts (eg trivial details or extra documentation) detract from other important aspects that may be more critical(eg increasing sample size)
- Safety monitoring occurs in the context of other efforts that record adverse effects.(eg reason for stopping a drug), and in the context of other previous and ongoing trials.
- Safety monitoring of trials should be risk based (doing everything in all trials will lead to fewer, smaller and less reliable studies)
- *Understanding how **more attention to detail** can lead to **less reliable answers** is a critical aspect of good clinical trials methodology!*

Consider

- What are we asked to report ?
 - vs
- What do we *need* to know to assess the risks vs benefits of an intervention ?
- Same approach when we know **little** vs a **lot** about a therapy?
 - What is needed is knowledge of the **relative** frequency vs placebo or alternative therapy?

Goals of Characterizing Safety using Adverse Event Reporting

- Known serious adverse events:
 - Quantify relative frequency to inform prescribers and patients
 - Provide evidence for balance of benefits and risks in specific populations
- Unexpected serious events:
 - Sort out drug risk vs disease risk (placebo)

Both of the above are important in understanding the safety of an intervention

- Minor adverse events
 - In general need an unbiased *estimate* (but does not have to be absolutely accurate)
 - In comparative effectiveness when trading off benefits and risk, comparative and approx frequency is adequate to inform decision makers about choices

How to Collect Data

Individual case reports may be helpful for :

- Unexpected, truly rare and serious events
- Not part of the disease or an event common in the specific age group

However individual SAE reports for events that can occur with the disease independently of the drug

- are not helpful (and may be even misleading) in understanding the prevalence of these events
- are very expensive and
- detract from other critical elements of trials

How to Collect Data

- For unexpected, serious and rare events reporting each case may be useful, but comparative data are preferable.
- Unstructured single event reporting may be useful early in development when very little is known about the drug
- General frequency estimates stabilize at about 1500 cases (“rule of 1500”)
 - Once a stable estimate is available, why continue to collect it?
- When one knows to look for an event the use of structured data collection (checkbox on data form)
 - Vastly improves accuracy
 - Doubles or triples reporting rate

Assessing “Causality”

- Very hard to assess for common events (serious or not) on a case by case basis
- May be possible to assess for rare, unusual events
- What do we really know about the reliability and value of “causality” assessments of an individual SAE?
 - New study in planning stages
 - blinded causality assessment compared with statistical difference (or lack thereof) at the end of the trial
 - Other than “weird”, rare, serious events, can investigators sort signal from noise on a case by case basis?

How are safety data reported currently?

- Each adverse event (whether or not known as part of the disease, or previously reported on the intervention) is recorded on detailed forms.
- Some (SUSARs) are reported in an expedited fashion to sponsors, regulators, investigators and to their REBs
- Reported on a case by case basis, not as groups.
- Since “relatedness” involves being on the active drug , if unblinding is done, then only those seen in the active arm are reported. So invariably this process reports SAEs that may not be increased by the intervention.
- Cost implications of each SAE reporting, review by REBs, etc are HUGE in a large trial and rarely leads to useful insights or improvements in patient safety

Examples in real trials

- **Trial A**: 18,000 people of a new entity X 2yrs (but already studied in >4000 people) for a few months.
 - No. of AEs:125,000
 - No. of SAEs: 6000
 - No. of SAEs associated with the drug:500
 - No. of SAEs that were demonstrated to increase with the drug: 0
- Estimated costs about 12 mill !
- **Trial B**: 12,000 people X 5yrs.25,000 AE s, 5000 SAE s, <500 drug related, no info that was not known previously.

Who To Report To?

- Regulatory bodies
- Companies
- Individual sites and the ethics committees (REBs) participating in studies
- Data and safety monitoring boards (DSMBs)*
- Study steering committees
- Share holders?

* Only group that looks at aggregate data on risks and benefits systematically in a specific trial.

What do the others do with the information during the trial conduct?

What to Report?

- Consider events in 3 categories
 - Occur as part of the natural history of disease
 - Are rare, unexpected and serious
 - Minor/nonserious
- What should be done with “causality” assessments?
- Should you unblind each event?

The methods of reporting each category may differ by the stage of a trial and previous info ie a risk based and graduated approach should detect important adverse effects without detracting from the overall efforts.



More General Landscape

- Entire trial program
 - Summary reports across trials
- Trials in same class
 - Sharing among DMCs
- FDA-AAA
 - REMS—required postmarketing trials focused on particular safety issues
- National databases (US example, ? UK even further along)
 - Spontaneous reports
 - Required prospective registries
 - Sentinel network (100,000,000 records in US)
 - Office of the National Coordinator of Health IT (ONCHIT)—‘qualified medical records’--\$31 billion over next 5 years

When a plan is made for an individual trial, the context of these other sources of data should be considered.

Balancing Risk & Benefit

Except for rare, unexpected, serious and non-disease related, all trial data needed by randomization to make sense of SAEs

Safety events usually come in more quickly than benefit/outcome data

Also judged by different standards

Examples

- Intracranial hemorrhage caused by thrombolytics but there is a reduction in mortality
- Catheter ACS: thrombus with fondaparinux versus mortality/bleeding

Value of Collecting Information on Factors Precipitating the Event?

- Early in experience or for serious, unexpected, rare and not disease related
 - Other drugs (at all visits or when there is an unexpected SUSAR)?
 - Concomitant disease situations?
 - Actual compliance at the time of the event?
 - Measure of effects of drugs e.g. INR with OAC & bleeding?
 - Some blood/other fluids*to measure blood levels of the drug or metabolite?
 - » **generally impractical*
- *Later in experience and for nonserious, expected and/or disease related*
 - *Checkbox for items of interest*

Approach to Reporting

- Should vary depending on the amount of safety knowledge about the intervention (“the 1500 rule”) and risk based.
- Early phase: Conventional method + DSMB review
- Later phases: Best done by DSMB with delegation of reporting to sponsor & regulatory bodies only when harm is obvious and outweighs benefit (challenges of cath thrombus in OASIS 5).
- *Little value in reporting individual SAEs to all sites in all trials (and their REBs).*

Tale of 2 Oncologists and 2 Drugs

- Average of 50 IND safety reports per month (doesn't count all the other drugs!)
- If each report takes 20 mins, that's 20.8 hrs per month just to process them at the investigator level
- Only 2% came from studies in which the investigator was conducting
- Only 1% met the criteria for unexpected event adding potential new information to safety profile meriting sending to IRB (but the investigators forward them, as a defensive strategy!)

Tale of 2 Oncologists and 2 Drugs (cont.)

- The 2 sponsors of the these 2 drugs have 148 ongoing trials at 6800 sites listed in clinicaltrials.gov
- If there are 50/month going to 6800 sites, that's 340,000 reports a month
- At 20 mins a report, that's 6,800,000 mins of investigator time a month
- This does not count company time, FedEx costs and IRB time, nor the carbon cost to global warming!
- This is uncompensated time
- These people have other things to do, like taking care of cancer patients!
- This is insane!!!!
- We can probably get the relevant information is a much simpler way!

Safety assessments are facilitated if DSMB integrate Data from Outside?

- Access to unblinded existing safety data in the company database
- Opportunity for DSMB chairs of studies of the same or similar agents to speak if necessary.
- Validating signals on unexpected adverse events
 - Need for replicating: Cancer & ARB/ACE-I
 - Need for meta analysis: Ezetemibe

Recommendations for Clinical Trials that Measure Outcomes

- Sustain and enhance requirements for independent data and safety monitoring committees.
- Engage in long-term efforts to house clinical trial databases in not-for-profit institutions; these efforts must include the development of more effective infrastructure by academic medical centers.

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Califf, Blazing & Harrington
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Recommendations for Clinical Trials that Measure Outcomes

- **Require all major clinical trials that have outcome data to have independent steering committees chaired by a leader or leaders widely recognized for expertise in the field of interest and in the practical running of clinical trials.**
- **Reform Securities and Exchange Commission regulations, in light of the special rules that clinical trials require, by creating an orderly process for revealing major results of clinical trials to the public and to corporate research sponsors that may be affected.**

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Clinical Trials Transformation Initiative (CTTI) Project Plan

- **Objective 1: To document the current range of practices for safety monitoring and reporting of unexpected SAEs to investigators**
- **Objective 2: To quantify the personnel time required by investigators to receive, analyze, interpret, and communicate information in individual expedited safety reports and the perceived value of this information in updating the risk profile of investigational products.**

Clinical Trials Transformation Initiative (CTTI) Project Plan

- **Objective 3: To compare current practices with an alternative approach for notifying investigators of unexpected SAEs (European Commission guidance)**
- **Objective 4: To convene a broadly representative group of invited experts to integrate the information generated by this project and to develop a set of recommendations for optimal reporting of unexpected SAEs to investigators that will improve human subject protection.**

Recommendations

1. Immediate consideration to streamlining of adverse event documentation, reporting and evaluation using a **risk based and graduated** approach.
2. Current approaches are extremely wasteful and so broad that they:
 - Focus on irrelevant information
 - May obfuscate relevant, rare events (eg, excess of mortality with antiarrhythmics)
 - Don't really use the best method (comparisons between groups) during the conduct of the study

Recommendations (con't)

3. Reporting, evaluating & unblinding individual adverse events on a case by case basis is burdensome, more often misleading than informative, and at times creates chaos.
4. Aggregate Data Safety Monitoring comparing treatment to placebo or comparator should be the cornerstone of the process:
 - DSMB for large outcome trials
 - Could be an unblinded “safety officers” for small studies
 - Assess risks and benefits of treatment simultaneously.
 - Sharing information(level of detail and how often) with regulators should be customized to the relative knowledge about the intervention, and need a threshold based approach that is periodic rather than individual.
 - Reporting individual SAEs to centers is unhelpful and a waste.