Purpose of Monitoring

- The purposes of study monitoring during the conduct of clinical research, are to
  - Protect the patient from avoidable and often unforeseen risks of participation (requires real-time monitoring)
  - Ensure research continues to be ethical, scientifically valid and worthwhile, and feasible over the entire time period of its conduct
  - Ensure that the trial is stopped as soon as a reliable conclusion can be drawn from the data

Philosophy

- The philosophy is that you must be prepared for unexpected events and effects
- The data and safety monitoring plan must be developed to address what could possibly happen, not what is expected or likely to happen
- This is a major paradigm shift for many investigators

Financial Disclosures

- Employee
  - County of Los Angeles, Department of Health Services, Harbor-UCLA Medical Center
  - David Geffen School of Medicine at UCLA
  - Los Angeles Biomedical Research Institute
  - Berry Consultants, LLC
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  - Food and Drug Administration/CBER
- Support from
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  - National Institutes of Health/NHLBI
- Other consulting
  - Octapharma

Philosophy

- In designing a clinical trial you never know as much as you think you do!
- Study populations do not behave like general patient population (common to see lower event rates)
- Minor adverse events may be very important
- In drug development, many toxicities only appear late
Monitor versus DSMB/DMC

- A Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a group of independent experts who review accumulating data from an ongoing trial to determine whether the study should be continued, modified, or stopped.
- A “Monitor” or “Independent Medical Monitor” (IMM) is a one-person DSMB.

Other Use of the Word “Monitor”

- Industry sponsors of trials send “study monitors” to verify that information on CRFs can be validated with source documentation.
- There is no relationship between the “monitoring” of CRFs and data and safety monitoring of a clinical trial.

Goals of Safety Monitoring

- Detection of intervention-associated adverse events against background rates in population.
- Identification of unanticipated intervention-associated adverse events.
- Identification of subgroups at increased risk of adverse events.
- Verification that expected adverse events are not occurring more often than expected.

Adverse Events

- An adverse event (AE) is anything bad that happens to the patient while they are in the study, regardless of perceived causality.
- An adverse drug experience is an AE that occurs after the patient is given a drug (21 CFR§312.32).
- An adverse device effect is an AE in a device trial (21 CFR§812.3).

Serious Adverse Events (SAEs)*

- An AE that results in “Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.”
- Other “important medical events” may also be SAEs, based on medical judgment.
- No requirement for causation.
- Death is always an SAE.

*21 CFR§312.32

*21 CFR§312.32

Unexpected Adverse Event (UAES)*

- “Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere....”

*21 CFR§312.32
Adverse Events

- There may also be adverse events that can be anticipated and are particularly relevant for the drug or trial (e.g., coumadin and bleeding, suicide attempts in a trial of an antidepressant)
- These should be:
  - Mentioned in investigator brochure
  - Disclosed as risks in the informed consent document
  - Specifically tracked in the data monitoring plan

Severity and Attribution

- Adverse events are further characterized by severity and attribution
  - Severity often uses a protocol specific grading scheme (don’t use “serious”)
  - Attribution is the investigator’s judgment regarding causality
- If reporting is required, a description of the AE, along with assessment of severity and attribution, and follow up information is generally reported to the IRB and sponsor, and tabulated in reports provided to the DSMB (if any)

Requirements for Monitoring

- Intensity of monitoring (e.g., local safety officer, independent medical monitor, data and safety monitoring board) depends on complexity and risk of trial participation, stage of investigation, and sponsor requirements
- NIH requires a DSMB for
  - All phase III studies
  - Blinded phase I/II therapeutic studies
  - Any high risk phase I or II clinical trial
- NINDS requires that all clinical trials involving interventions that entail more than minimal risk to participants have a DSMB

Safety Officer

- In small, single-site studies, safety monitoring is often performed by a statistician in conjunction with a Safety Officer. The Safety Officer is:
  - Appointed by the grantee institution
  - Reviews adverse events (AEs) and Serious Adverse Events (SAEs) on an ongoing basis to determine action, if needed

Independent Medical Reviewer

- For NINDS-sponsored studies which are likely to entail risks, an independent Medical Reviewer is often appointed by the Statistical (or Data Management) Coordinating Center to review serious adverse events in a “real time” manner

Data and Safety Monitoring Boards & Data Monitoring Committees
Purposes of a DSMB

- **Primary**
  - To protect subjects from avoidable risk
  - To ensure trial integrity and validity
- **Secondary**
  - To provide an assurance that the trial is conducted in an unbiased manner
  - To enhance credibility and impact of trial results
- **Tertiary**
  - To operationalize sponsor’s goals and values regarding continued product evaluation

DSMB Process

- The DSMB accomplishes its task by reviewing accumulating efficacy and safety data during the conduct of the trial (e.g., interim analyses)
- This informs recommendation for the continuation, modification, or termination of the ongoing trial
- The DSMB has both expertise and access to data that the IRB does not, giving the DSMB a unique and critical role

DSMB Basics

- **Membership**
  - Scope of expertise (medical domain, trial methodology and statistics, ethics, pharmacokinetics, regulatory requirements)
  - Balance of perspectives, ability to incorporate and yield to the expertise of others
- **Charter**
  - Defines structure for and rules under which the DSMB operates
  - Timing, content, and format of meetings, contents of reports, confidentiality and firewalls

DSMB Preparation and Education

- There is little training of DSMB members in general, let alone for an adaptive trial
- Greater time is required to understand an adaptive design
- DSMB should learn about the design from the team that designed it, ideally before first patient is enrolled

DSMB Basics

- Open vs Closed vs Executive Sessions
  - Open: includes “interested parties” (e.g., sponsor, principal investigator, etc.); only aggregated and process data presented;
  - Closed: DSMB members and those preparing unblinded data (e.g., DCC statistician); and
  - Executive (rare): Only DSMB members
- Recommendations vs Decisions
  - DSMBs make recommendations
  - Most, but not all sponsors/Pis, follow them
DSMB Preparation and Education

- An early, face-to-face DSMB meeting is essential
  - Prior to final protocol and DSMB charter
  - Detailed explanation of design, rationale, and expected results
  - Principle efficacy and safety considerations
  - Expectations for committee member behavior and responsiveness

Cautionary Comments

- The DSMB works in isolation and can really screw up the trial
- The DSMB must understand what the trial is supposed to do so they can determine
  - If something is going wrong; or
  - If what the trial was designed to do is no longer the right thing to do; and
  - Recognize the potential impact on trial validity of making changes to the design after they’ve seen unblinded data

Expertise and Conflicts of Interest

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DAWN Interim Analysis n=200

The DSMB Chair

- An effective chair must:
  - Have a working understanding of clinical, statistical, logistical, and regulatory considerations
  - Be able to facilitate deliberations incorporating all relevant expertise and perspectives
  - Be aware of regulatory considerations
  - Have the ability to “flex” substantial time to devote to DSMB activities

The Marketing/KOL Trap

- Sometimes sponsors choose KOLs for DSMBs, as a first marketing step
- Such choices can be problematic
  - Limited time for preparation and DSMB work
  - Pre-formed opinions regarding product
  - Authority that exceeds understanding of the trial design or the limits of sparse data
  - Lack of familiarity with considerations of trial integrity, preservation of designed operating characteristics, and regulatory issues
Conclusions

- The membership of a DSMB overseeing a clinical trial should include a variety of expertise
- DSMBs need to actively monitor
  - Efficacy, safety, futility
  - Fidelity to and appropriateness of the original design
- The DSMB members must understand the considerations surrounding the conduct and modification of a trial, including regulatory considerations
- Pre-trial education of the DSMB, and a detailed pre-trial meeting, is essential to protect trial validity

DSMB Examples

North American Symptomatic Carotid Endarterectomy Trial

- Powered to detect a 50% reduction in patients with high-grade stenosis with planned n=600 and 5 years of follow up
- Stopping rule: P < .001 for 6 months and results deemed unambiguous and clinically important
- Included a futility rule as well
- Early stopping recommended with about 1.5 years follow up among the 659 participants
- A clinical alert was quickly circulated to physicians regarding the benefits of endarterectomy
Topiramate in Amyotrophic Lateral Sclerosis

- After the randomized trial of 198 subjects, 122 patients elected to participate in an open-label continuation phase.
- At the end of the randomized component, the DSMB recommended immediate termination of the open-label phase, based on:
  - Faster decline in strength (primary endpoint).
  - Excess number of cases of thromboembolism (12 cases [6%] vs 1 case [1%]), P = .07.

A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients

- African-American Antiplatelet Stroke Prevention Study
  - As part of interim DSMB monitoring, futility analyses were performed.
  - After ~80% of the planned number of events, there was < 1% chance that ticlopidine would be shown to be superior to aspirin, and a 50% chance that aspirin would be shown to be better.
  - The DSMB recommended termination of follow-up based on the cost, dosing, and potential adverse effects of ticlopidine, since proving the superiority of aspirin was not deemed relevant.