Data Monitoring Committees History (1965-2013) & Future

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Greenberg Report
Recommendations for CT Monitoring

- Report to NIH 1967 (ref: CCT 1988)
- Develop a mechanism to terminate early if
  - Question has been answered
  - Trial can't achieve its goals
  - Unusual circumstances
  - Hypothesis no longer relevant
- Sponsor (i.e. NIH) should not terminate a trial without outside consultants
- Led NIH to use of external DMCs-DSMBs

DMCs in Industry Trials

- **Occasional use of DMCs in industry sponsored trials prior to 1990's**
  - **Trials with mortality endpoints**
  - **Cardiovascular trials (e.g. ART, PARIS)**
- **Increased use of DMCs since 1990**
  - **Increasing industry pipeline**
  - **More trials with "major" endpoints**
  - **Heightened awareness of value of independent monitoring in some circumstances**
  - **NIH funding for clinical trials limited**
  - **Increased academic-industry collaboration**

A 45 Year History

- Year 2000 triggered greater DMC emphasis
  - Death of gene transfer patient
- Creation of NIH & FDA DMC Guidelines
- More DMCs for Phase III trials and some Phase II trials
- A long 45 year history of success to build on
- A continual learning process
- New challenges for DMCs

DLD Opinion

- Monitoring of Clinical trials not better today than 10 years ago
- The FDA-NIH guidelines are generally consistent with clinical trial fundamentals
- Statistical monitoring methods for benefit, harm & futility well worked out
- One problem is in the interpretation of those guidelines and their practice
- DMCs subject to more public scrutiny

Some Common Myths

- DMCs should be blinded
- DMCs must follow a SAP exactly
- DMC meetings must be scheduled precisely & limited in number
- DMC reports must be on cleaned adjudicated data
- DMC reports can be totally preprogrammed – following SAP
- DMCs review each AE or SAE

Some Recent Concerns (1)

- 1. DMC Charters should be a set of guidelines and principles, not a legal contract, getting longer,……
- 2. DMC member contracts are becoming very long and legal looking – very one sided - should be simple without needing a lawyer to review – should cover
  - Confidentiality
  - Intellectual Property
  - Consulting Rate
  - Indemnification

Some Recent Concerns (2)

- 3. DMC Indemnification
  - Sponsors often propose DMC insure them
  - DMCs cannot function if worried about litigation
  - DMC coverage needed with no escape clauses
- 4. Sponsors control: Limit number of looks at outcome data, just review safety, don't spend any alpha,…..
- 5. Some SDAC's budget for fixed number of meetings and analyses (tables), not flexible, puts DMC at risk

Some Recent Concerns (3)

- 6. DMC Chairs & Meetings
  - Some DMC chairs not sure of their role
  - Should review the DMC report, not just simply ask “any problems?”
- 7. DMC members should not socialize with the sponsor (eg pre meeting dinners) – “loose lips” and “body language”
- 8. DMC meetings should not be in resorts or exotic locations – OHare Hilton is good enough – perception of independence

Some Recent Concerns (4)

- 9. Sponsor compulsion about documentation , not about the main purpose
  - Frequent updated and signed CVs
  - Constantly changing DMC Charter(?)
  - Constantly changing DMC SAP (?)
- 10. DMC Report ≠ NDA
  - Don’t need tables with all variations
  - Medra type AE coding systems almost useless to DMC

New Clouds on the Horizon
What constitutes evidence?

- Supreme Court Rules Against Zicam Maker (March 22, 2011)
- Investors claimed sponsor suppressed evidence of a side effect (loss of smell)
- Post marketing surveillance data
- Justice Sonia Sotomayor, rejected that information can be material only if it meets standards of statistical significance.

Implications for DMCs

- DMCs tend to require some level of statistical evidence before acting
  - Sequential monitoring and group sequential methods
  - Large lists of AEs and SAEs
  - Subgroups
- Ruling implies that statistical evidence not required – a lawyers dream

Another Cloud

- SUPPORT trial (NEJM, 2010) of high vs lower dose of oxygen in 1300 premature babies
- 85-91% O2 saturation vs 91-95%
- Results: lower dose had lower risk of retinopathy but an increased risk of death
- OHRP (2013) challenged the informed consent: claiming it failed to describe adequately risks and discomforts
- See editorial, NEJM (5/23/2013)

Possible Implications for DMCs

- What DMCs monitor may need to be more explicit in the consent form.
- Example
  - A primary outcome such as MACE+
    - (CV death, MI, stroke, plus hospitalization, angina,…..
  - DMC monitors MACE (a harder endpoint)
    - (CV death, MI & stroke)
- Consent form describes study of MACE+
- If MACE+ significant, DMC may not stop unless MACE is also significant

Data Tsunami

- Atul Butte Presidential Lecture
- “300 Billion Points of Data”
- DMCs will have access via internet to ancillary data on a drug/device
- Challenge as to how to use this data, if at all, as AEs begin to emerge
- “Like drinking from a fire hose”
- Public expectation, legal implications, ethical obligations

What Needs to Be Done?

- Turn the tide on making process more complicated that it needs to be
- Training, training,…
  - DMC members & chairs
  - Sponsors
  - SDACs supporting DMCs
  - Regulators?
- Respect for independence of the DMC process

DMC Summary

- NIH Clinical Trial Model – 45 year history of success
- Adaptation for industry can be made
- SC, DMC, SDAC or DCC are critical functional components
- Independence of DMC essential
- Some issues need further discussion