The Independent Statistician Model: How well is it working?

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COI Declaration

- Partly responsible for the development & promotion of the concept of the SDAC version of the independent statistician
- UW-Madison a long history of SDACs
- Early Heart Failure Trials
  - PROMISE (milrinone,1991, NEJM)
  - PRAISE-I (amlodipine, 1996, NEJM)
  - PRAISE-II (amlodipine, 2013, JACC)
  - MERIT-HF (metoprolol, 1999, Lancet)
  - COPERNICUS (carvedilol, 2001, NEJM)

Statistician Roles

- **Four Possible Separate Statistical Functions**
  - Sponsor
  - Steering/Executive Committee
  - Statistical Data Analysis Center (SDAC)
    - **Independent Statistician**
  - Data Monitoring Committee (DMC)
- **Last two might be the same individual but not recommended**

Independent Statistician

- Responsible for DMC Report
  - Individually
  - Leads a team of statisticians
- Must be thoroughly familiar with Protocol, Statistical Analysis Plan, DMC charter and trial data base / case report forms (CRFs)
- Needs to be knowledgeable regarding statistical methods
  - Design
  - Interim Monitoring
  - Final Analysis

Greenberg Report
Recommendations for CT Monitoring

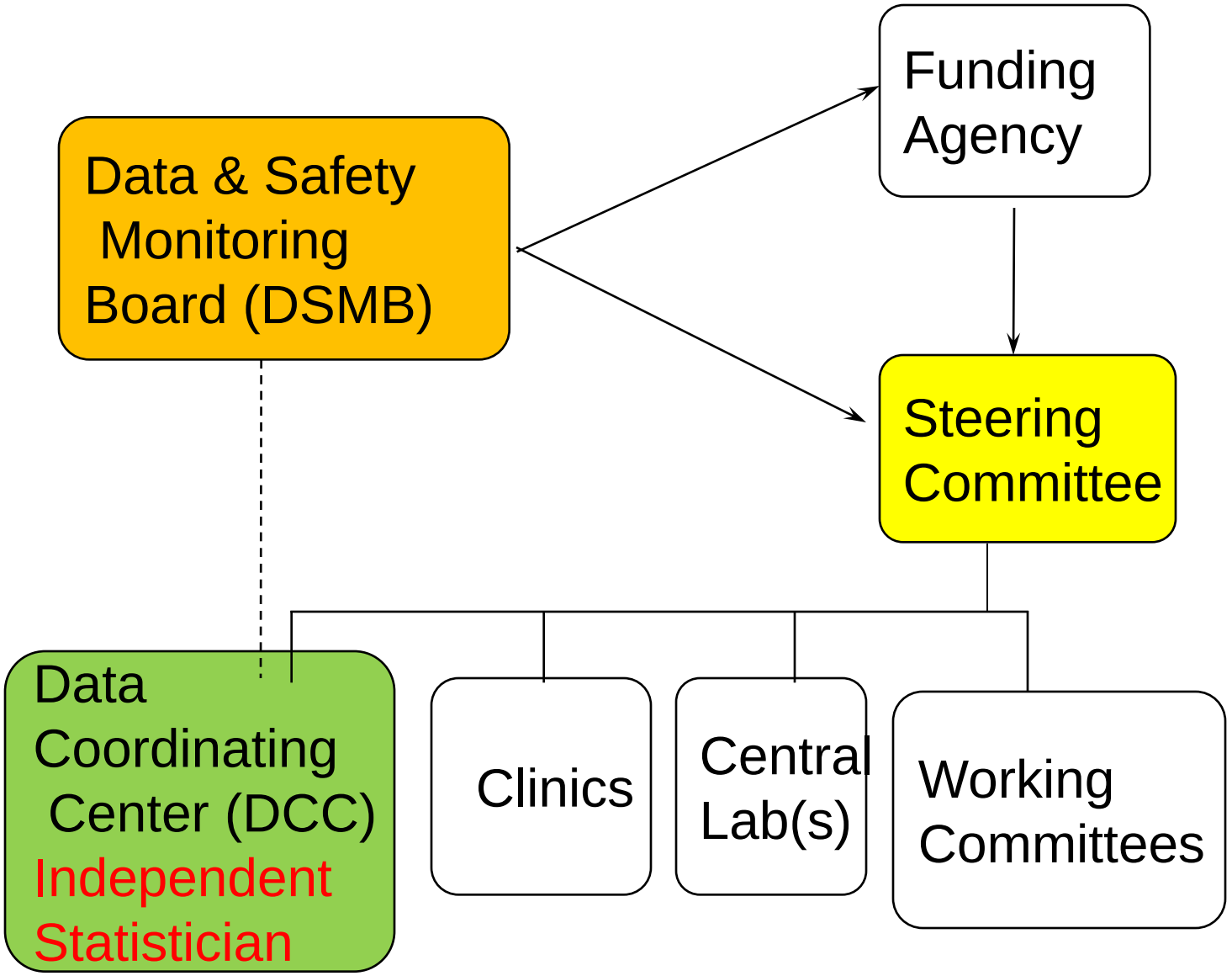
- Report to NIH 1967 (ref: CCT 1988)
- Develop a mechanism to terminate early if
  - Question has been answered
  - Trial can't achieve its goals
  - Unusual circumstances
  - Hypothesis no longer relevant
- Sponsor (i.e. NIH) should not terminate a trial without outside consultants
- Led NIH to use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

DMC Recommendations

1. **Continue Protocol Unmodified**
2. **Modify Protocol**
3. **Terminate Trial**
   - **Serious Toxicity**
   - **Overwhelming evidence of benefit**
   - **Futility or no trend of interest**
   - **Serious design flaws**

- **Independent statistician/ SDAC must prepare report & analysis to support those recommendations**

NIH CT Model


Funding Agency
Data & Safety Monitoring Board (DSMB)
Steering Committee
Data Coordinating Center (DCC)
Independent Statistician
Clinics
Central Lab(s)
Working Committees

Statisticians in Data Coordinating Center

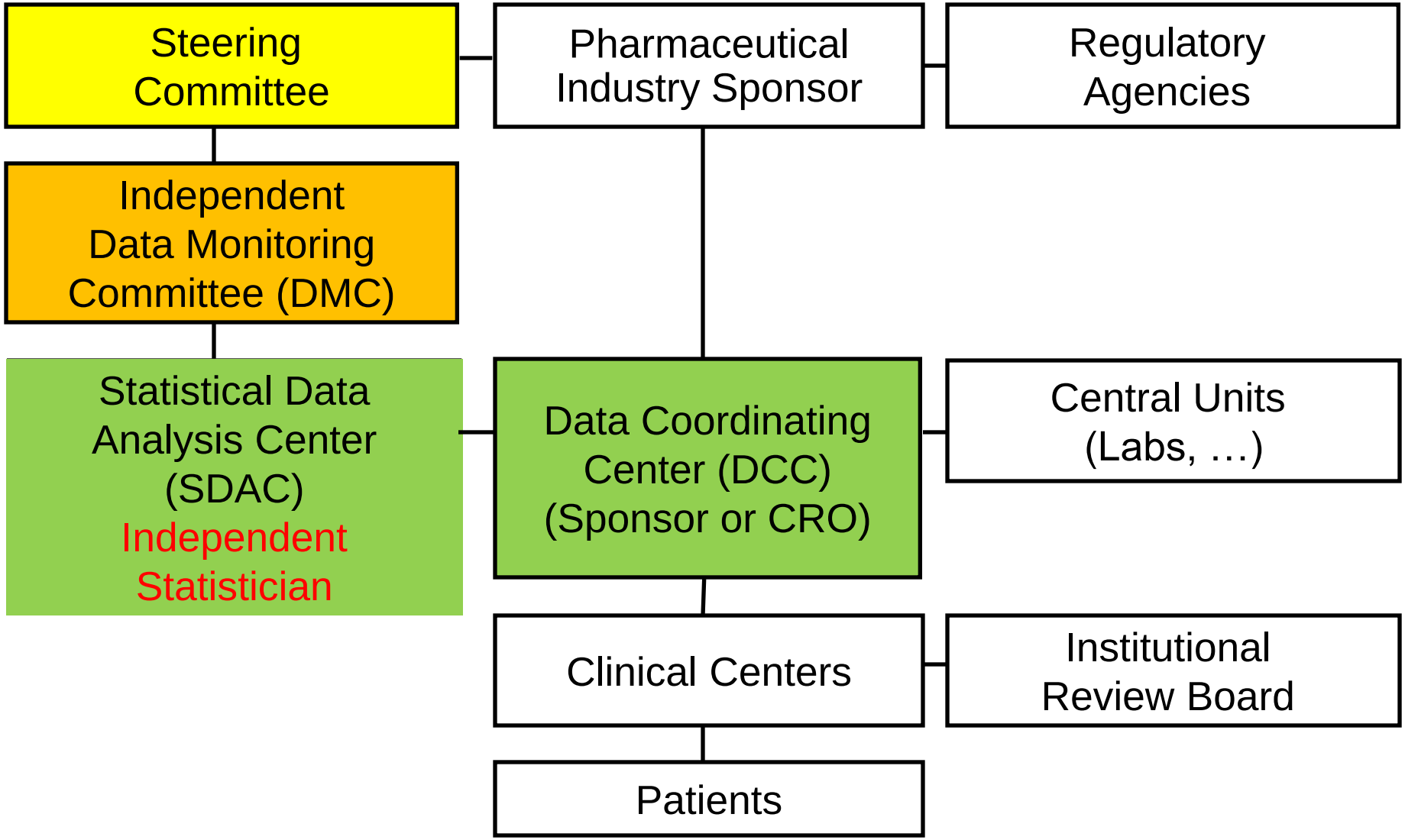
- Multiple statisticians
- Historically played multiple roles
  - Collaborated with sponsor
  - Collaborated with the steering committee
  - Prepared reports for the DSMB
- Later, roles become more differentiated
  - One statistician or team designated to prepare DSMB reports, not interacting with investigators directly during trial

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" clinical endpoints**
  - **Heightened awareness of value of independent monitoring in some circumstances**
  - **NIH funding for clinical trials limited**
  - **Increased academic-industry collaboration**

Industry-Modified NIH CT Model

(PROMISE, 1991, NEJM)



Statistical Data Analysis Center (SDAC)

- **Led by independent statistician**
- **May be involved with some protocol design**
  - **Interact with sponsor and investigators**
- **Primarily prepare interim analyses reports for DMC**
- **May provide final analysis for publication due to recent journal requirement for independent analysis**
- **Possible limited presentation at regulatory review**

Levels of Statistical Independence

- **Trial infrastructure totally In-house**
- **Internal DCC, Internal SDAC, External DMC**
  - **Firewalls hard to build and effect in top two**
- **Internal DCC, External SDAC, External DMC**
- **External DCC (e.g. CRO), External SDAC, External DMC**

SDAC Pushback

- When separate SDAC concept was introduced, many said this would not work
- Belief that independent statistician needed direct contact with the CRFs, investigators, etc
- However, “loose lips sink ships” and independent SDAC helps to prevent this
- By now after nearly three decades, several successful SDAC examples
- BUT……

DLD Opinion

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

So What Is Going Wrong?

- Need to recall DMC / SDAC Purpose!
- Primary DMC goal is to protect patients from harm & unnecessary experimentation on behalf of investigators & IRBs
- Other constituents are important but are secondary or tertiary
  - Sponsor
  - Regulatory Agencies
  - Financial Markets
- DMC no better than the SDAC DMC report
- SDAC role is critical for the DMC to do its work

Maintaining Independence of Independent Statistician

- Most SDACs selected by sponsor and work under sponsor contract
- However, SDACs must work for the DMC without sponsor interference (eg)
  - DMC may need to have poor performing SDAC replaced (eg)
- SDACs must “represent” the data without prejudice (eg)
- Built in COI – if SDAC doesn’t perform according to sponsor preference, may not get further sponsor business (eg)

Emerging SDAC / Independent Statistician Issues

- Supply & Demand
  - Clintrials.gov suggests several hundred DMCs
    - 100,000 interventional trials registered
  - Not enough clinical trialists with DMC experience or training in methods
  - Not enough statisticians familiar with DMC Report process & requirements
- As a result, too many groups sign on to be SDACs
  - But lack DMC experience
  - Poor understanding of what a DMC report is really about
  - Have no statistical depth to handle complex issues
  - No senior biostatistician as “the independent statistician”

DMC Reports

- DMC Report ≠ NDA Report
- Needs to meet the needs of the DMC
- Appropriate length, not only tables and listings but make extensive use of graphs
  - Topics
    - Recruitment
    - Baseline covariates by arm
    - Adherence to intervention
    - AEs & SAEs
    - Primary & Secondary Outcomes
    - Key subgroups
- Analyses evaluating benefit and harm
  - Must anticipate additional analyses

Questionable DMC Report

- Literally 3,000 + pages of listings, standard tables
- Dozens of separate pdf's
- Single report but no page numbers or table of contents, difficult to navigate
- Poor use or no use of graphics for repeated measures
- Reports with no validation, prone to errors
- Based on limited data base, no opportunity for unanticipated analyses

DMC Charters

- Charters describe DMC membership, process & interim analysis including SDAC
- Should be a set of principles, not rules
- Becoming more detailed, many pages
- Imply that interim analysis is algorithmic, follow statistical analysis plan (SAP) exactly
- Becoming more legalistic
  - Contracts say must abide by charter (or else)
- No charter can fully capture DMC challenges
- Independent statistician must be very familiar with the SAP but adjust analyses according to DMC needs

Increasing Restrictions on DMC/SDAC

- What data is presented by SDAC to DMC
  - Edited / “cleaned” only vs
  - Best available preferred
- Some sponsor desire to pre-program DMC Report
  - Changes or additions would require sponsor involvement, potential for unblinding
- Limit Frequency or timing of interim analyses
  - E.g., only one interim analyses for benefit, perhaps at 50%, Spending alpha phobia
- SDAC contract with sponsor must be flexible to conduct as many analyses as needed by the DMC and when they need it

Data Tsunami

- Atul Butte SCT 2013 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
- How will SDACs deal with this?

New Clouds on the Horizon
What constitutes evidence?

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

Implications for SDACs

- DMCs tend to require some level of statistical evidence before acting
  - Sequential monitoring methods
  - Consistency across primary & secondary outcomes
  - Consistency across key subgroups
  - Quality of data and protocol adherence
- Ruling implies that usual statistical evidence not required – a lawyers dream
- Legal liability of SDACs & independent statistician

What Needs to Be Done?

- Turn the tide on making process more complicated that it needs to be
- Retain respect for independence of the DMC process & the SDAC / independent statistician
- Training, training,…
  - SDACs supporting DMCs
    - Independent statistician must have more than classical MS/PhD trainng
  - DMC members & chairs
  - Sponsors & Regulators?

Summary

- DMCs in industry have a long history of success as well as for NIH/academia
- Basic SDAC model for DMC support can work very well, but has not in all cases
- Challenges in training exist –
  - Far too few adequately trained SDACs & independent statisticians
  - Having a classic MS / PhD biostatistics or statistics training not adequate preparation