Data Safety Monitoring :

Why do we need a DSMB and what is its role?

Lynne M. Quittell, MD
Columbia University, College of Physicians and Surgeons
Associate Chair, CFF DSMB

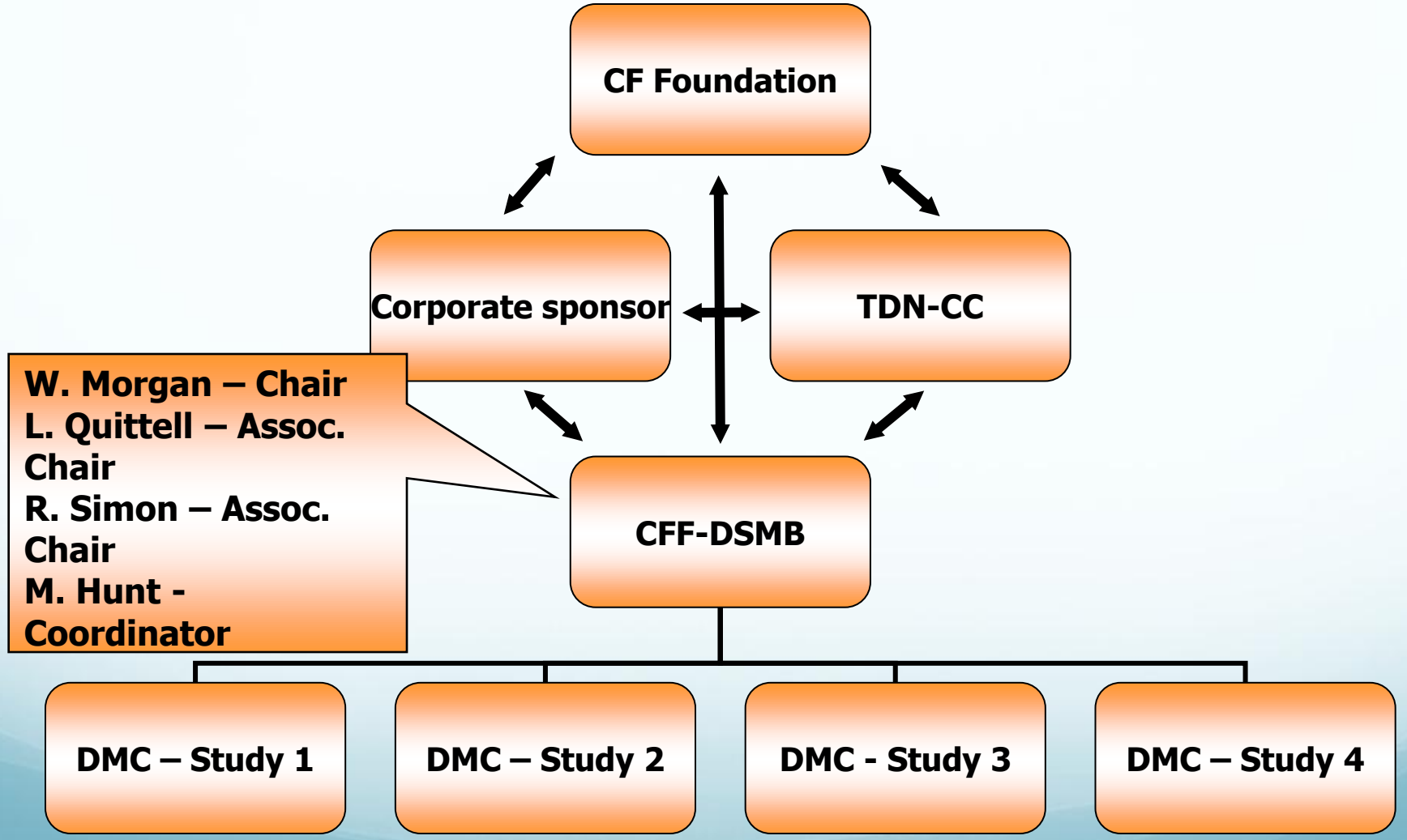
Objectives

- The role of the CFF DSMB
- Conflict of interest
- International studies
- Case examples

DEADLY MEDICINE

VANITY FAIR, January, 2011

Structure


CF Foundation
Corporate sponsor
TDN-CC
W. Morgan – Chair
L. Quittell – Assoc. Chair
R. Simon – Assoc. Chair
M. Hunt - Coordinator
CFF-DSMB
DMC – Study 1
DMC – Study 2
DMC - Study 3
DMC – Study 4

Overall Responsibility of DSMB

- Primary: protect the safety and welfare of patients
- Ensure the integrity of the clinical trials
- Maintain equipoise (be a non believer)

DSMB Relationships or who do we answer to?

- Funded by CFF with both philanthropic and contracted support
- Independent consultant to the CFFT/TDN and Sponsor of the study
- DSMB is not a regulatory group, but most IRB's require a DMC
- Advice unlikely to be ignored; the process is interactive one
- May need consultation/advice from CFF, TDN, Sponsor, or FDA

DSMB Membership

- Large pool with varied backgrounds:
  - Clinical care and research (Pulmonary, ID, GI, Immunology etc.)
  - Basic science
  - Bio-statistics, drug development and clinical trials
  - Medical ethics and informed consent
  - Ad hoc members

Why do we need a DSMB?

- Cystic Fibrosis patients constitute a vulnerable population
  - Strong relationships to their treating CF Center
  - Investment that a new therapy will alter their disease
- New drugs and/or procedures including gene and small molecule therapies in the setting of a very complex disease (phase I and II)
- Patients and stakeholders need to be assured that safety is our first priority

Specific Role of DMC

- Review study design prior to implementation
- Review significant adverse events and toxicity data
- Examine accumulated outcome and safety data in order to make recommendations concerning continuation, termination or modification

DMC Charter

- The charter varies according to the nature of the study and planned monitoring. In general DMC charters have two purposes:
  - To clearly define, before the start of the study, the function, composition, and operating expectations of the DMC
  - To provide information to regulatory agencies regarding the safety and monitoring oversight of the proposed clinical study
- Defines:
  - Frequency of interim analyses for efficacy and futility
  - Appropriate stopping rules
  - Identification and reporting of SAE's and AE's
  - Review of final data and/or manuscript

Conflict of Interest - Challenges

- Clinical trials in CF commonly require large numbers of CF care centers to be involved
- Experts in CF and clinical research are one and the same
  - Limited in number
  - Associated with centers capable of high quality clinical research
  - Ideal candidates for DMC

Factors unique to CFF DSMB

Highly centralized decision making private foundation

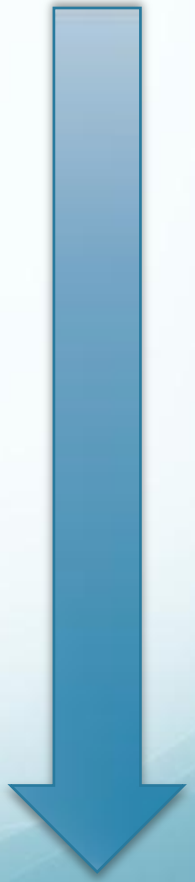
Close relationships between patients and team

Potential lack of synchrony between CFF DSMB and home institution

How can we manage COI? A few guidelines:

- Accept an element of COI that needs to be managed:
  - Relations with colleagues and patients?
  - Involvement in recruitment?
  - Management of CF center budgeting of money and time?

1. DMC member should be removed from recruitment and study proceedings
2. Ensure a fire wall between DMC member and funds from the clinical trial and study sponsor



DSMB's in International Studies

- Increasing number of international studies
- International representation is consistent with the guidelines for DMSB's
- Issues specific to resource-poor countries- inadequate data, drug may not be approved
- Regulatory guidelines differ among countries- data may not be accepted even when adequate

Studies gone crazy

Record study

- **May 1, 2007- Meta-analysis of rosiglitazone (increases insulin sensitivity) clinical trials showing a HR for MI of 1.43 was submitted to the NEJM by the author**
- **Drug sales has reached $3 billion/year**
- **5/3/07- An academic reviewer sent the draft manuscript to the sponsor with a cover page marked confidential and urgent**
- **The sponsor distributed the paper to internal scientists who agreed with the findings. There were internal company documents showing they already knew of a 30-43% risk of MI**

Nissen, SE. JAMA,March 24/31, 2010, Vol 303, No 12

- Sponsor decided to unblind and publish the ongoing RECORD study with or without the consent of the academic steering committee
- The steering committee agreed to unblind and publish the interim study but did not know that the sponsor had already unblinded themselves 2 weeks previously
- Interim analysis was too underpowered to make conclusions about safety
- Final RECORD manuscript published in 2009 had inconsistent data

SEAS- Simvastin and Ezetimibe in Aortic Stenosis

- **Study to determine the benefit of simvastin and ezetimibe in the treatment of AS**
- **Data showed an increased risk of cancer**
- **The sponsors interacted with PI's and DSMB's of 2 on-going studies (SHARP and IMPROVE-IT) to unblind the cancer data of these two studies**
- **2008, NEJM published the cancer data from all 3 studies without knowing the background story**

Califf RM, Harrington RA, Blazing MA. Premature release of data from clinical trials of ezetimibe. N Engl J Med 2009;361:712-7.

What should have happened?

- **DSMB's might have been able to assess the risks of each of these studies to determine if they could be completed or stopped thus avoiding incomplete data:**
- **RECORD trial:**
  - **DSMB should have been notified of May 2007 article and been able to check the RECORD data for adverse cardiac events**
- **SEAS trial:**
  - **Sponsors should have informed DSMBs of other two trials about the cancer risks**

Brazen, JM, Wood AJJ, NEJM 363:5,2010

The Case of the Phase III Folly

- Phase 3, randomized, DB, PC trial of an FDA approved oral antibiotic
- 100 patients each arm, 48 weeks
- Problem#1: Primary endpoint for the study proposed a non-standard measure of lung function not previously used to obtain FDA approval
  - Does the DMC think this is a fatal flaw?
  - Has the sponsor discussed this with FDA to ensure that they will accept this?

- Problem #2: Sponsor intended to have member of company leadership be unblinded to data
  - Introduced bias to the study
- Problem #3:The protocol required that patients stop chronic azithromycin therapy:
  - Need strong justification for withholding any standard therapy especially for such a long period
  - Withholding of a standard treatment needs to be clearly stated in the consent

Don’t mess with the DSMB

- **Public confidence in clinical trial process has been undermined**
- **Suggested changes:**
  - **DSMB should be appointed by an independent public body**
  - **Sponsor should provide funding to this 3rd party which will choose the DSMB, supervise its activities and ensure integrity**
  - **Final manuscripts should be approved by the DSMB to assure that they are representative of the study**
  - **NEJM now requires evidence of DSMB independence in any study that reports early stopping or interim analysis**

N Engl J Med. 2010 Jul 29;363(5):477-8. doi: 10.1056/NEJMe1007445. Epub 2010 Jul 7.

Summary

- As we continue to expand the number of clinical trials with increasing complexity and work on a global platform, we need to remember our primary responsibility of patient safety.