

# DMC Roles in Adaptive Trials

Dario Gregori

Unit of Biostatistics, Epidemiology and Public Health

Department of Cardiac, Thoracic and Vascular Sciences,

University of Padova

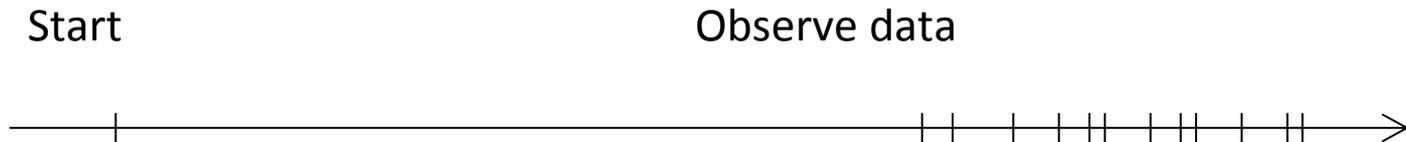
[dario.gregori@unipd.it](mailto:dario.gregori@unipd.it)

# Adaptive Designs Logic

Conventional fixed sample size design



Clinical trial reality: gradual accumulation of data



Adaptive design:

Use interim analyses to assess accumulating data

Adapt design for remainder of trial

# AD definition

- Recently, there has been considerable research on adaptive designs (ADs).
- The rapid proliferation of interest in adaptive designs and inconsistent use of terminology has created confusion about similarities and differences among the various techniques.
- For example, the definition of an “adaptive design” itself is a common source of confusion.

# PhRMA WG 2006

- PhRMA Working Group on Adaptive Designs (2006):
- “By adaptive design we refer to a clinical study design that uses accumulating data to modify aspects of the study as it continues, without undermining the validity and integrity of the trial”
- “...changes are made by design, and not on an ad hoc basis”
- “...not a remedy for inadequate planning.”

# AD challenges

- General principle: access to interim results and unblinded data should be **strictly controlled, and in particular should not be available to personnel managing trial operations, study investigators, or trial sponsors.**
- Main motivations.
  - **Access to interim results diminishes the ability** of trial personnel to manage the trial in a manner which is totally objective, and will be seen to be totally objective by regulators and the scientific community.
  - Knowledge of interim results by investigators, the scientific community, or the public could **introduce unknown biases into the trial and its results**, perhaps causing changes in characteristics of patients recruited, specific details of administration of the intervention, endpoint assessments
- For AD
  - What should be the processes for interim data analysis, review and decision making, and what **differences** might be suggested for adaptive trials versus current monitoring conventions?
  - For what **types** of adaptive designs might the level of information which can be inferred from viewing an adaptation be considered to compromise the integrity of the trial or have potential to introduce bias into its results? In such cases, can any additional actions be taken to minimize such concerns?

# AD types

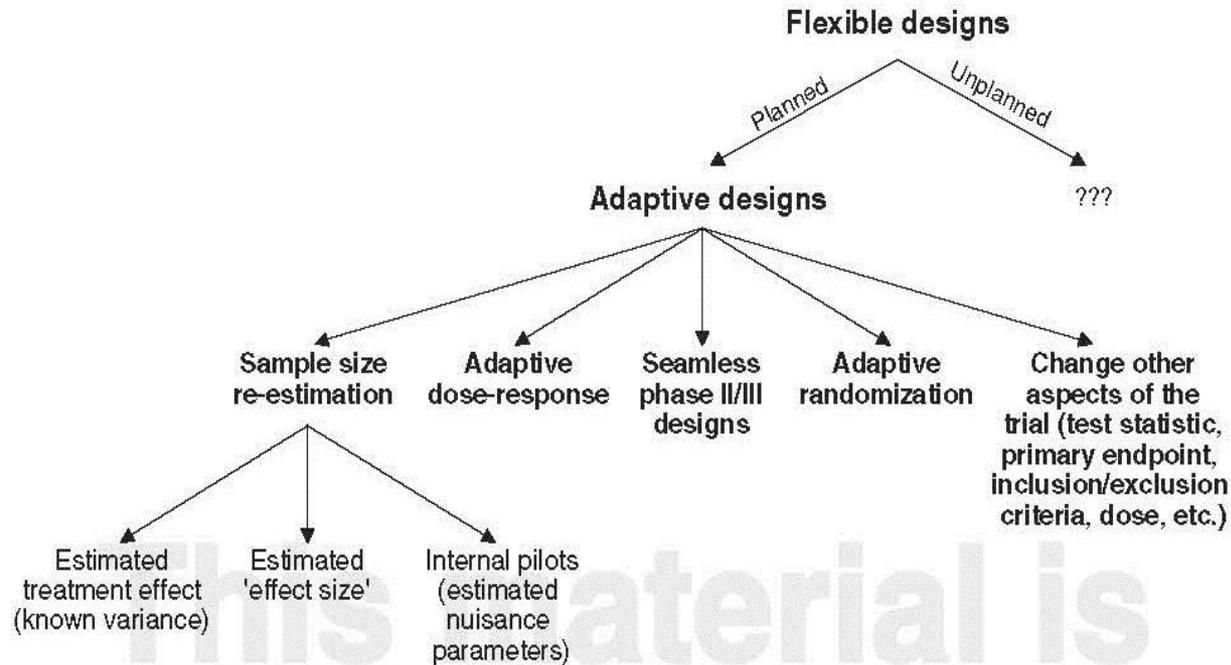


Fig. 1. Summary of different types of adaptive designs for clinical trials.

Coffey CS and Kairalla JA (2008). Adaptive Designs: Progress and Challenges. *Drugs in R&D*, 9(4): 229-242.

# Guidance for Clinical Trial Sponsors: Establishment & Operation of Clinical Trial Data Monitoring Committees

- Became available March 2006
- Started IND submissions on newer adaptive designs – guidance not address newer adaptive DMC monitoring
- Discussed firewalls & protection of interim results
- Discussed interactions with FDA vs FDA role in a GSD
- Discussed multiple models for independent statistician

# Monitoring with an adaptive design

- Interim unblinding
  - Beyond group sequential design
  - Desidered sponsor's engagement
  - **Frequent (rule driven) vs defined timing for unblinding**
- Different levels of concerns
  - Exploratory (learning trials)
  - Confirmatory (registration trials)
  - Seamless phase 2/3
    - Design characteristics: learn or confirm
    - Confusing and ongoing

# Clinical Trials Committees

- SC (Steering Committee)
- Sponsor
  - siDMC
  - IRC (Internal Review Committee) vs SC
  - Senior management designee
- ISAC (Independent Statistics Analysis Center)
- eDMC, DSMB, DMC
- .....
- Data management

# Data Monitoring Committee Role

- In a randomized and double-blinded clinical trial, a Data Monitoring Committee (DMC) has the principle responsibility to **monitor the emerging results** of the trial (Ellenberg, Fleming and DeMets, 2003)
- Society for Clinical Trials (SCT) Working Group on Data Monitoring, policy guidelines from the US National Institutes of Health indicate that a *“data monitoring plan should exist for all clinical trials be they exploratory (Phase I, II) or confirmatory (Phase III)”*
- The role of the DMC is to **monitor trial outcomes** (i.e. efficacy and/or safety data unblinded to intervention actually received) to detect early benefits of the intervention or potential harms, to evaluate the benefit-risk of trial participants, and based on these considerations make recommendations to the trial’s Sponsor that the trial’s protocol be modified or the trial be terminated.

# DMC approaches

- **eDMC**. Normally the DMC is external to the trial's Sponsor that provides funding for the clinical trial. The eDMC is a **multidisciplinary group** providing scientific peer review of accumulating information during the execution of a clinical trial. The typical make-up of an eDMC includes clinical researchers with knowledge of the biomedical field under investigation and a biostatistician with experience in the interim monitoring of clinical trial data. The two key members of the eDMC are the eDMC Chair and the eDMC biostatistician.
- **siDMC**. Single standing internal DMC (or siDMC) with similar characteristics to an eDMC but with more flexibility typically required for exploratory trials. The siDMC would be partially independent (i.e. Sponsor staff are members of the siDMC but "independent" of the Sponsor staff conducting the exploratory trial monitored by the siDMC). The responsibilities and processes of the siDMC should be documented in two Charters:
  - a general charter detailing the standard operating procedures of the siDMC across all the Sponsor-funded exploratory trials and
  - a trial-specific charter detailing the standard operating procedures (e.g. frequency of interim reports, monitoring guidelines) for an individual exploratory trial. The standardized charter template developed by the DAMOCLES Study Group (Lancet, 2005) can be used for both the general and trial-specific charters

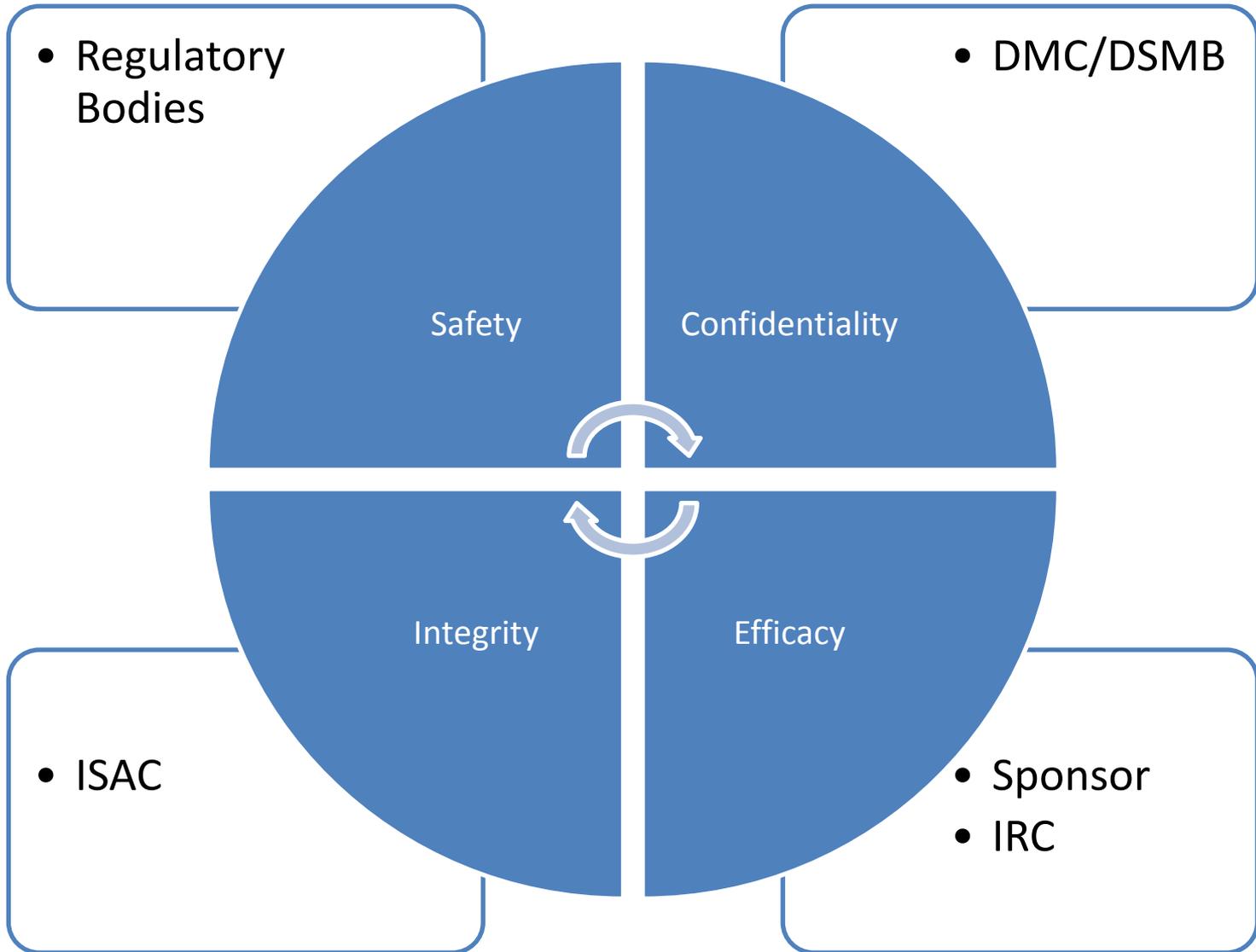
# DMC responsibilities

## Before Adaptive Designs

- Study enrollment
- Data quality
- Patient safety
- Recommendations on conduct of clinical trials, trial monitoring
- Membership, Documentation,
- Process, Implementation
- Open vs closed meeting

## With Adaptive Designs

- Expanding scopes to include
  - Recommendation on design changes of a ongoing trial
- Can still meet expectation on
  - Maintain ‘independence’ & avoid conflicts of interests?
  - Confidentiality (closed meetings)
  - Trial integrity
- **Uncharted** and evolving



# Sponsor's roles in AD

- The sponsor representatives should be a minimum number of individuals possessing the perspectives necessary to assist in **arriving at the best decision** (in confirmatory trials this may ideally involve only one or two individuals in senior management);
- These individuals should **not otherwise be involved** in the trial;
- These individuals will have access to results only at the **times of adaptation decisions**, and they will see only the information relevant to the decision with which they are assisting (e.g. unlike a DMC with whom they might be working, which will usually have a broader and ongoing role);
- **Appropriate firewalls** should be in place to ensure that access to the results is appropriately limited and information will not be disseminated beyond those authorized to receive it (in particular, the trial team, investigators, Steering Committee, etc. will not have access).

# Models

Unblinded interim adaptation requires establishment of written charters and procedures for adaptive monitoring, interim analysis, adaptive recommendation and adaptive decision to assure validity and integrity of trial results.

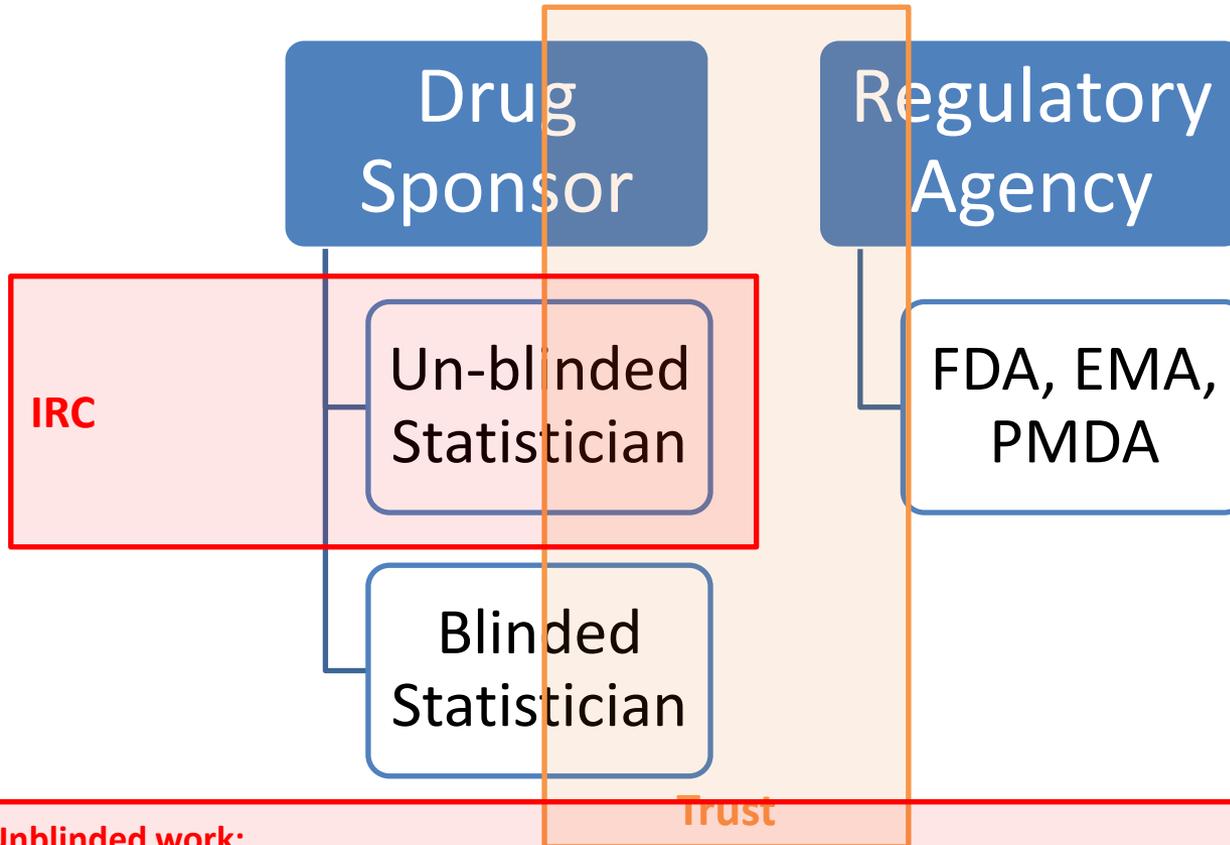
The different trial logistics models will depend on the principles as to **whether complete independence of the interactions among the involved parties is feasible via established firewalls.**

Sue-JaneWang, Society for Clinical Trials 2012

# Logistic models

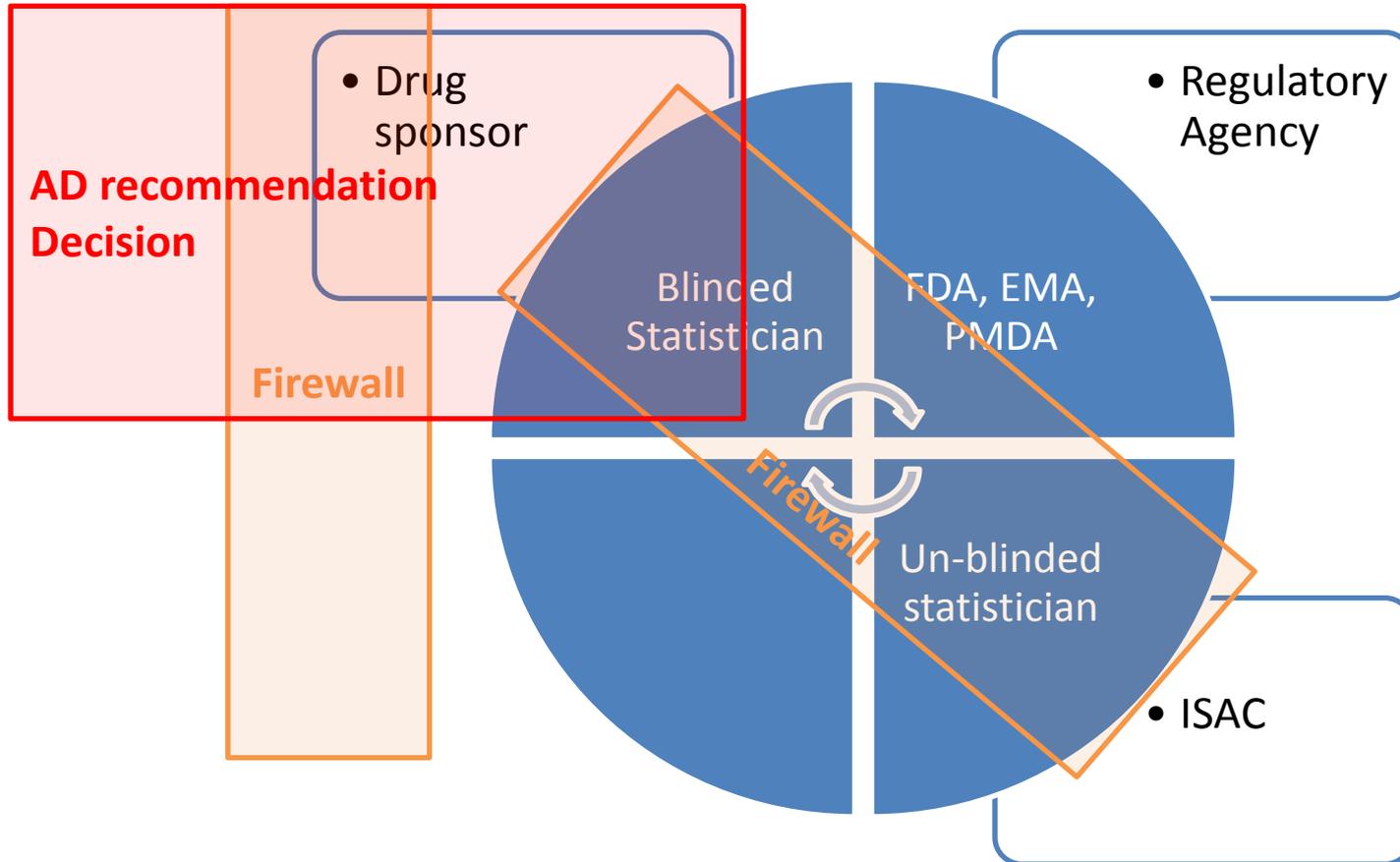
- For exploratory AD trials
  - Sponsor Only Internal (SOI) Model
  - Independent Statistics Analysis Center (ISAC) Model
- For confirmatory AD trials
  - Data Monitoring Committee (DMC) Model
  - Academic Governance Model
  - Combination Model
- For mixed AD trials
  - Adaptive Monitoring Logistics Model

# Sponsor Only Internal (SOI) Model

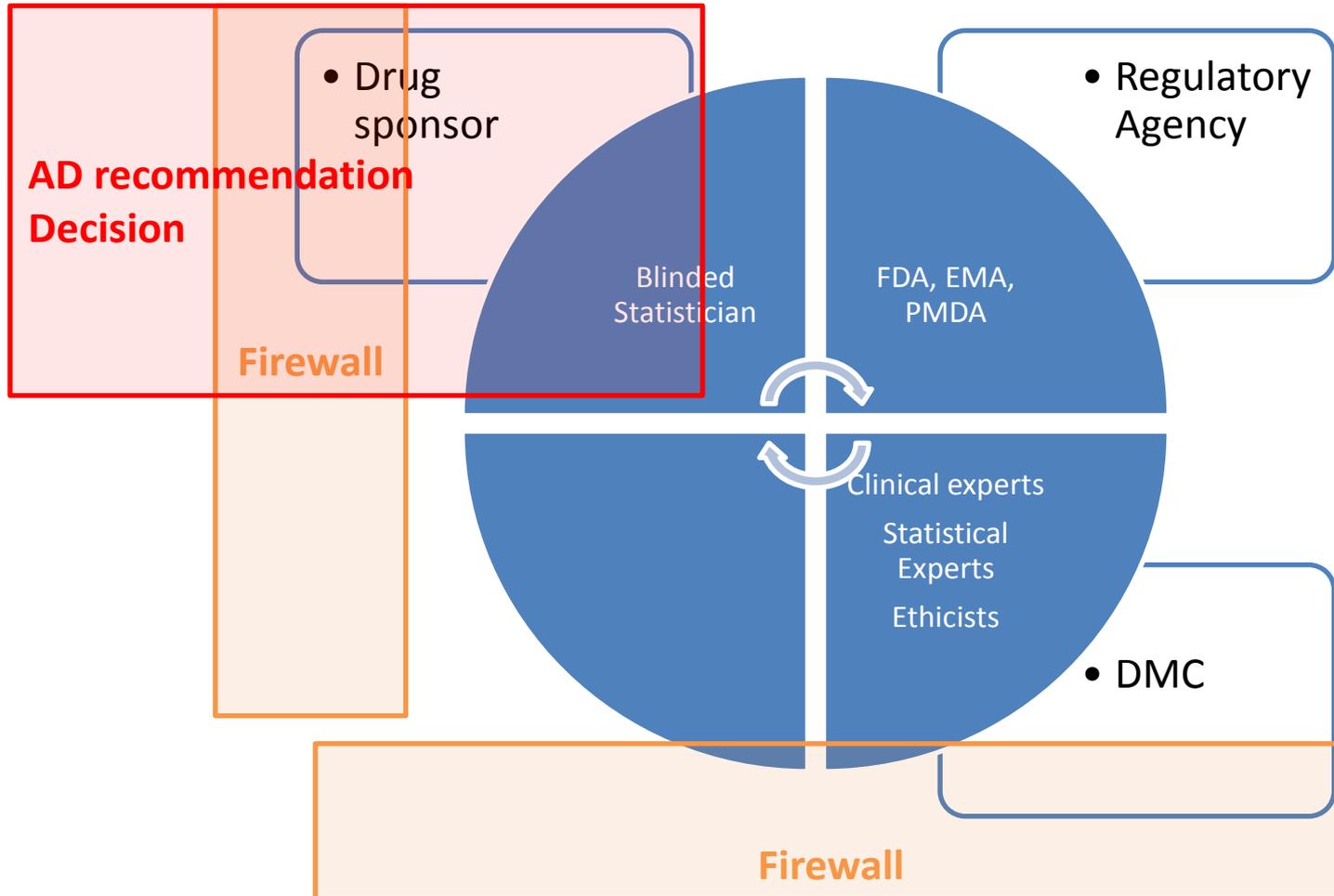


- **Unblinded work:**
  - statistician to perform Interim Analysis (IA) following adaptation rules
  - Internal Review Committee (IRC) to make AD decisions
- **Blind Regulator and maintain blind for in-process control of an ongoing trial**

# Independent Statistics Analysis Center (ISAC) Model



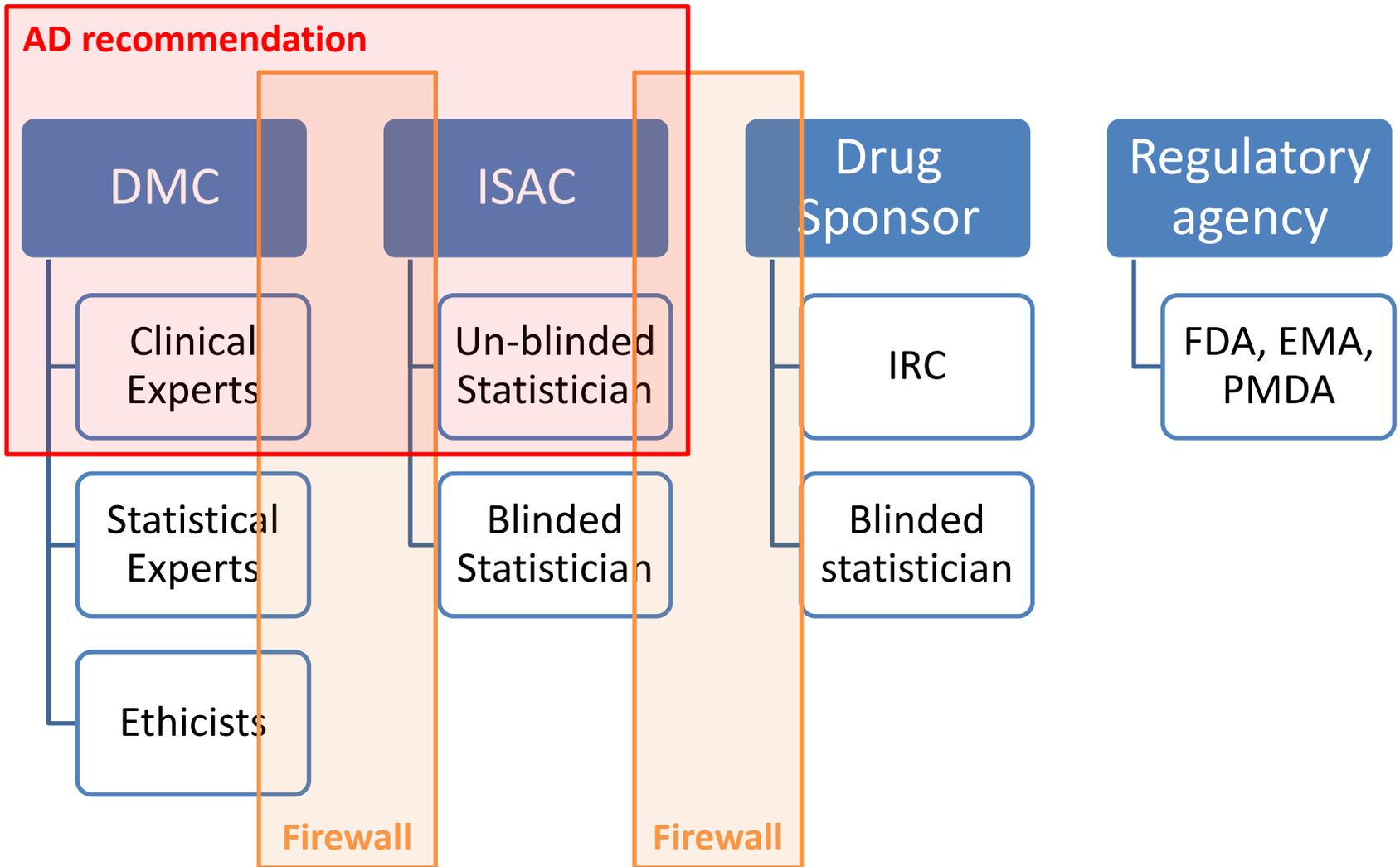
# Data Monitoring Committee (DMC) Model



# Academic Governance Model

- SC includes academic investigators having full access to all of the trial data and reports
- SC appointed by drug company, trial data is exclusively controlled by company and 'access' provided to investigators
- Authors can send query to company
- SC doesn't have a copy of trial data
- No outside statistician has independent access to raw data
- Uncertain on “extent and depth” of statistical confirmation

# Combination Model



# Adaptive Monitoring Logistics Models

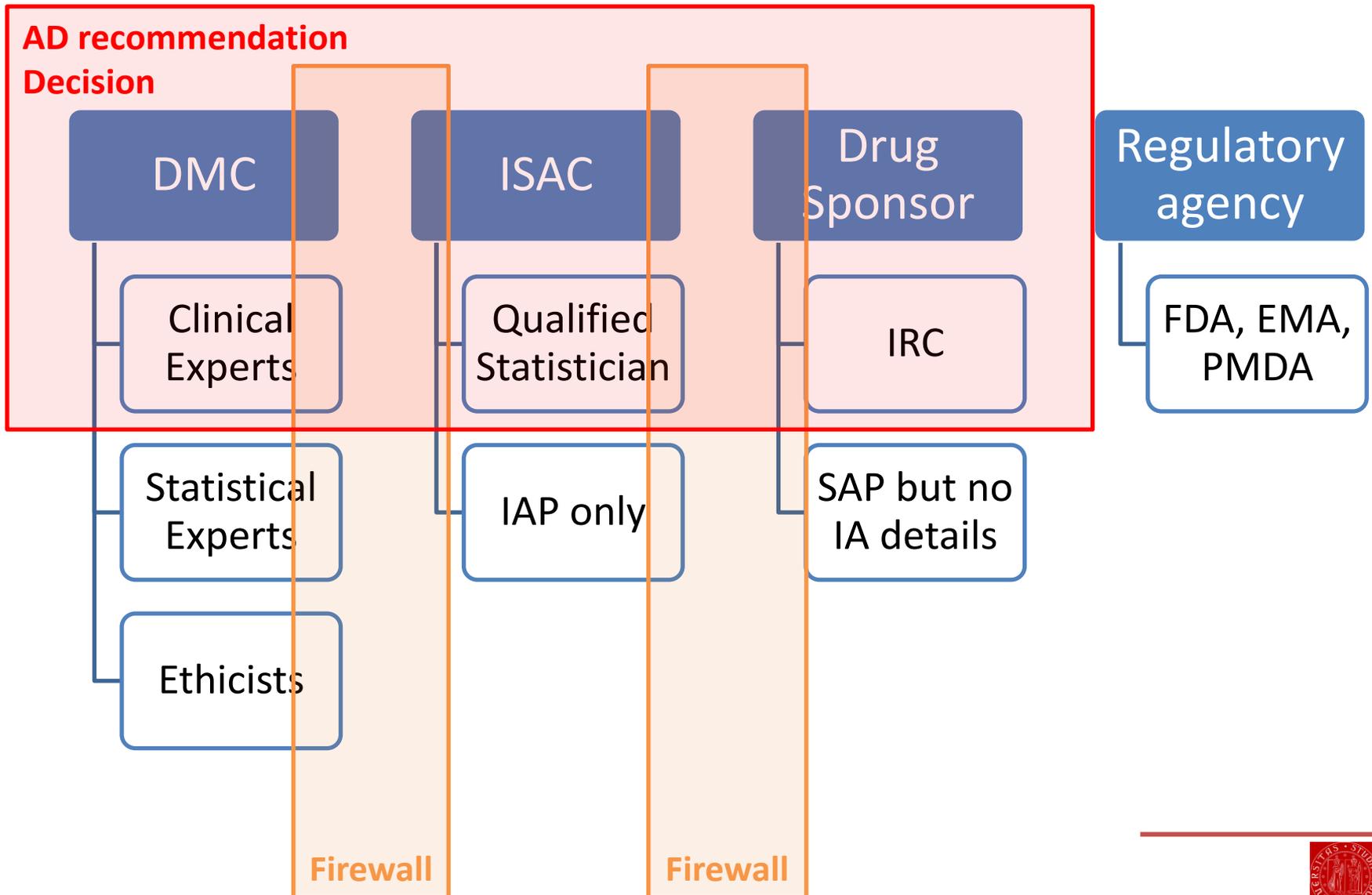
## When without a DMC

- Formal DMC may not be required
- If Sponsor-Only-Internal Model
  - Confidentiality agreement: legal consequence (Wang, 2012)
- If ISAC Model
  - Firewalls within ISAC
  - Rely on professional ethics
- Sponsor's decision to adapt

## When with a DMC

- Safety Monitoring needed
- If DMC Model
  - Discretion (can overwrite)
  - Objectivity of 'safety'
  - Tend to follow adaptive rule
- If Combination Model
  - Separate roles of adaptation recommendation from safety monitoring
- Who should make adaptive recommendation
- Sponsor's decision to adapt

# Modified Combination Model for AD



# Modified Combination Model for AD

- Roles of ISAC(s):
    - Blinded Adaptive
    - Unblinded Adaptive
    - IAP Only (No SAP)
  - Roles of DMC when required:
    - Safety Monitoring
    - Provided with Emerging Data
  - Roles of Sponsor:
    - Responsible for Adaptive Decision
  - Role of SC:
    - Depends on committee composition
  - Roles of Regulator:
    - Public Health
- Major need for inputs
- Responsibility for Adaptive Recommendations
- Confidentiality Agreement enforcement
- Separate IAP vs. SAP (only ISAC or DMC sees IAP)

# Summary of logistic models

## Principle – Independence and objectivity

- Sponsor-Only Internal Model: blinded  $\leftarrow$  █  $\rightarrow$  unblinded
- ISAC Model: ISAC (blinded  $\leftarrow$  █  $\rightarrow$  unblinded)  $\leftarrow$  █  $\rightarrow$  Sponsor
- DMC-Only Model: DMC  $\leftarrow$  █  $\rightarrow$  Sponsor
- Combination Model: ISAC
  - $\swarrow$  █  $\leftarrow$  DMC  $\leftarrow$  █  $\rightarrow$  Sponsor  $\rightarrow$  SC
  - $\searrow$  █  $\leftarrow$  Sponsor

- $\rightarrow$  Relevance to Multi-Regional Clinical Trials
- $\rightarrow$  Any legal consequence to confidentiality agreement ?
- $\rightarrow$  Need more experiences and some proposals

# Impact of AD on DCM

- Use of AD's may require a different way of thinking about the structure and conduct of DSMB's.
- For confirmatory AD's, investigators should **include decision trees and triggers in trial design** to minimize the role of DSMB judgment.
- Statisticians who serve on DSMB's for trials that use an AD should be **familiar with theory and practice of AD's**.
- DSMB's should assure trial has **data managers who are knowledgeable about special needs of adaptive trials**

# STRATEGIC PLAN

Version: May 2016

## Areas of Strategic Focus

Improvements in the clinical trials enterprise happen through transformative and incremental change. CTTI efforts focus on making change in the following areas:

- Systematic approach to evidence generation, including use of non-traditional clinical trial data sources and technical innovations
- Patients as equal partners across the research and development continuum
- Clinical trials that are designed with a focus on efficiency and quality
- Trials that address emerging public health concerns
- Safe and ethical trials that are streamlined



## Build knowledge

# Sample size re-estimation (SSRE)

- **Type I.** Sample size re-assessment that accounts for the variance of effect size or the response rate of the placebo group. Data from both treatment groups can be pooled to reestimate the variance and the blind can be maintained. In addition, the p-value as conventionally calculated generally remains statistically valid
- **Type II.** Interim estimate of the treatment difference or treatment effect to be tested, meaning the treatment groups are unblinded to the analysts. Thus, when the estimated effect size in an interim analysis of the trial is much smaller than the initially postulated effect size and this smaller effect is still deemed worthwhile, it may be of interest to increase the sample size based on the pre-specified adaptation algorithm.
  - Under this type of re-estimation, the p-value as conventionally calculated is no longer statistically valid and requires an upward adjustment, such as a prespecified weighted z-statistic (e.g., Cui et al., 1999) or a stagewise p-value combination (e.g., Bauer and Kieser, 1999).
  - The blind needs to be broken to perform this calculation, which can potentially have adverse impacts on trial conduct and trial integrity.
  - This involves the issues of ‘who should see what,’ how to establish proper firewalls to protect trial conduct, whether standard operation procedures are sufficient, how regulatory agencies can review logistics and trial conduct, etc. In fact, these issues arise commonly in any adaptive designs that require breaking the blind.

# Blinded vs. Un-blinded SSRE

- When the maximum sample size is not set at the protocol stage and if the interim observed treatment effect estimate is the basis for sample size re-estimation, the final sample size can, at least theoretically, be any sample size as the interim estimator of the effect size can be much larger or much smaller than the postulated effect size.
- **SSRE in confirmatory trials is reasonable in response to a larger variance than expected.**
- However, adjusting the sample size based on a smaller than the hypothesized effect size is generally regarded as not a good idea unless a **reasonable maximum sample size is pre-specified.**
- **Blinded sample size re-assessment is generally encouraged**
- If an unblinded sample size reestimation is to be planned, **carefully stated criteria for adaptation** are needed, like the “50 per cent-conditional-power approach” (Chen, 2004)
- It is critically important that under an unblinded sample size re-estimation, the issues with trial conduct and integrity due to such re-assessment need to be **prospectively** addressed (Hung et al., 2014).

# Modes of adaptive trials

- Exploratory adaptive trials
- Confirmatory trials
  - “Learn-versus-Confirm” paradigm (Wang & Bretz, 2010) if combining data from both the exploratory stage and the confirmatory stage is intended to make formal statistical inference of the selected patient population or the selected dose regimen (21CFR314.126)
  - For statistical inference, the learning portion is not free of type I error and thus this stage needs to be a part of statistical error control of the entire study (Wang et al., 2013)
    - **Bayesian response adaptive randomization** (West and Harrison, 1997) Start with a small sample burn-in period followed by assigning the next dose based on accumulating short term responses or outcomes or the immediately previous cohort response until the pre-specified maximum number of patients randomized is reached and the fixed randomization ratio is generally proposed in the confirming stage
    - **“modeling and simulations”** (Wang 2009, Bretz and Wang 2010). The problem of controlling the study-wise type I error rate under complex adaptive design generally does not have an analytical solution needing simulation studies to examine the type I error rate
  - Open questions (Wang, 2015)
    - Are there interpretability issues from combining the results from two or more stages of the trial that are potentially heterogeneous?
    - How should the evidences, primary versus secondary, be quantified when they are adaptively obtained for the primary endpoints, then, for the secondary endpoints?
    - Should there be some priority considerations for pursuing an adequate and well-controlled adaptive design trial, e.g., choices for control of false positive conclusion, probability of success of phase III registration trials, confirmatory evidence requirements, total sample size, total trial duration, and choices among design options including fixed designs?

# Best Practices (Gallo 2010)

- In line with current conventions, access to unblinded data and knowledge of interim results should be viewed as having **potential to compromise the trial results**. This is particularly important for confirmatory trials.
- Review of accruing results and decision making regarding adaptations are best performed by an **authorized board of qualified individuals not otherwise participating in the trial**. Sponsor participation in such activities may be justified, but a clear rationale for this need should be able to be described. Appropriate **procedures and firewalls** should be in place to prevent unwarranted dissemination of information, and subsequent documentation of compliance with those procedures should be produced.
- Knowledge by observers or trial participants regarding selection decisions such as continuation or termination of particular doses or patient sub-populations in a seamless design, but **not of the specific numerical basis** on which those decisions were made, should usually not be perceived as information with potential for compromising the trial.
- Adaptations which are based upon treatment effect estimates in an algorithmic manner can in effect unblind an observer to comparative interim results. Thus, the confidentiality issues must be considered particularly carefully in attempting to implement such approaches; if possible some variation of methodology should be considered which **makes the actual treatment effects less apparent**.
- Procedural steps should be considered in individual cases to limit knowledge of comparative information during ongoing trials, if feasible and ethical; for example, full statistical details governing an adaptation plan might be withheld from a protocol and placed in a document of more limited circulation if that could **decrease the potential for observers to make inferences about the nature of interim analysis results**.

# Matter of discussion

- Survey
  - Who is involved in AD?
  - Who has to do with DMC in AD?
- Main concerns about DMC/AD