Monitoring Processes and DMC Composition (1)

- In line with current practice in non-adaptive settings, access to interim comparative information should be restricted from all personnel involved in the trial.

- The decision-making board
  - should have no other role in the trial
  - should not have broader potential for influence on the trial
  - should possess all necessary expertise relevant to their task

Monitoring Processes and DMC Composition (2)

- The adaptation decision may be complex and may lie in a domain which is traditionally a sponsor responsibility
- The sponsor perspective may be relevant
- Important sponsor interests may be involved
- But current practices and guidelines in more familiar monitoring settings would hold that sponsors not have access to interim confirmatory data while trials are ongoing.
  - Sponsor concern: ***unanticipated complexities*** that might not fit a pre-specified algorithm.
- Can we find operational models that resolve this conflict, while satisfying the key concerns and maintaining trial integrity?

Monitoring Processes and DMC Composition (3)

- "Sponsor" is a broader term than sometimes implied in this discussion.
  - Sponsor personnel who would most naturally be the decision-makers, or need to approve a recommendation, might very naturally have *no role in trial operations*.
  - Keep in mind the *principle*: information must be kept from those whose activities could influence the trial.
- Balancing *trial integrity* versus *sponsor interests* ??
  - ***Trial integrity is a sponsor interest !!***

Monitoring Processes and DMC Composition (4)

A proposal for a model for sponsor involvement
(example: a long-term seamless phase IIb/III program)

- Potential sponsor participation in the process in confirmatory adaptive trials should require:
  - a clear rationale for the involvement, based on the complex nature of the decision and its implications
  - individuals properly '*distanced*' from trial operations
  - clear understanding by all involved of the issues involved and risks to the trial, documentation of the processes followed, and restrictive firewalls / procedures in place

Monitoring Processes and DMC Composition (5)

- Model for sponsor participation (continued)
  - "minimal" sponsor exposure to make the needed decision:
    - *smallest number of individuals* who can supply the needed perspectives
    - *only at the adaptation point* (which often will be at a relatively early point within the trial)
    - *only the minimally relevant information* (e.g., unlike a DMC with whom they may interact, which may have a broader ongoing role).
- (Note: similarity to Section 6.5, FDA DMC Guidance)

Monitoring Processes and DMC Composition (6)

- This is not a ***one size fits all*** issue!
  The circumstances should determine the needed level of involvement.
- Information flow details, procedures for restricting access from those involved in the trial, and any relevant steps implemented to avoid possible bias need to be described in detail in the DMC Charter.
- The burden will necessarily fall on the sponsor to make a strong case that effective procedures and safeguards are in place, *and are followed.*

References

- Gallo P. Confidentiality and Trial Integrity Issues for Adaptive Designs. *Drug Information Journal* 2006;40:445-449