Session #18

DSMB Roles in Adaptive Design Trials: Regulatory Experiences & New Challenges

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* Professional views expressed are those of the authors and not necessarily those of U.S. FDA

Acknowledgments

FDA/CDER Review Teams/Divisions/Offices Coordinated Efforts with Office of Biostatistics

Guidance for Clinical Trial Sponsors:
Establishment and operation of clinical trial data monitoring committees

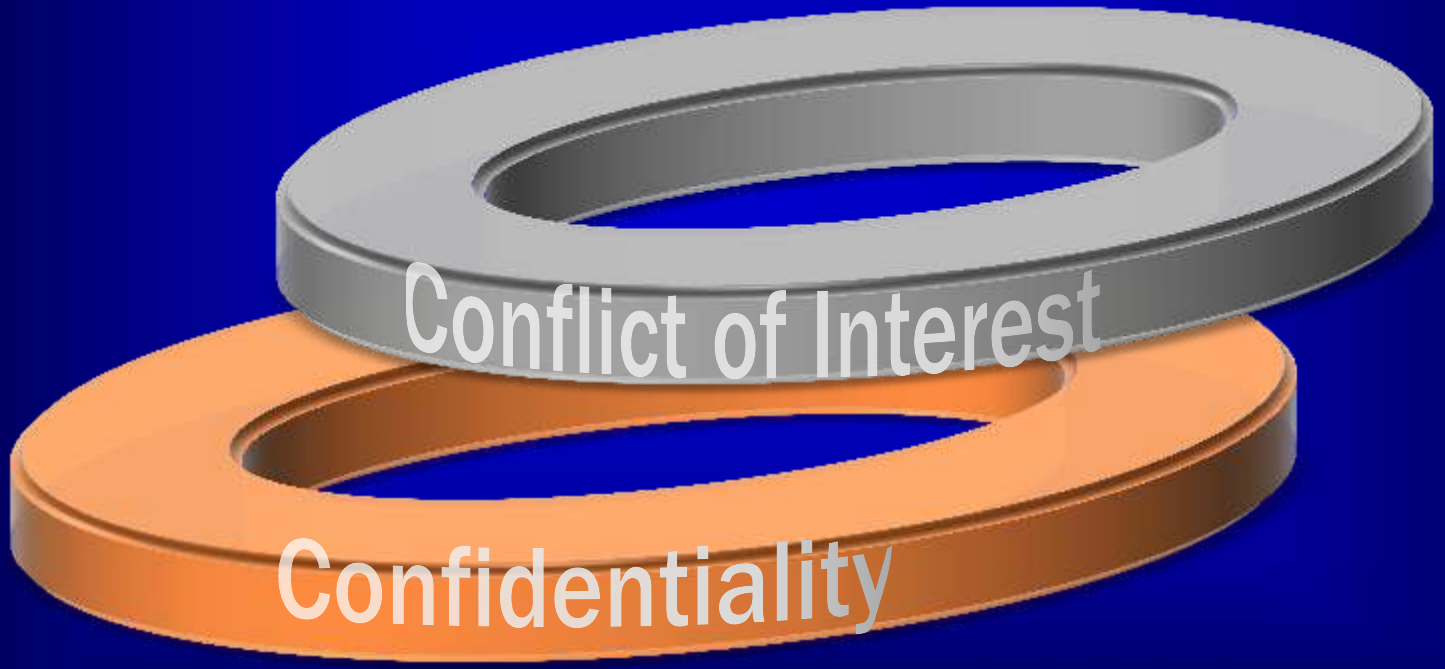
Educational Efforts via Case Sharing
Scientific vs Regulatory Review Recommendations

Wang, Hung, O'Neill (2011, European Neuropsychopharmacology Journal 21:159-166)

Over-arching principles

“The well-being of trial participants takes precedence over societal interests” – The World Medical Association Declaration of Helsinki

Key components for a successful Adaptive Design Trial



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

- Became available March 2006 – time to revisit
- 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
  - Desired 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?

Clinical Trial Committees

- Steering Committee
- Sponsor
  - siDMC
  - IRC vs SC
  - Senior management designee
- ISAC
- IDMC, DSMB, DMC
- …….
- Data management

Regulator

DMC

Sponsor
IRC

Firewalls

ISAC

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?

Q: Can still meet expectation on

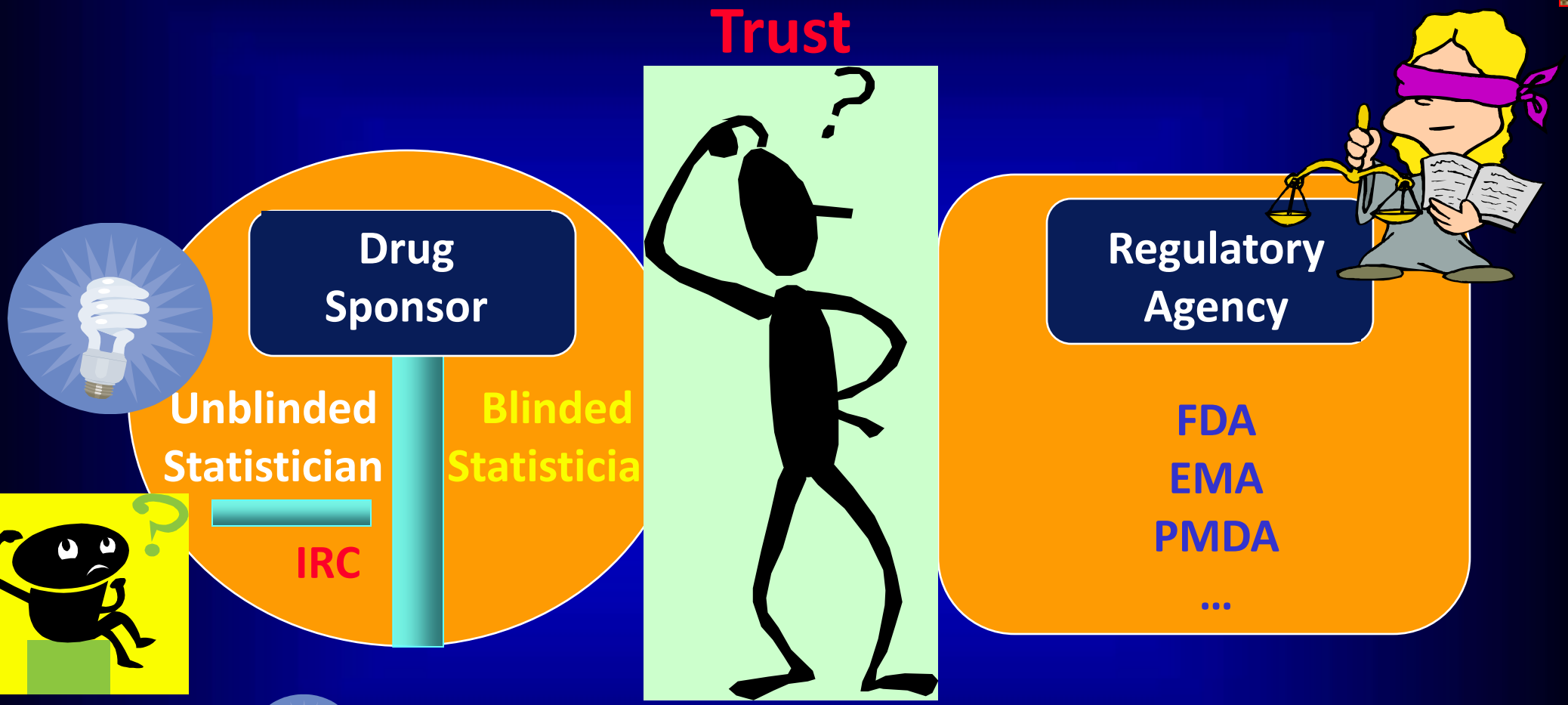
(i) Maintain 'independence' & avoid conflicts of interests?

(ii) Confidentiality?

(iii) Trial integrity

Uncharted and evolving !

Sponsor Only Internal (SOI) Model

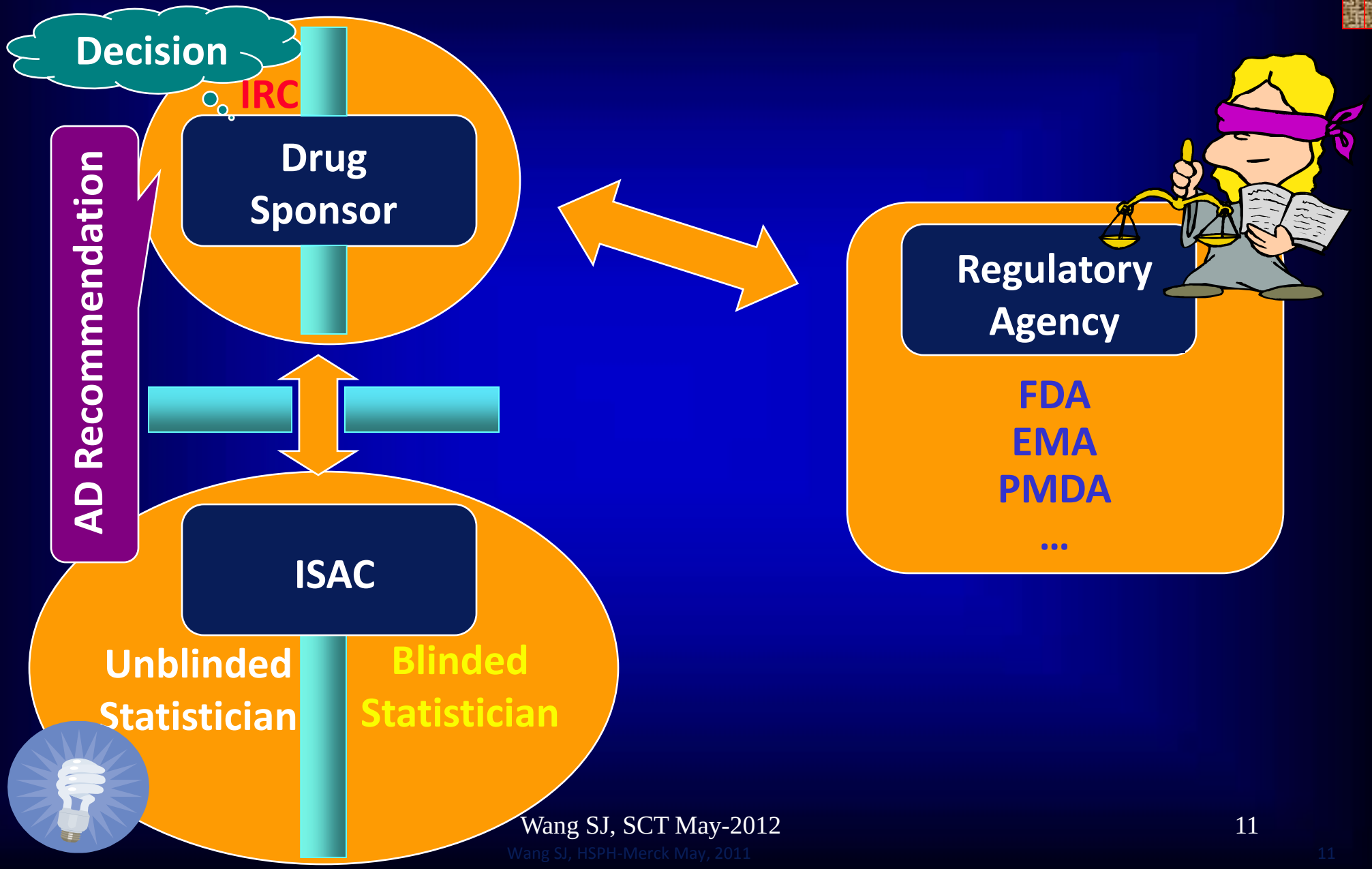


Firewalls

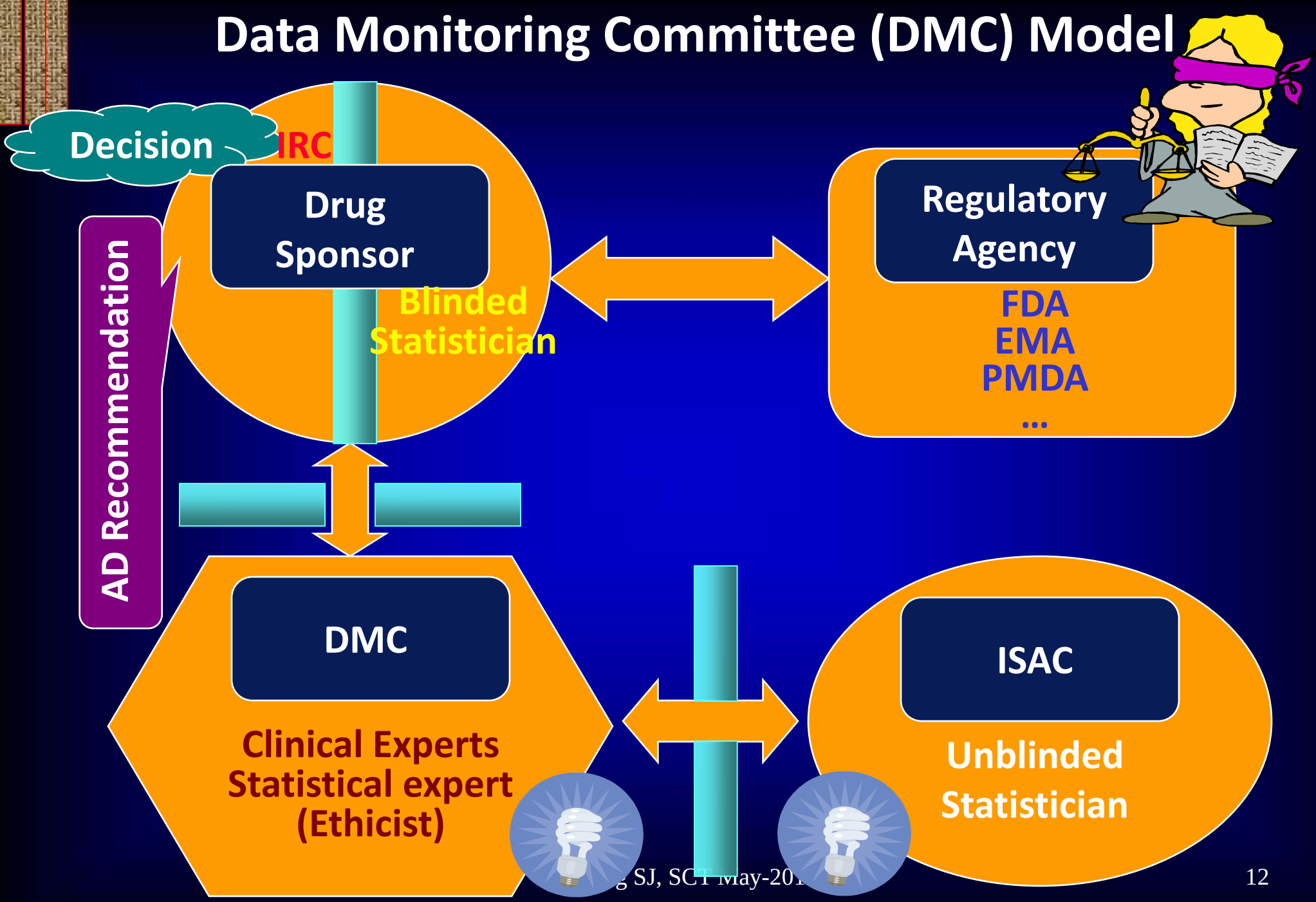
Unblinded party: Stat to perform IA following adaptation rules; Internal Review Committee (IRC) to make AD decision

Blind regulator & maintain blind for in process control of an ongoing trial

Independent Statistics Analysis Center (ISAC) Model



Data Monitoring Committee (DMC) Model

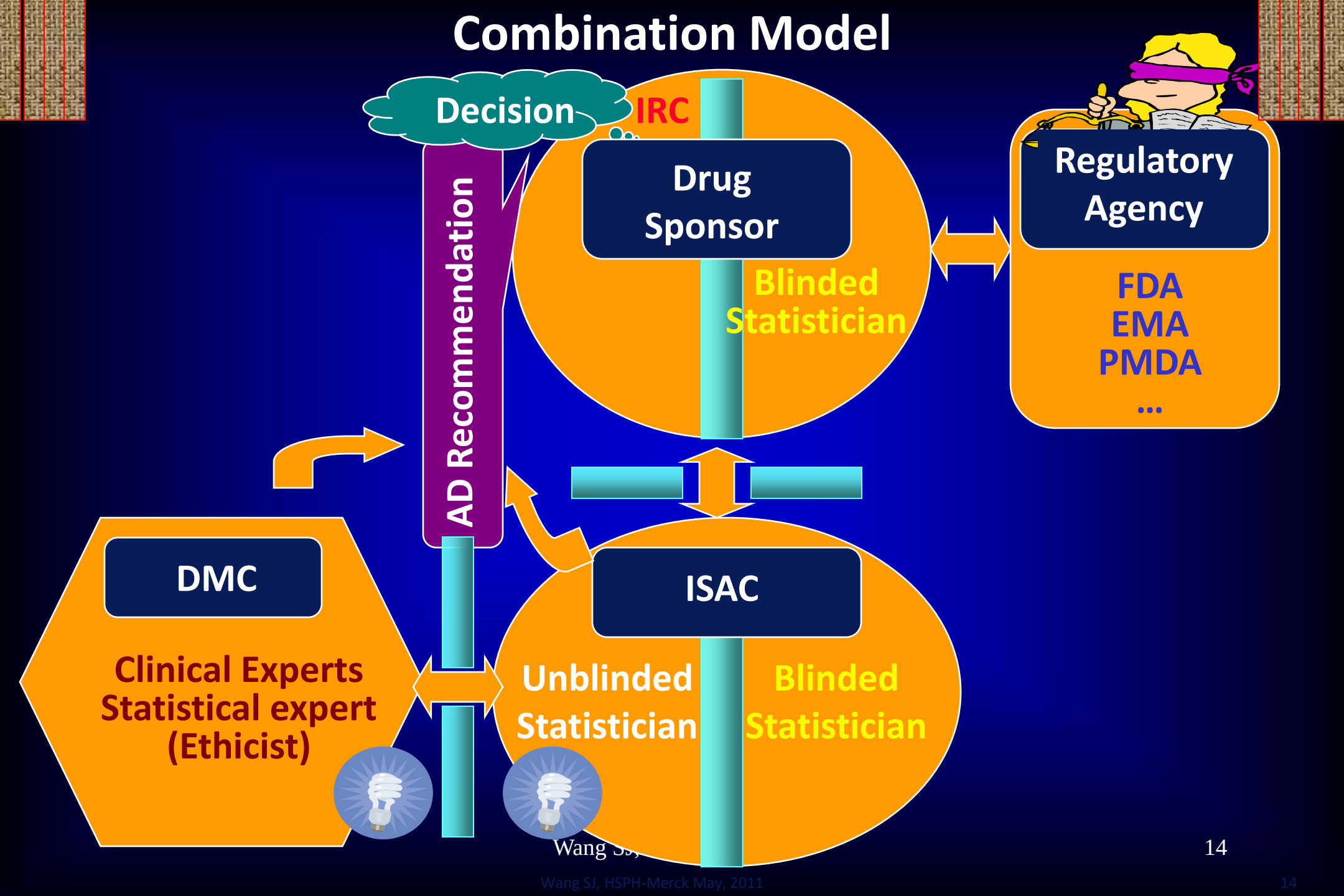


Academic Governance Models

- 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

Nissen SE 2010

Combination Model



Adaptive Monitoring Logistics Models

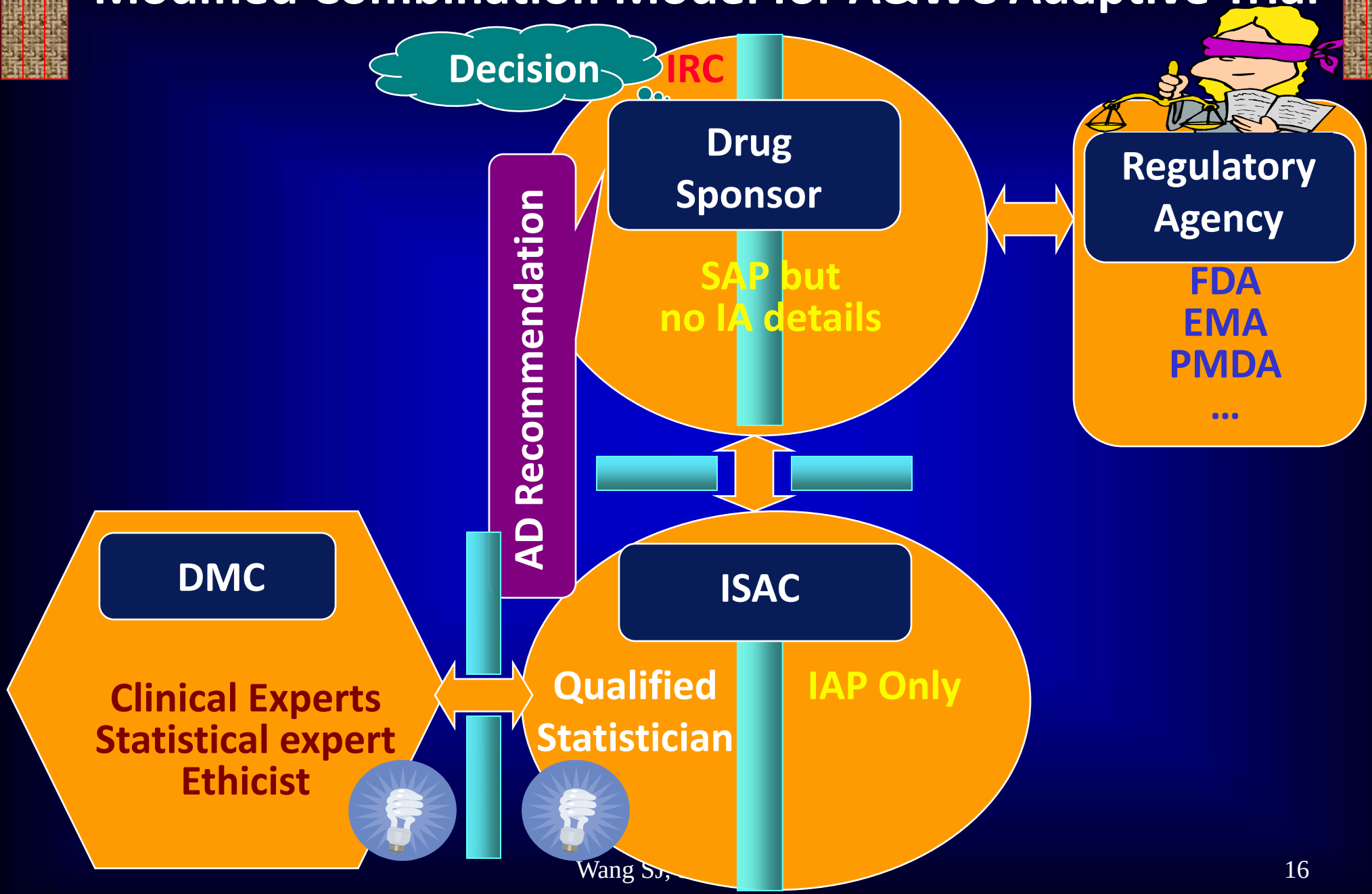
When without a DMC

- Formal DMC not required
- If Sponsor-Only-Internal Model
  - Confidentiality agreement: legal consequence ???
- 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 A&WC Adaptive Trial



Modified Combination Model for A&WC Adaptive Trial

Good Adaptive Monitoring Practice

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

- Those Needing More Inputs/Debates/Discussions/ Experiences
- Who should make Adaptive Recommendation?
- Who should enforce Confidentiality Agreements?
- Separate IAP vs SAP and only ISAC or DMC sees IAP?

Wang SJ, SCT May-2012

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Concluding Remarks

- From well-understood GSD to less well-understood AD
- CRO and related organizations – a growing industry that collect, clean and analyze data, unblinded role and provide summary (semi) unblinded data to DMC's
- Is there a need of a new models for governance and trial decision making as such the integrity of the trial is maintained and efficiency is improved so as to streamline AD clinical trial and build quality into it simultaneously?
- An objective of the Clinical Trials Transformation Initiative