Statistics•Collaborative

Navigating Between Sponsor, iDMC, and Regulators
or
Who Talks to Whom and How?

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By Zoom

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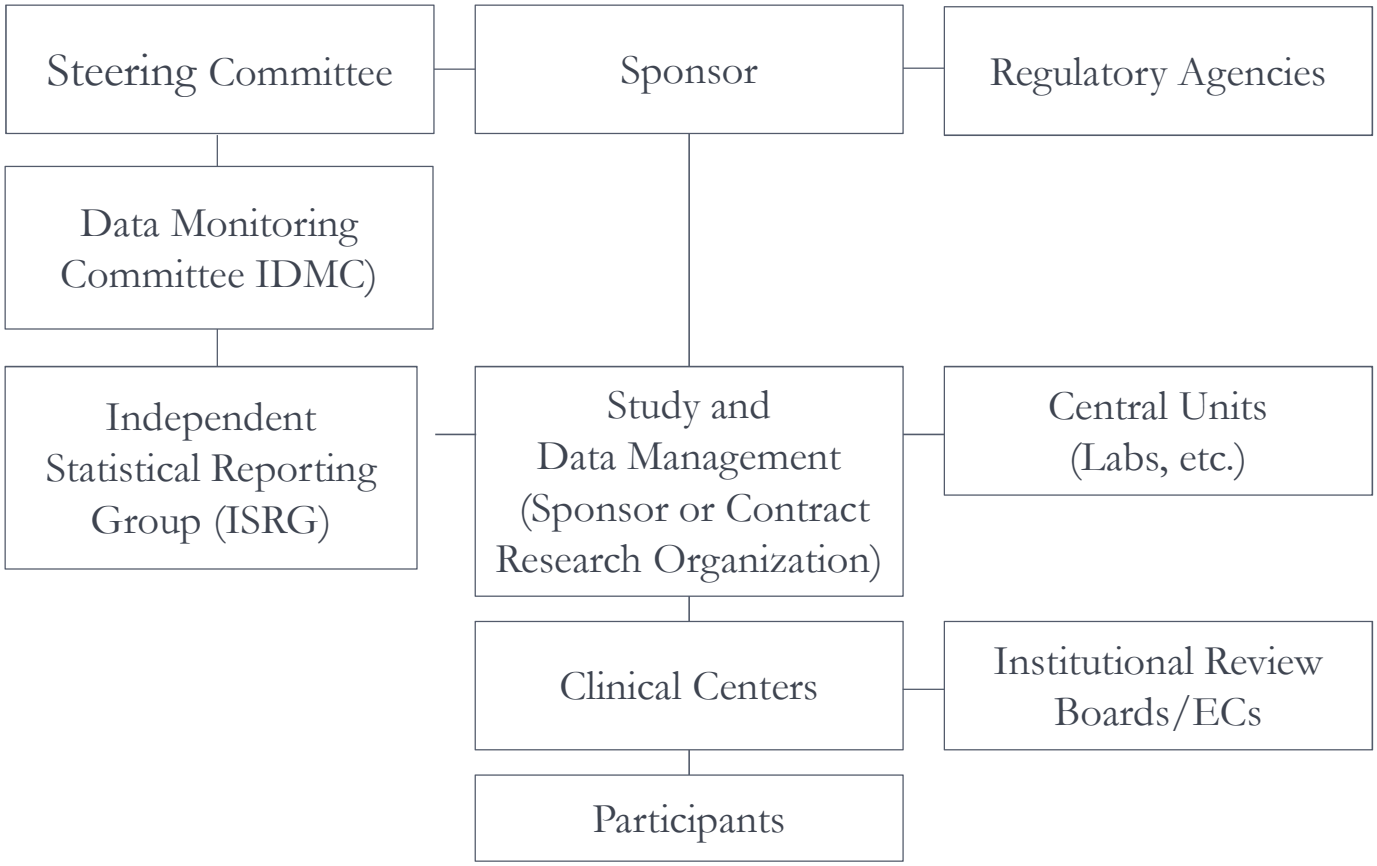
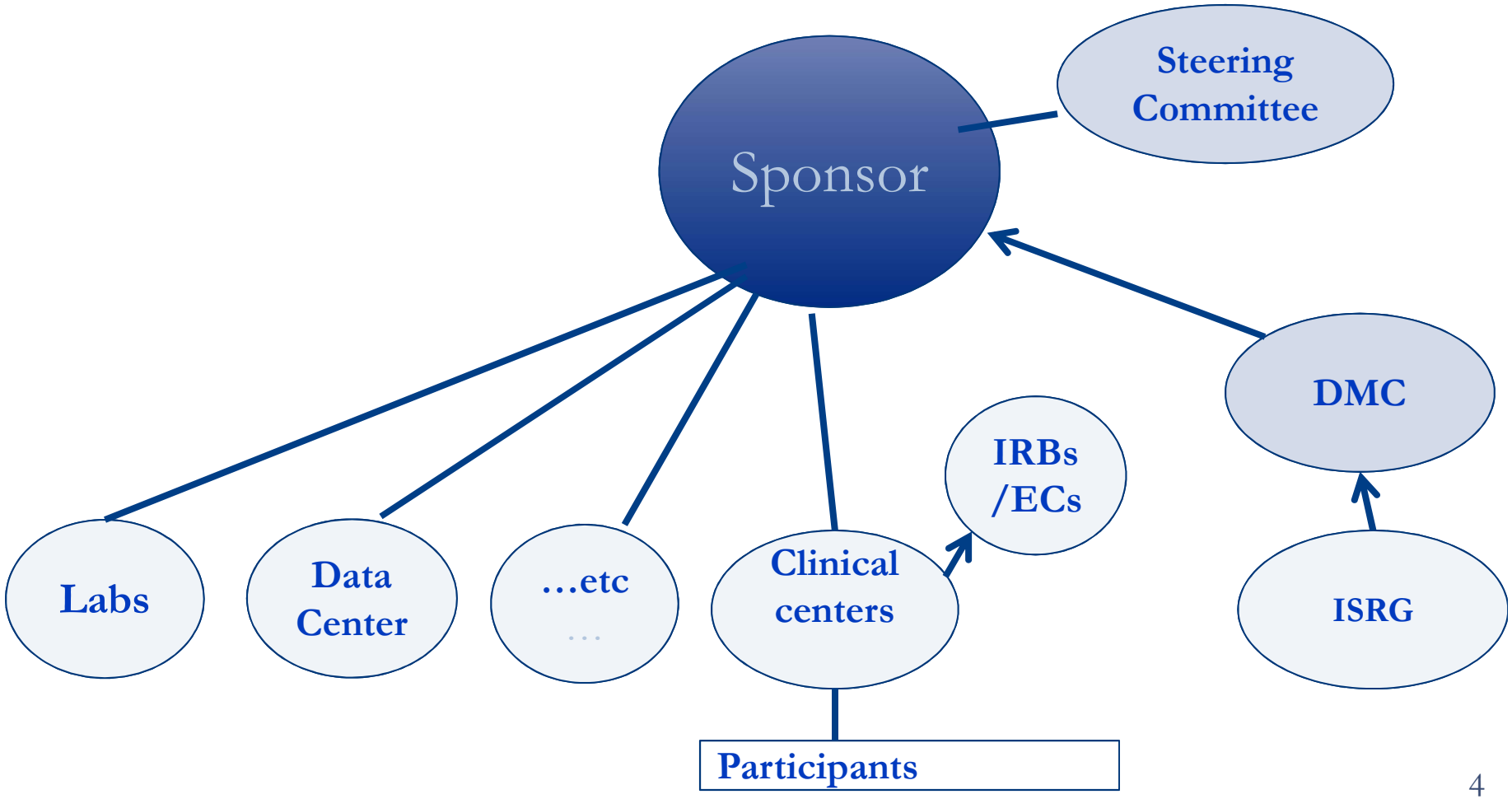
Disclosures

- I personally sit on many DMCs
- My employer, WCG Statistics Collaborative, reports to many DMCs
- The examples in this talk all come from studies where I am past my period of confidentiality

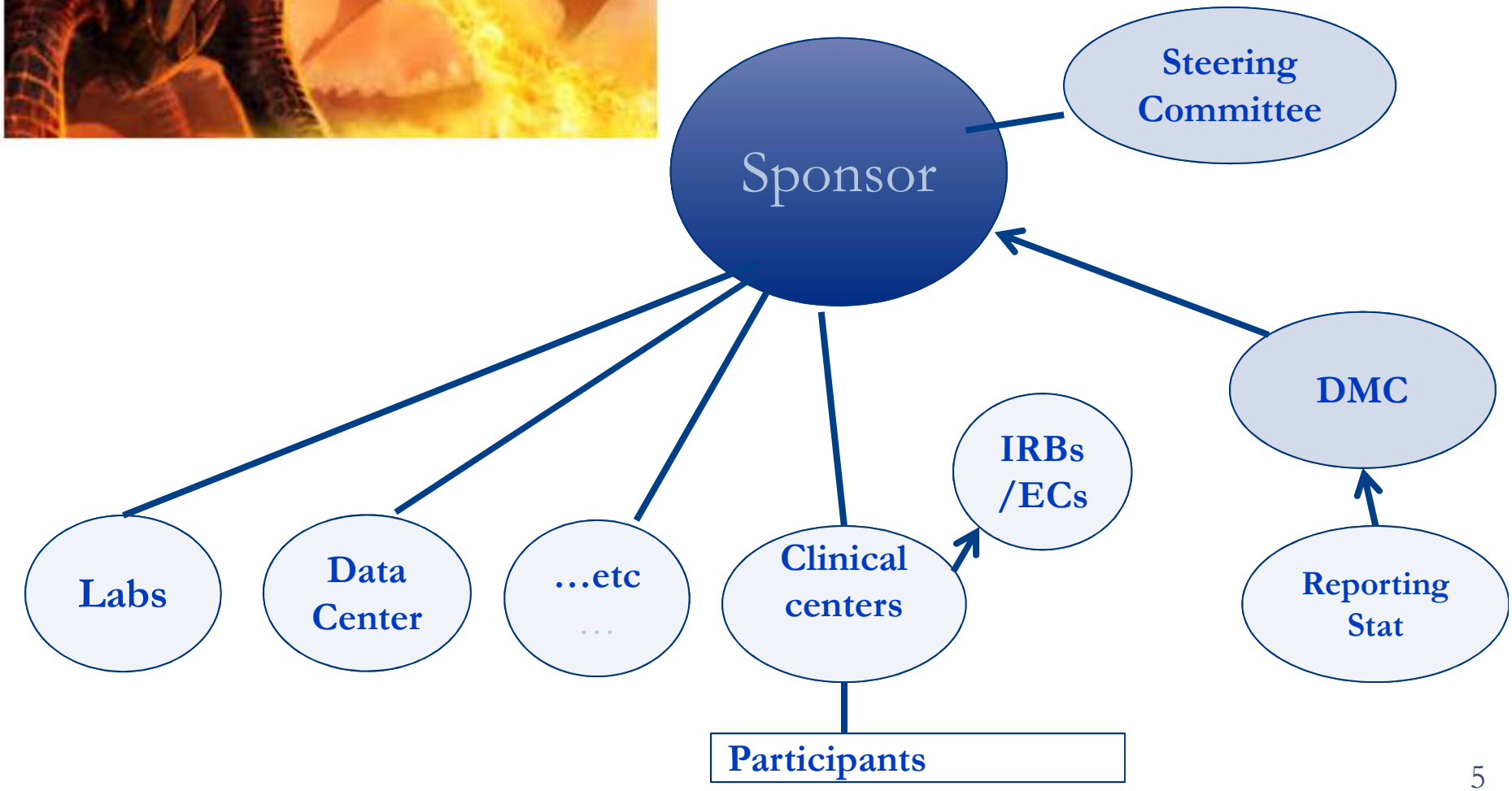
Structure of a clinical trial



The Sponsor's View

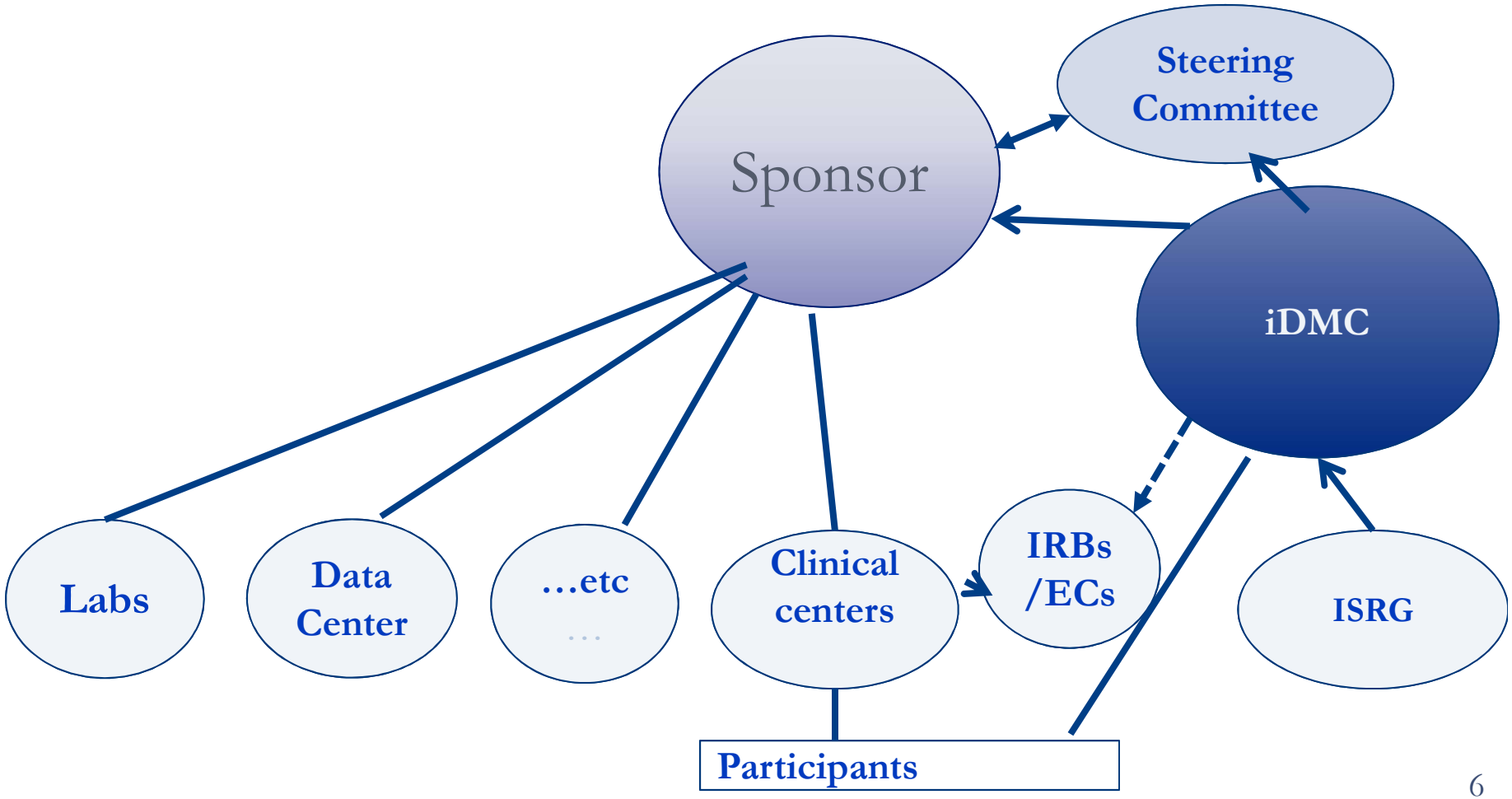


The Sponsor's View



Regulators

The iDMC's View



Regulators

The iDMC's View

Sponsor

Steering Committee

iDMC

Labs

Data Center

…etc

…

Clinical centers

IRBs

ISRG

Participants

In the normal course of events….

- The iDMC meets
  - 2-5 hours
  - Maybe an extra session to review some additional data
- The iDMC writes an anodyne letter
  - Typical language, "The iDMC has no concerns about safety and recommends the study continue with no change in protocol"
  - OR, "The iDMC encourage {faster recruitment, additional steps to prevent drop-out, quicker adjudication}. It has no concerns about safety…"
  - That is almost certainly not true – of course it has concerns

In a better normal course of events….

- The iDMC meets
  - 2-5 hours
  - Maybe an extra session to review some additional data
- The iDMC uses Charlie Hennekens' language
  - After reviewing the data from this trial and from all available external evidence, the iDMC sees no cogent reason to alter the protocol.

When does the iDMC "speak" to regulators?

- Answer – very rarely, very gingerly, but not never
  - Let the situation be your guide!

When does the iDMC "speak" to regulators?

- The regulators ask a question
  - To the Sponsor
  - Directly to the iDMC
- The iDMC sees surprisingly large benefit not covered by the IA
  - Reports to Sponsor who goes to regulators
  - Goes directly to the regulators
- The company has violated important terms of the iDMC charter

Regulators ask a question: e.g., RUTH

- The RUTH trial – Raloxifene Use for The Heart
  - Raloxifen vs. placebo in women at high risk for CV events
  - 10 member DSMB
- French regulators asked Lilly to report to them about ovarian cancer in the French participants randomized to raloxifen
- Lilly came to DSMB to answer the question
- I wrote a letter as DSMB chair saying we would:
  - Look at ovarian cancer each meeting overall & in the French participants
  - Inform the Sponsor if we saw a worrisome signal

- Barrett-Connor et al. Effects of Raloxifene on Cardiovascular Events and Breast Cancer in Postmenopausal Women. N Engl J Med 2006; 355:125-137

The iDMC sees surprisingly large benefit not covered by the formal interim analysis

- iDMC goes directly to Sponsor who goes to FDA
  - Watch literature for paper with neurology example
  - Early BMS studies on nivolumab (see old pink sheet)

The iDMC goes to the FDA without telling the sponsor: Lucentis: MARINA and ANCHOR for AMD

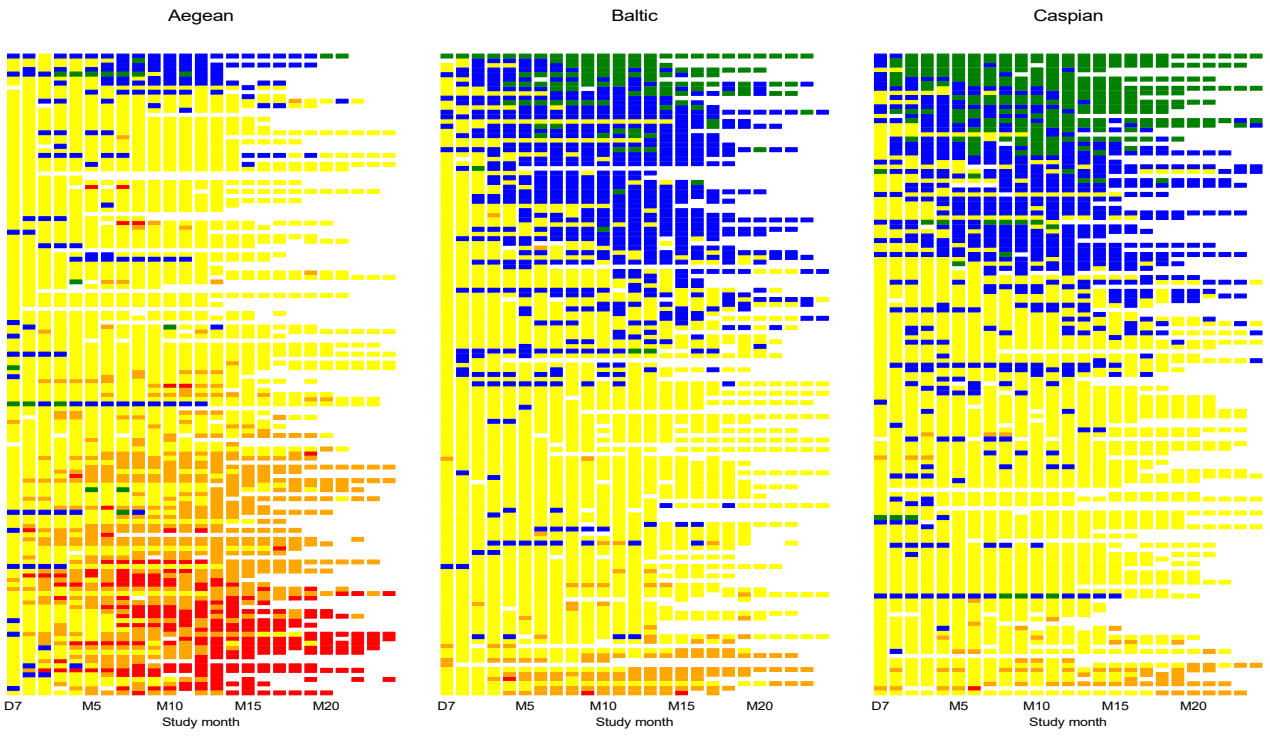
- Genentech to iDMC: DO NOT RECOMMEND STOPPING
  - We know the drug is highly effective
  - But the FDA needs more safety data
  - If you recommend stopping, we won't get approval

Results are overwhelmingly positive

Interim 2 year data

Placebo – low dose – high dose

Green: 30 letter gain; red 30 letter loss



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iDMC is torn

- The dilemma
  - "Blindness is the death of the eye, study must stop"
  - But disaster if we say "stop" & FDA does not approve
- iDMC goes to FDA on a snowy day and shows the data
- FDA says, "thanks, but don't stop; we'll expedite review"

- Rosenfeld PJ, et al. for the MARINA Study Group. N Engl J Med 2006; 355:1419-31.
- Brown et al. for the ANCHOR Study Group. N Engl J Med 2006; 355:1432-1444.

Four pleas…

1. Do not assume that your drug won't work well
2. Explain the regulatory issues to the iDMC
3. iDMC needs two statisticans for the future health of the system
4. Don't be afraid of your ISRG
   - Tell them which group is which
   - Do not use an ISRG that has only 1 or 2 unblinded staff

Summary

- Free flow of info from Sponsor to iDMC
  - Limited flow back
    - To the study team – only operational aspects
    - To the overseeing group – recommendations
      - Not only when the recommendation is to continue
- Free flow of info back and forth between iDMC and ISRG
- Direct to regulators
  - Only in very limited conditions
  - Walking on thin ice (but sometimes you need to if you want to get to the other side)
  - Sponsor needs to choose effective chair, strong iDMC, and trustworthy ISRG