Introduction to Clinical Trials - Day 2

Session 5 - Independent Data Monitoring Committees

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Purpose of an IDMC

Mechanisms for ensuring ethical treatment of study subjects

- Before starting the study:
  - Institutional review board (IRB)
- During conduct of the study:
  - Data safety monitoring board (DSMB)
- After studies completed:
  - Regulatory agencies (e.g., FDA)

Motivating Example

Trial 002 of the CPCRA

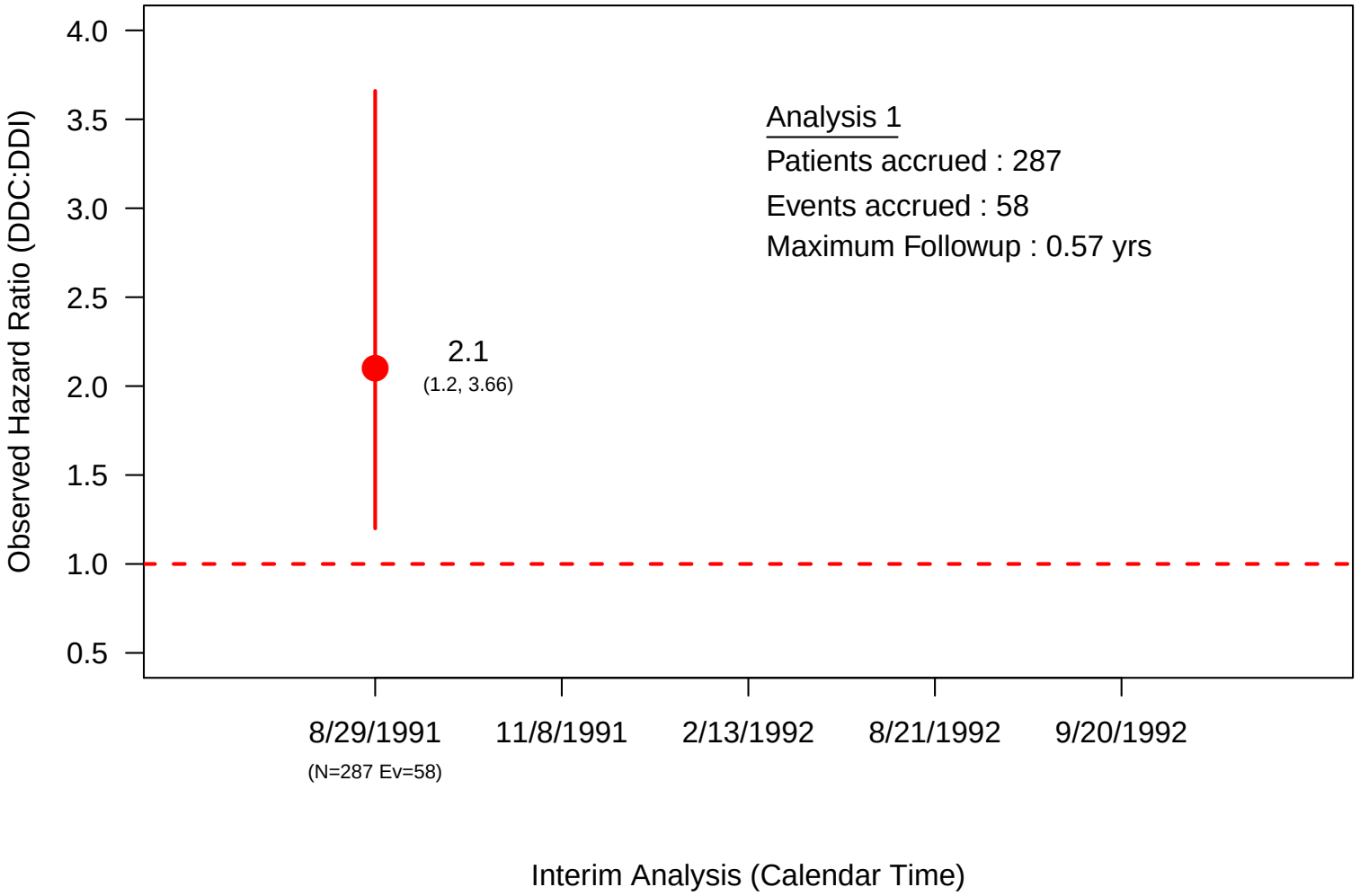
- Community Programs for Clinical Research in AIDS (CPCRA)
- Designed to compare the efficacy of two antiretroviral agents
  - Zalcitabine (DDC) - New experimental treatment
  - Didanosine (DDI) - Active control
- Patient population: Non-responders to zidovudine (AZT)
- Non-inferiority trial
  - DDI considered standard of care at the time

Motivating Example

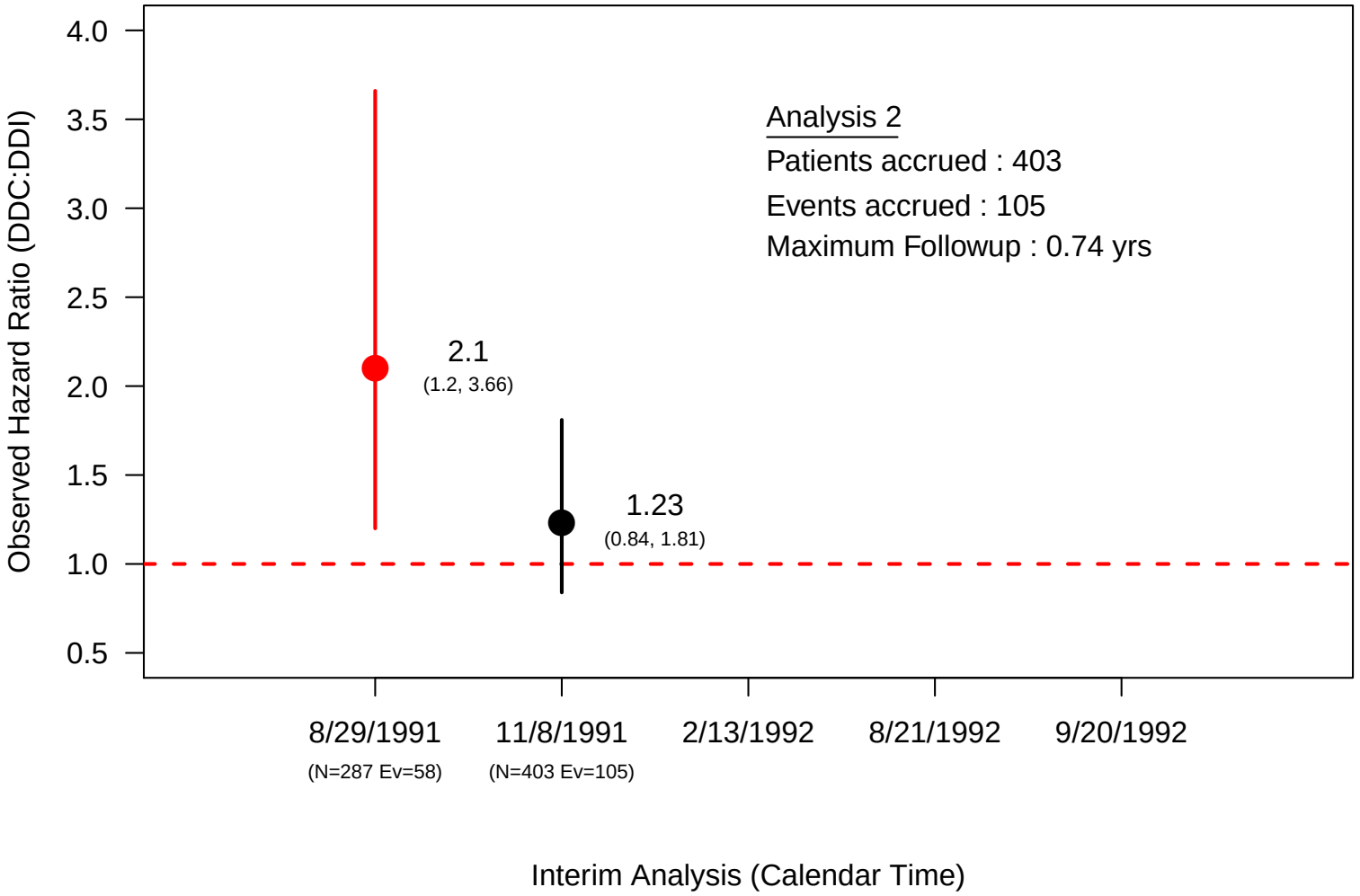
CPCRA Study Protocol

- Primary endpoint: Time to first of disease progression or death
- Sample size: 467 patients randomized
  - Powered for 243 events
  - Maximal duration expected to be 2 years
- Study initiated in December 1990
  - IDMC formed for monitoring approximately every 6 months

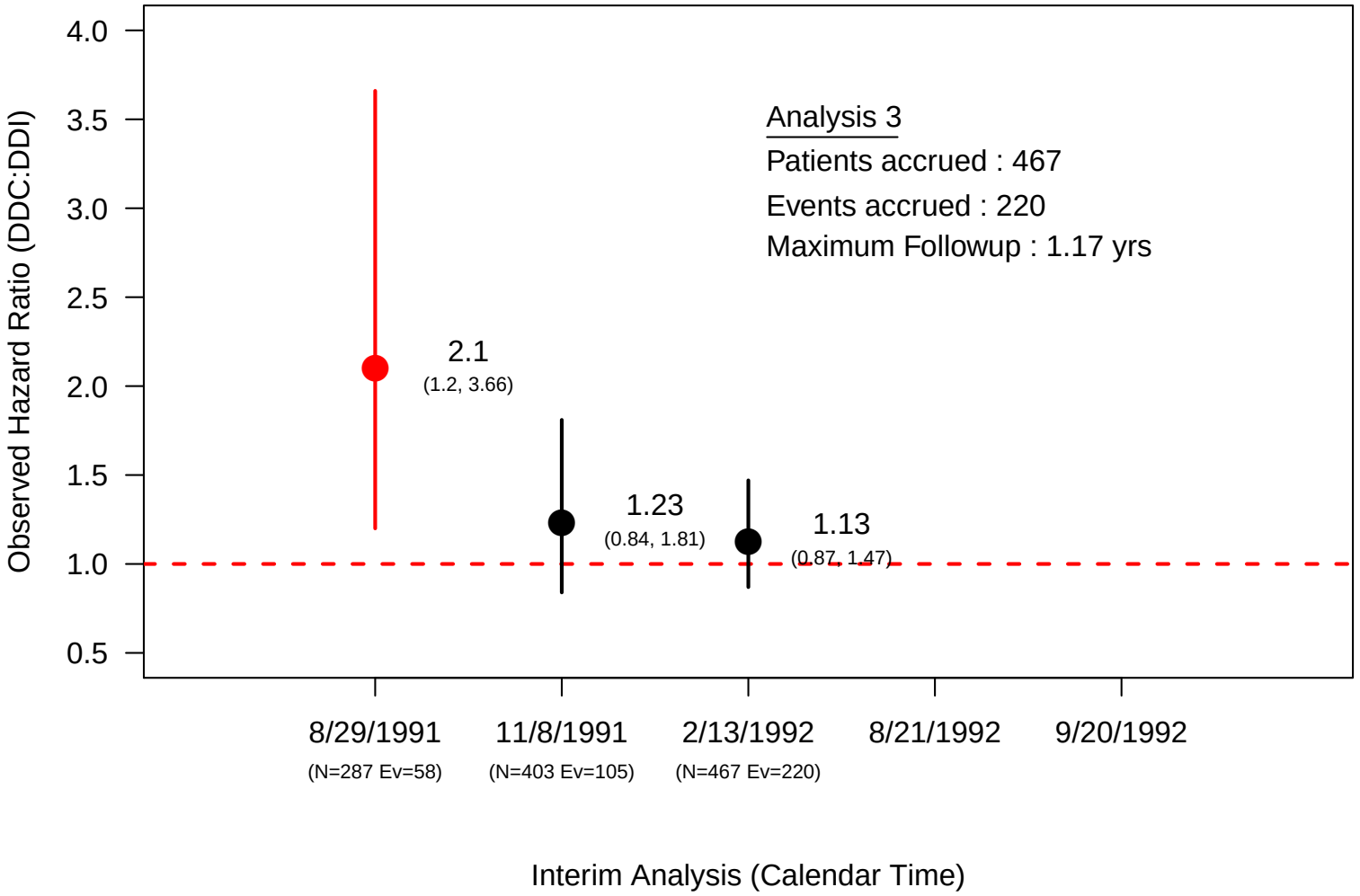
CPCRA Trial Results



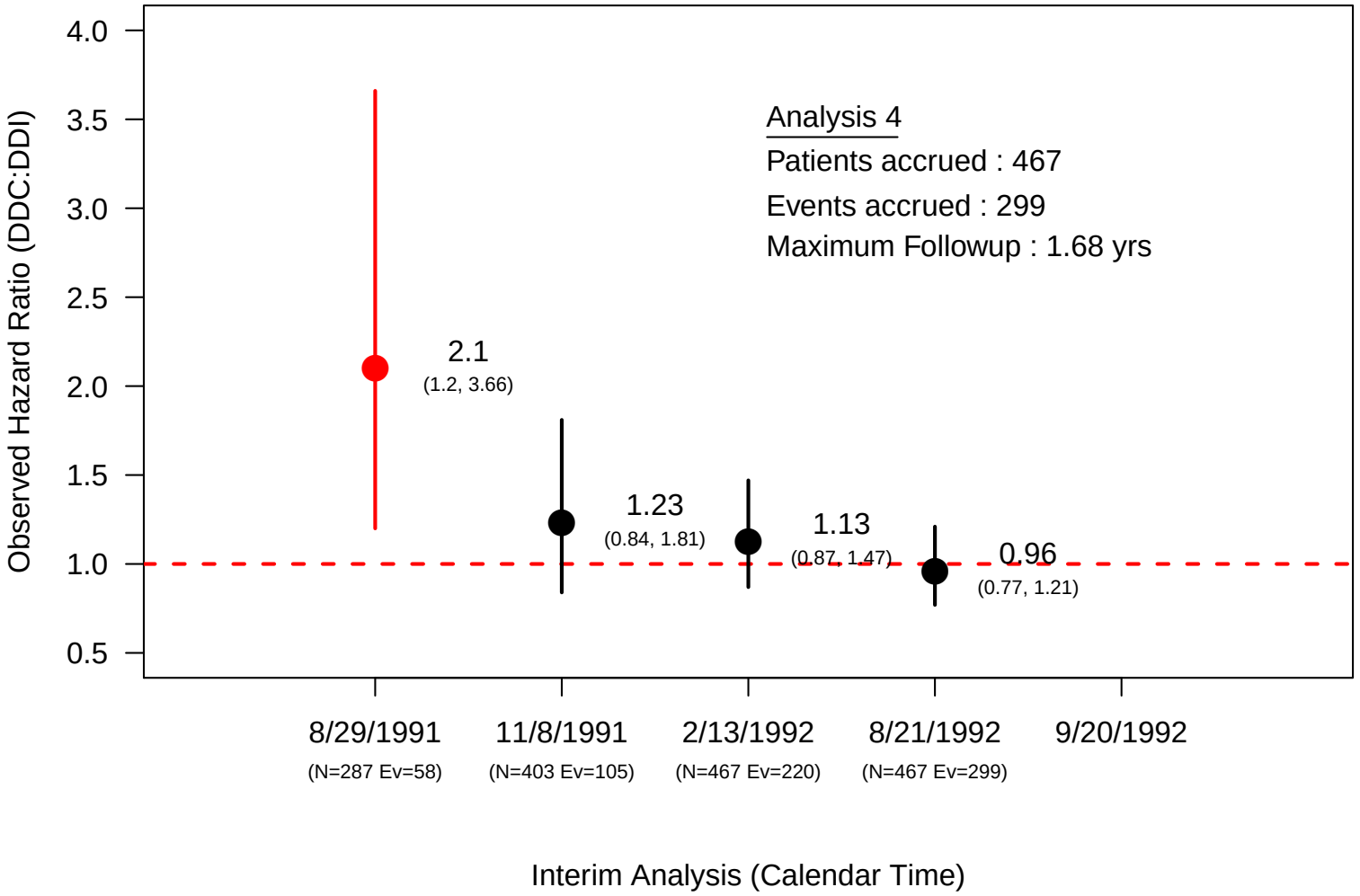
CPCRA Trial Results



CPCRA Trial Results



CPCRA Trial Results



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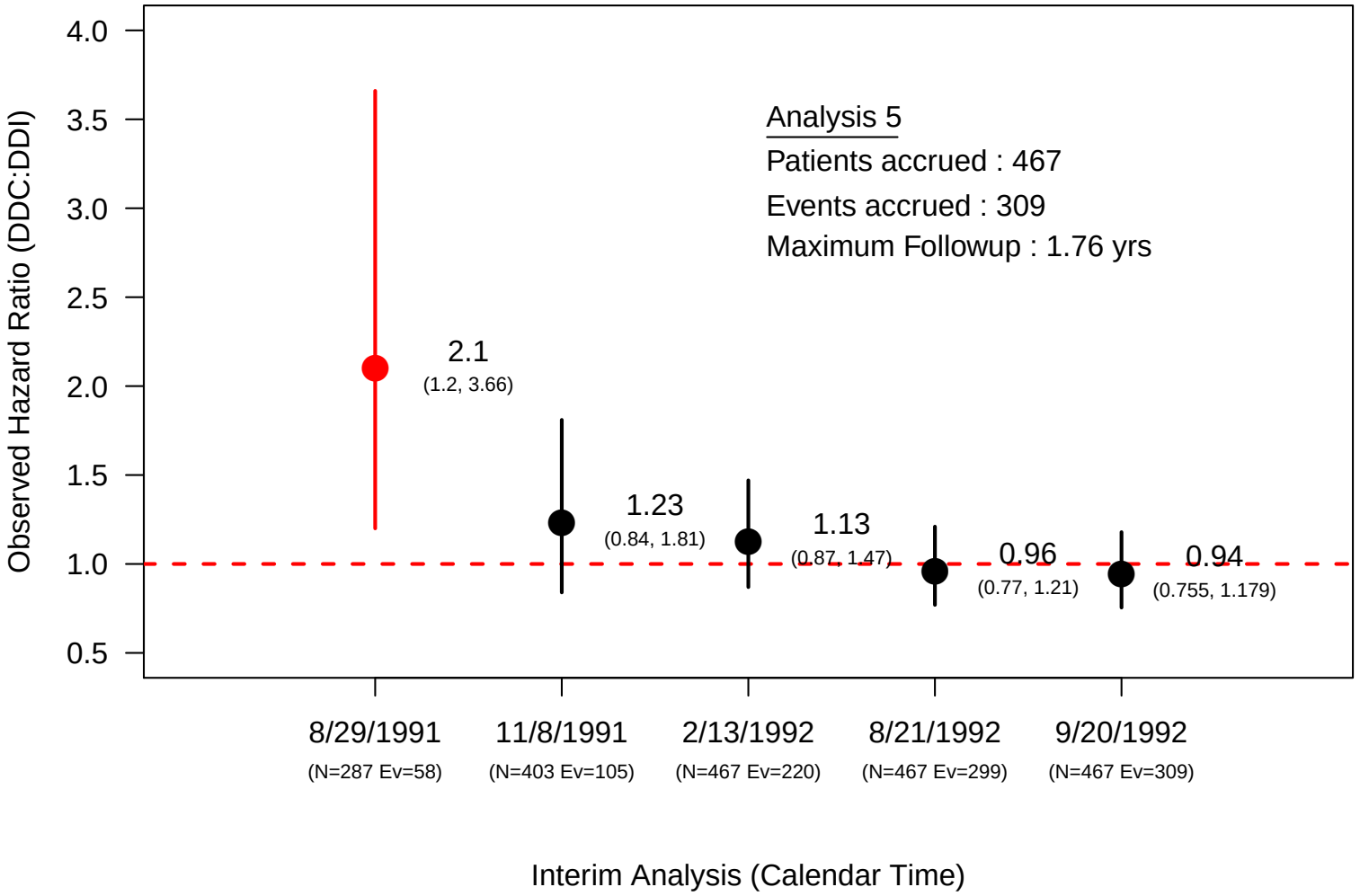

Motivating Example

Comments on the CPCRA Study

- IDMC considered confidence intervals when making continuation decisions
- IDMC was experienced to understand the need for early conservatism under highly variable estimates
- IDMC was able to weigh risk vs benefit

Purpose of an IDMC

Reason for Study Monitoring

- To protect the interests of the study participants
- To preserve trial integrity and credibility in a manner that will enable the clinical trial
- To provide timely and reliable insights to the broader scientific community

Purpose of an IDMC

Requirements

- Achieving the objectives of trial monitoring requires one to confront multiple complex issues beyond the simple implementation of group sequential stopping boundaries (even well-defined boundaries!)
- Ultimately, monitoring requires solid judgement that must be
  - Well informed (clinically, ethically, scientifically, and statistically)
  - Independent and scientifically objective
- This motivates the fundamental principles for DMC membership and function

IDMC Membership

Fundamental principles

- Multidisciplinary representation
- Freedom from apparent significant conflicts of interest
  - Financial
  - Professional
  - Regulatory
- Sole access to interim results on safety of interventions *and* relative efficacy

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IDMC Membership

Example: Topical hemostatic agent

- Five members
  - 1 Statistician
  - 1 Hematologist
  - 2 Surgeons (1 soft tissue, 1 bone)
  - 1 Immunologist
- Facilitation of IDMC by independent statistician (not a member of the IDMC)
- Membership excludes
  - Industry
  - Regulatory agencies
  - Study investigators

IDMC Membership

Example: First-line Treatment of T-Cell Lymphoma

- Four members
  - 1 Statistician
  - 3 Clinical oncologists (USA, France, England)
- Three non-voting members
  - 1 Statistician
  - 2 Clinical oncologists (USA, England)
- Facilitation of IDMC by independent statistician (not a member of the IDMC)
- Membership excludes
  - Industry
  - Regulatory agencies
  - Study investigators

IDMC Communication

Formal meetings

- When monitoring a single study it is typical for and IDMC to have at least two meetings a year
  - One teleconference
  - Highly recommended to have at least one face-to-face
- When monitoring multiple trials, more frequent meetings are likely necessary
  - DSMB for CFCCC at UCI meets monthly

IDMC Communication

Formal meetings

- General structure of a meeting generally follows a open, closed, and optional open session format
- Participants in each:
  - Open : IDMC, (Sponsor, Program Investigators, Regulatory), Independent statistician
  - Closed : IDMC, Independent statistician
  - Open : IDMC, (Sponsor, Program Investigators, Regulatory), Independent statistician

IDMC Communication

Open statistical report : Typical outline

1. Executive summary of the study design with schema
2. Overview of salient points of the trial protocol
3. Statistical commentary explaining issues presented in the Open Report figures and tables
4. DMC monitoring plan and summary of past Open Report data presented at prior meetings, along with prior open session minutes
5. Major protocol changes
6. Information on patient screening

*Note: All Open Report data presented in the Open Report should be pooled by treatment arm

IDMC Communication

Open statistical report : Typical outline (cont'd)

7. Study accrual by month and by site (actual and anticipated)
8. Eligibility violations
9. Baseline characteristics
   - Demographics
   - Laboratory values and other measurements
   - Concomitant medications
10. Measure of how up-to-date data are (use benchmark visits)
11. Days between randomization and initiation of treatment

*Note: All Open Report data presented in the Open Report should be pooled by treatment arm

Open statistical report : Typical outline (cont'd)

12. Length of followup data available ("censoring distribution")
13. Participant treatment and study status along with CONSORT diagram
14. Attendance at scheduled visits
15. Compliance with treatment

*Note: All Open Report data presented in the Open Report should be pooled by treatment arm

IDMC Communication

Closed statistical report : Typical outline

1. Detailed statistical commentary explaining issues raised by Closed Report tables, listing, and figures
2. DMC monitoring plan and summary of Closed Report data presented at prior meetings
3. All of items in the Open Report separated by treatment arm
4. Kaplan-Meier estimates of time to treatment and study discontinuation
5. Analyses of primary and secondary efficacy endpoints
   - Important for weighing risk/benefit

Closed statistical report : Typical outline (cont'd)

6. Analyses of adverse events and overall safety data
   - Broken down by system organ class and preferred term
   - All grades
   - Serious adverse events only
   - Stratified by grade
   - “Treatment emergent" adverse events
   - Adverse events leading to treatment modification or discontinuation
7. Listings of adverse events

- Finally, it is a common task of the IDMC to periodically request new analyses as concerns or questions arise during the progression of a trial

IDMC Issues

Issues : Blinding

- Not controversial : An IDMC should always be free to unblind themselves at any time
- However, there are differing opinions on whether the IDMC should start out unblinded

IDMC Issues

Issues : Blinding

- Pros of blinding the IDMC:
  - Avoids leaks in trial results (data falling into wrong hands)
  - Avoids inadvertent leaks of study results by DMC members
  - Avoids overreaction to early variable results
- Cons of blinding the IDMC:
  - Need timely and informed integration of patterns for weighing risk/benefit
  - Can provide earlier detaching of something “real" using evidence that has been observed

IDMC Issues

Issues : Blinding

- Ex: The CAST Trial
  - DMC blinded through X/Y coding for encainide and flecainide vs. placebo
  - First DMC meeting : 13 vs 7 deaths
    - DMC recommended continuation
  - Emergency DMC meeting : 56 vs. 22 deaths
    - DMC recommended immediate termination
- Had the DMC been unblinded, would they have acted sooner?

Issues : Blinding

- In my opinion, if the DMC does choose to be blinded then:
  - They should be able to unblind at any time it is felt necessary
  - If one member becomes unblinded, then all members should be unblinded
  - It is essential for all DMC members to play the hypothetical
    - When looking at a potential imbalance in safety events, must ask whether knowing the actual treatment codes would lead to a different recommendation
- Even if the DMC is unblinded, the Closed Report should have dummy labels with actual treatment codes available through a separate form of communication
  - Avoid unintentional leaking of trial results

IDMC Issues

Issues : Conflict of interest and sponsor/DMC relationship

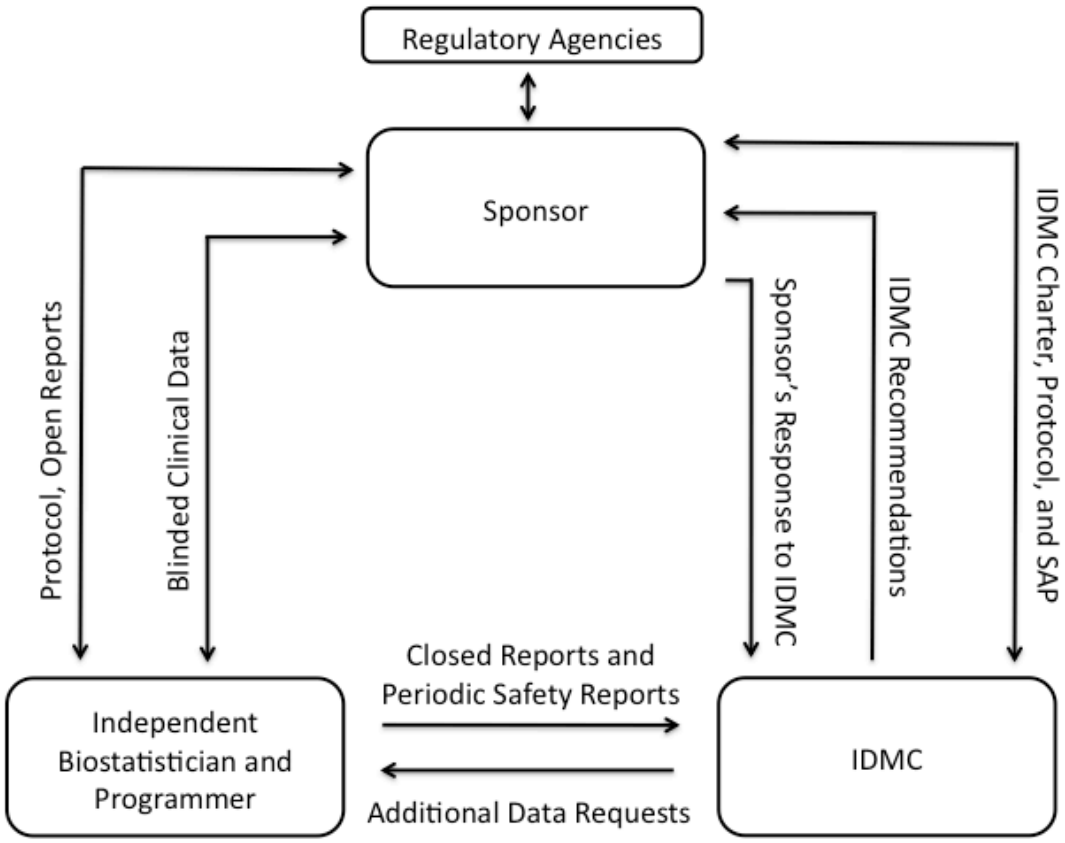
- Different strategies are taken in industry sponsored trials

1. No interim analyses
2. Strictly in-house monitoring
3. Independent DMC with in-house analyses
   - Loosely controlled in-house blinding, or
   - Only study statistician(s) unblinded
4. Independent DMC and independent statistician, with data collection in-house
5. Completely hands-off

IDMC Issues

Issues : Conflict of interest and sponsor/DMC relationship

- (4) and (5) are good approaches
  - Helps to keep sponsor above suspicion of “intention-to-cheat"



IDMC Issues

Issues : Conflict of interest and sponsor/DMC relationship

- Certainly the DMC members should be free of potential conflicts of interest:
  - Financial, scientific, or regulatory in nature
  - Shouldn't own (significant?) stock in company
  - No conflicts with competing products
- Conflicts should be updated as they arise

IDMC Issues

Issues : Indemnification of the IDMC

- DMCs or members can subpoenaed and become defendants in litigation
- DMCs must be indemnified by the sponsor or through some other defined process
- Indemnification language should be part of the DMC Charter as well as contracts
- Indemnification should be provided in order to keep DMC member free to use best judgement when issuing trial recommendations without fear of litigation