Summer Institute in Statistics for Clinical Research

Data Monitoring Committees

July 26, 2019

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* Ellenberg SS, Fleming TR, and DeMets DL: *"Data Monitoring Committees: A Practical Approach", Second Edition*, John Wiley & Sons, 2019
* Fleming TR et. al. "Maintaining Confidentiality of Interim Data to Enhance Trial Integrity & Credibility". *Clinical Trials* 2008; 5: 157-167
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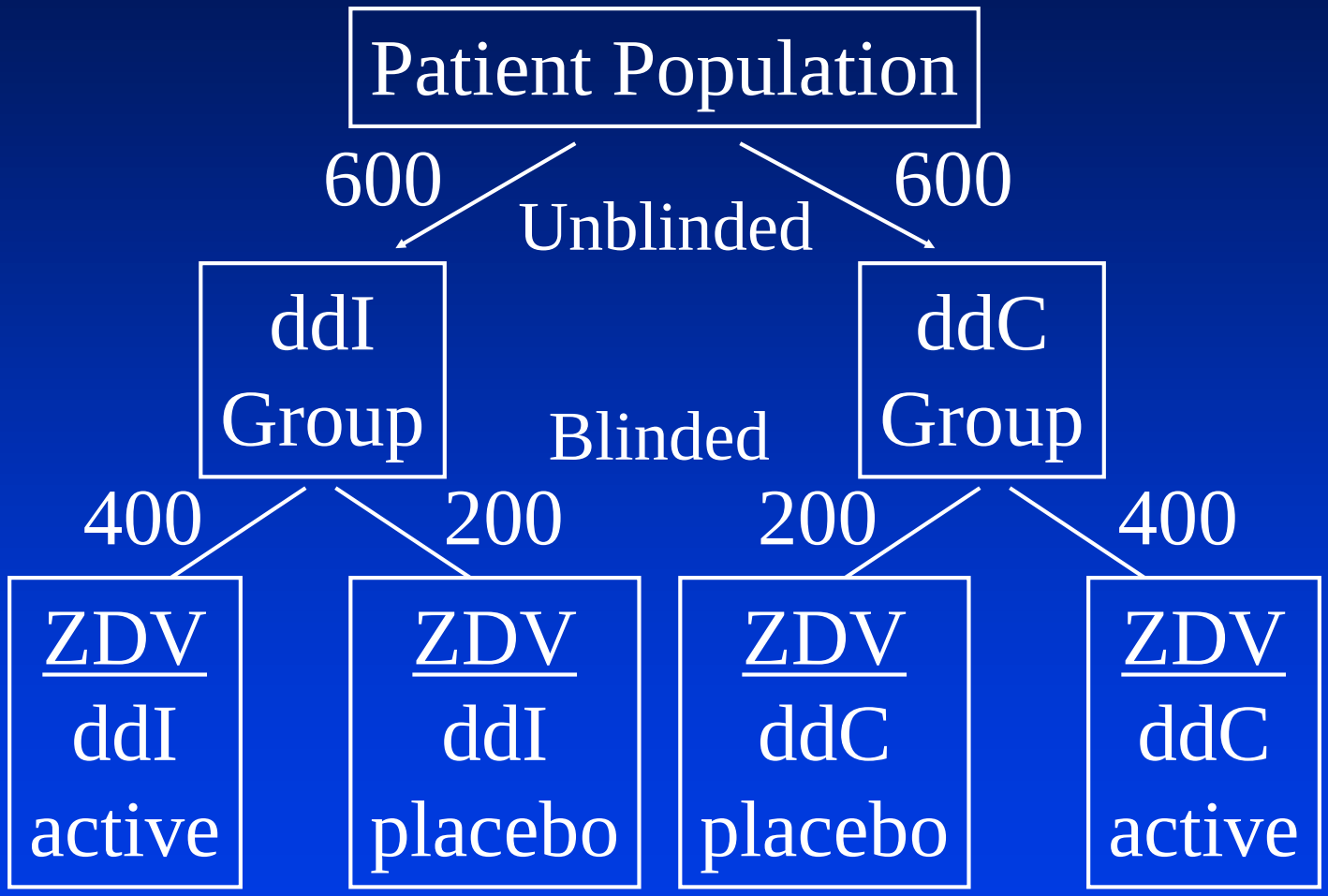
Mission of the DMC

CPCRA #007: Study Design



CPCRA #007: 5/92 - 5/95

DATE	A	B	p-value
8/93			
n	151	151	
Prog/Death	33	16	0.017
Death	**8**	**2**	0.11
11/93			
n	172	168	
Prog/Death	42	28	0.033
Death	**17**	**2**	<0.001
All Events	73	37	

CPCRA #007:

11/93	ZDV ddI Active	ZDV ddI Placebo	ZDV ddC Placebo	ZDV ddC Active
n	337	172	168	344
Prog/Death	55	42	28	62
Death	18	**17**	**2**	18
All Events	92	73	37	102

	ZDV ddI Active	ZDV ddI Placebo
n	337	172
Prog/Death	55	42
Death	18	17
All Events	92	73

Mission of the DMC

- To Safeguard the Interests
  of the Study Participants
- To Preserve Trial Integrity and Credibility
  to enable the clinical trial to provide
  timely and reliable insights
  to the broader clinical community

Some Fundamental Principles in Achieving the DMC Mission

To assist the DMC in achieving its Mission,
procedures are needed…

- To reduce pre-judgment of interim data
  - ⇒ *Maintaining confidentiality of interim data*
- To guide the interpretation of interim data
  - ⇒ Group sequential monitoring boundaries
  - ⇒ Unbiased judgment
    - … *Well-informed*
    - … *Independent*

… Motivates fundamental principles
for DMC functioning and composition…

Some Fundamental Principles

- DMC should have *Sole Access* to interim results
  on relative efficacy &
  relative safety of interventions
- DMC should have *Multidisciplinary* representation
  having experience in the DMC process
- DMC should be *Independent* with freedom from
  apparent significant conflicts of interest
  … financial, professional, regulatory

Evolution of DMCs: Brief History

- Greenberg Report to NIH in 1967 (Ref: *CCT* 1988)

  …Develop a mechanism to terminate early if:

  - ✓ Question has been answered
  - ✓ Trial can't achieve its goals

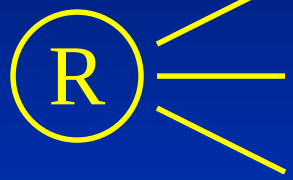
  …Guided by *recommendations of outside consultants*

  …Motivated development of statistical guidelines…

- Use in NIH-sponsor Cancer trials in late 70's-early 80's
- Increased use in Industry Trials since 1990
  - ✓ Value of *independent monitoring* is recognized
  - ✓ Creation of NIH & Regulatory DMC Guidelines

An Illustrative Experience:
Cancer Intergroup #0035 Colon Adjuvant

Duke's C



Observation	(327)
Levamisole	(328)
5-FU + Levamisole	(316)

Outcome:

Survival Time, Time to Recurrence

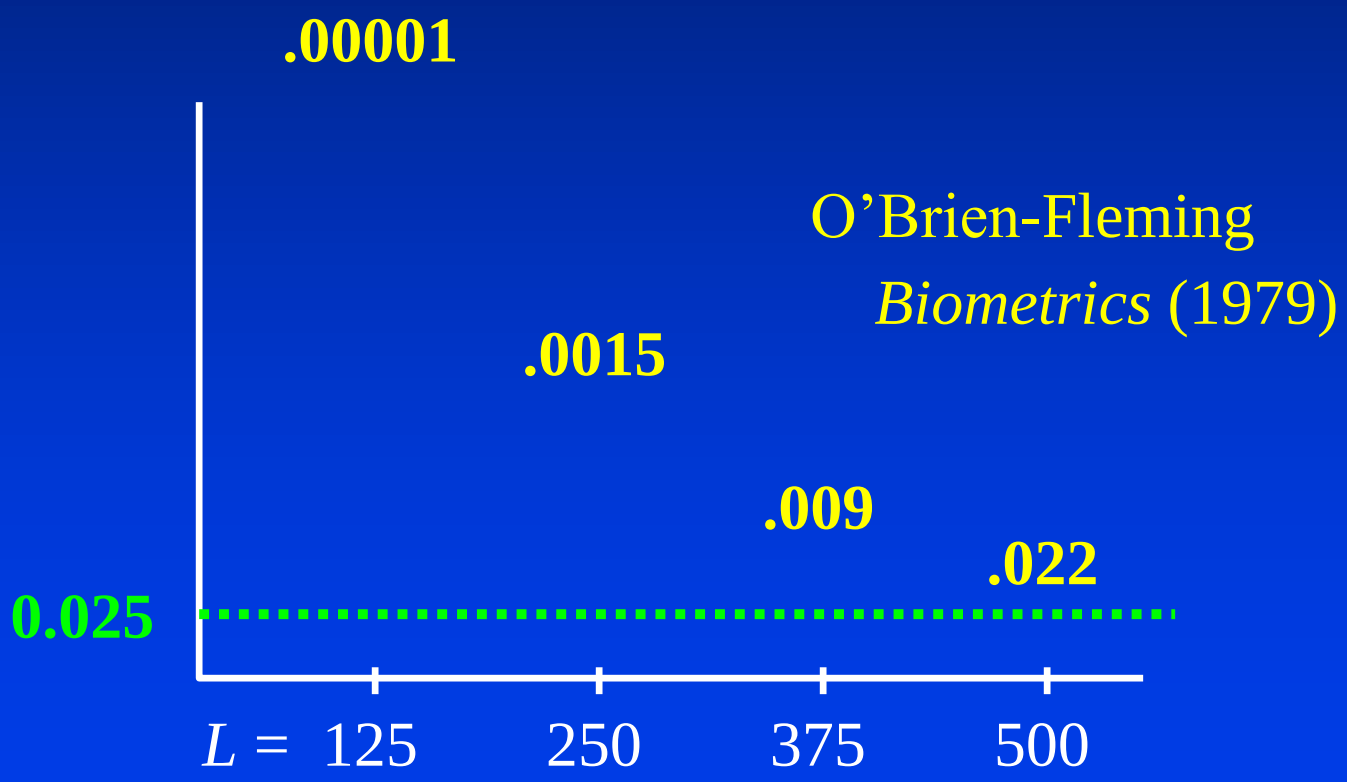
Follow-up to 500 deaths

Four look O'Brien-Fleming design

… one every 125 deaths

O'Brien-Fleming Boundary

Goal: With 4 analyses, preserve the (1-sided) false positive error rate: 0.025



Monitoring Clinical Trials

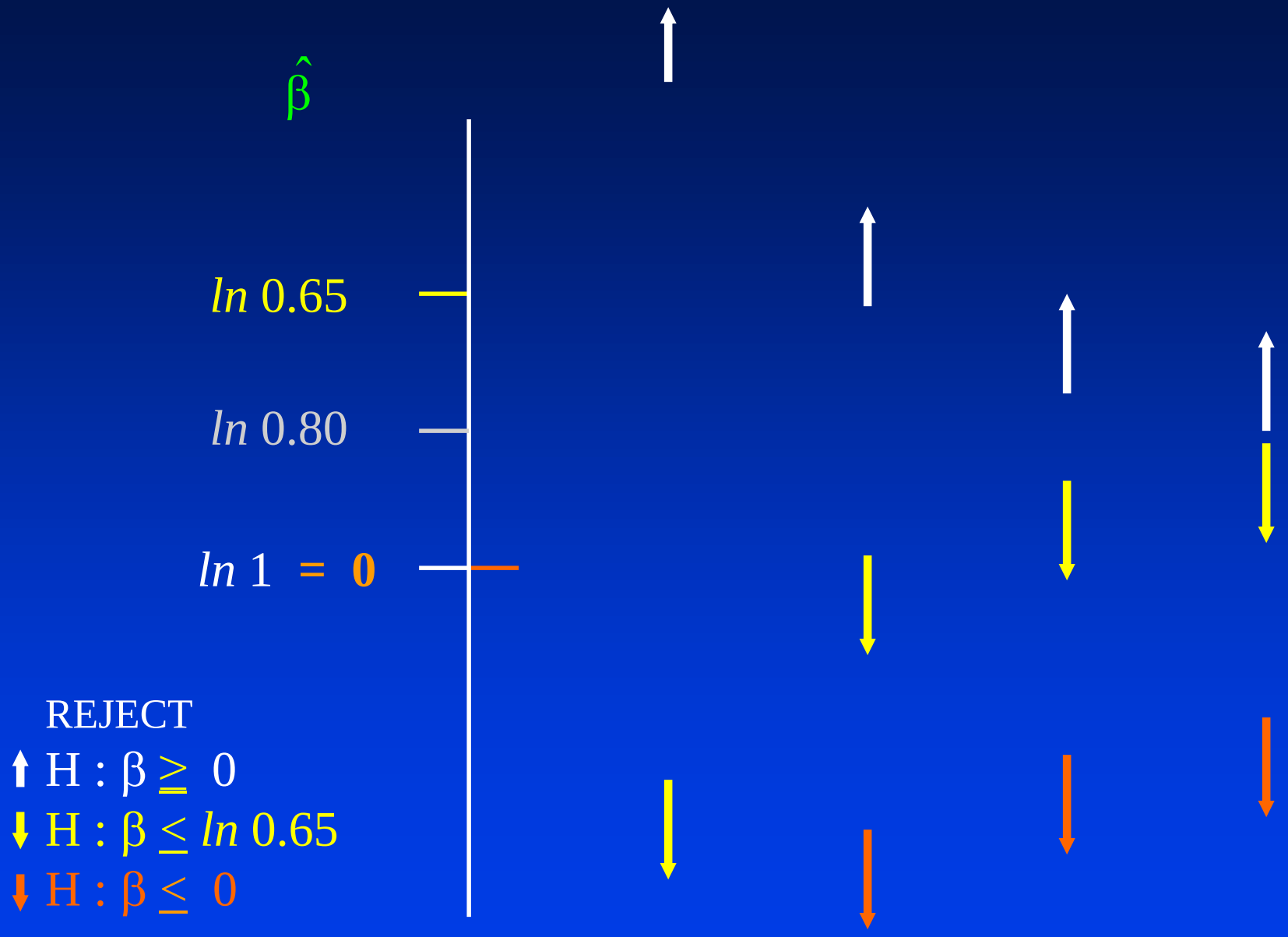
- How the O'Brien-Fleming guideline works:
  Arriving at recommendations about
  early termination of clinical trials

  ~ that establish benefit

  ~ that rule out benefit

  ~ that establish harm

Symmetric O'Brien-Fleming Group Sequential Boundaries



Cancer Intergroup # 0035: Colon Adjuvant

(1-sided) **O'Brien-Fleming Guideline**: Survival Data

<.00001

Spring '88
Survival: <18 mo med f.u.
Recurrence: Strong trends

.0015

.005

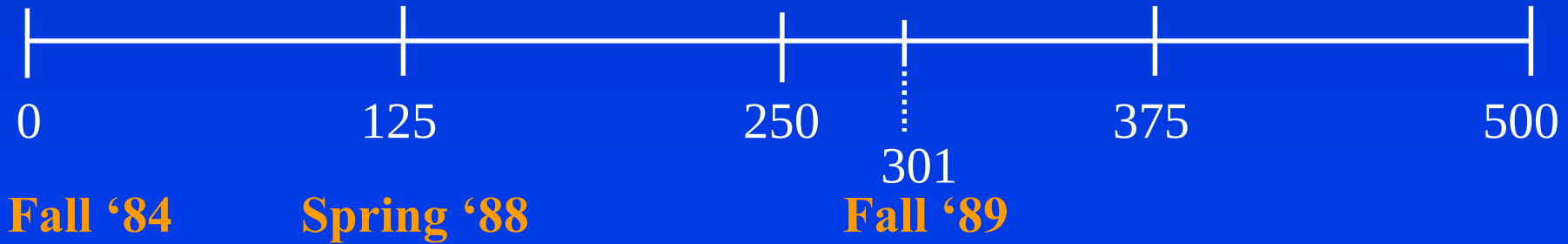
Fall '89
Survival: p = .003 < .005
Recurrence: p = .0001

Summer '88
FDA/NCI Confidential Review
… 1 day later, results publicly revealed

.009

Summer '89
Article in Science, Vince DeVita
Former NCI Director challenges DMC

.022



Consequences of Fall 1989 Release of Results:

- Immediate re-design of next generation Colon Adjuvant Trial

BEFORE

R → 5-FU + Leucovorin
R → No treatment

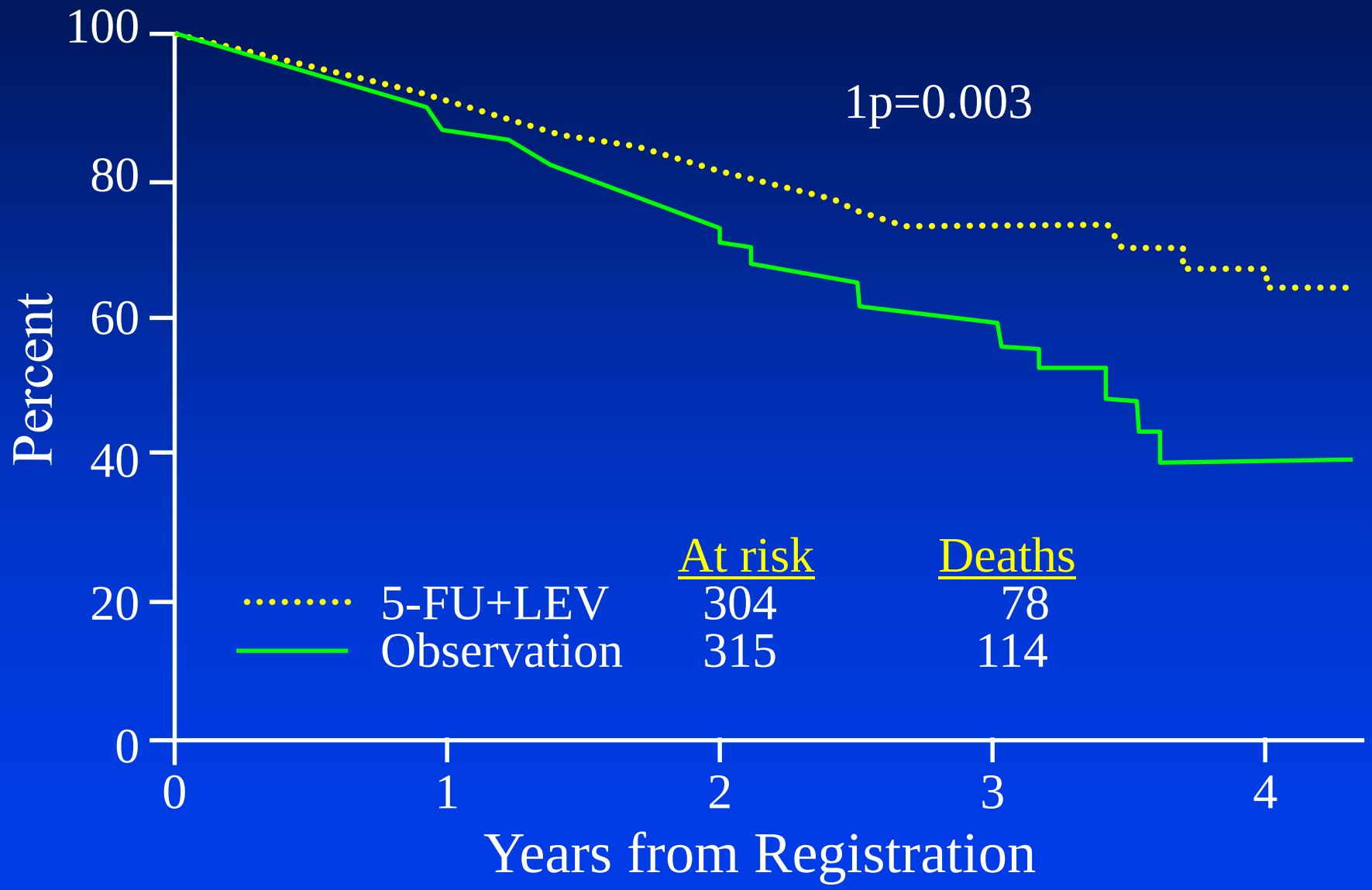
AFTER

R → 5-FU + Leucovorin
R → 5-FU + Levamisole

- 1990 FDA Approval of Levamisole NDA

Follow-up continued through March, 1993
Median follow-up increased
from 3 years to > 6 years

Duke's C Colon Cancer
Overall Survival



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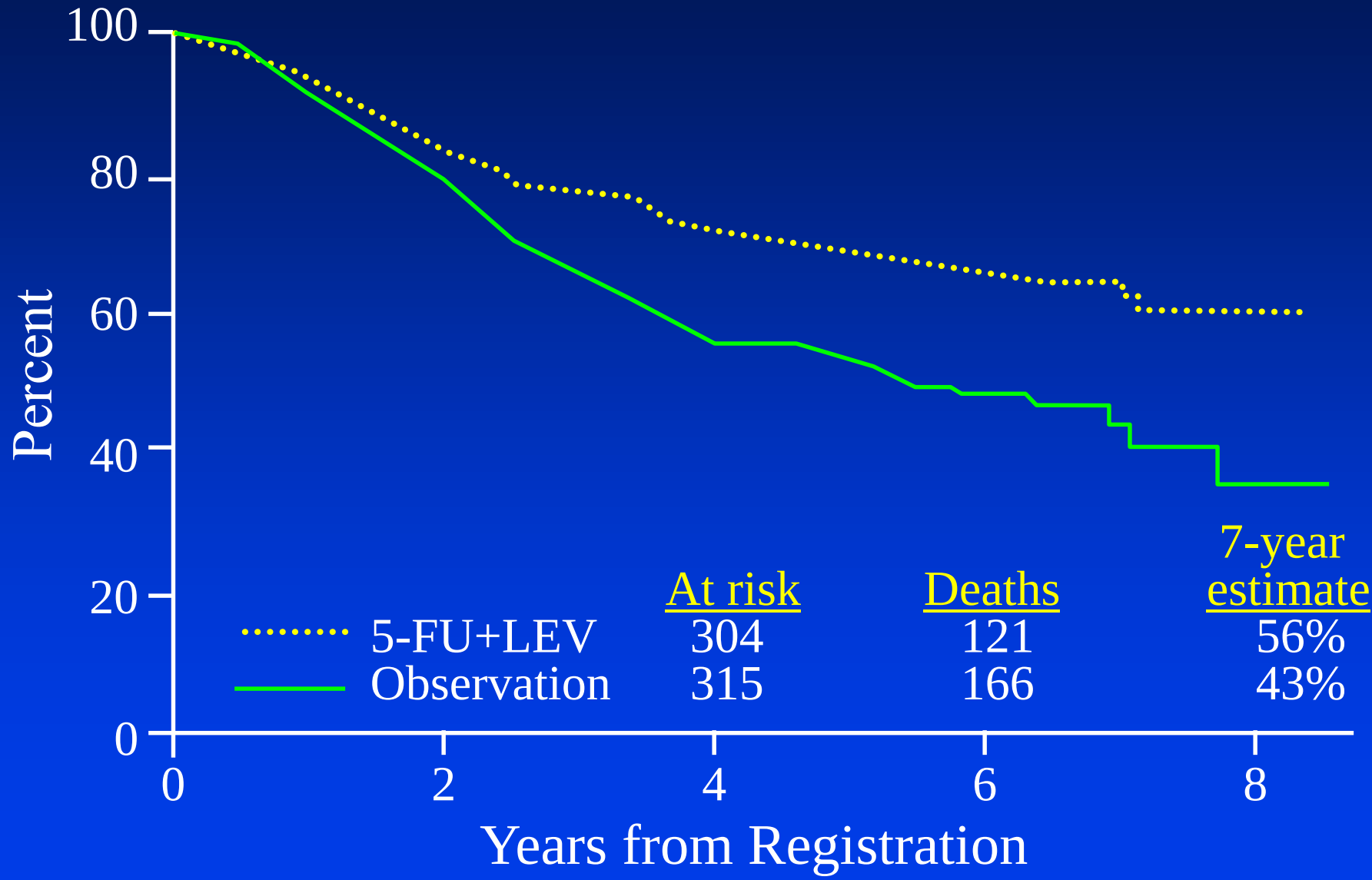

Types of Meetings of the Data Monitoring Committee

- **Organizational Meeting**
- Early Safety/Trial Integrity Reviews
- Formal Interim Analyses

Organizational Meeting

Data Monitoring Committee:

- **Ethically & Scientifically Supportive of:**
  - Study Objectives & Design
  incl. specified endpoints & monitoring guidelines
- Refine the draft of the DMC Charter
- Endorse & Refine the Content and Format
  for Open and Closed Reports
- Confidence in Procedures for
  Capturing Relevant Information
  of High Quality

Supportive of Study Design (Advisory Capacity to Sponsor/Investigators)

Illustrations:

1991 NIMH:

HIV-infected Patients with Cognitive Impairment

- X-over at 6 mo. . . . . Longer term f.u.
- Exclude “dropouts” . . . . Intent to treat
- Safety only . . . . Safety & Efficacy

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Safety/Trial Integrity Reviews

Eg. Cancer Intergroup # 0035: Colon Adjuvant

Duke's C → R

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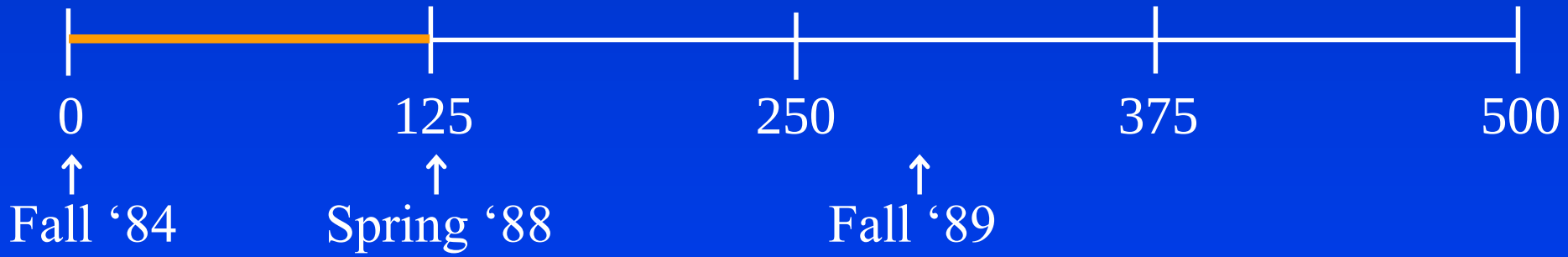
≈ every 125 deaths



Safety/Trial Integrity Reviews

- Patient Safety Data
- Accrual rates
- Treatment balance
- Eligibility violations
- Adherence to treatment
- Pooled event rates
- Completeness of follow-up

Types of Meetings of the Data Monitoring Committee

- Organizational Meeting
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- **Formal Interim Analyses**

Formal Interim Analyses

- **Trial Continuation**
  with recommendations to address ethical, safety or trial integrity issues

- **Trial Termination** due to :
- **benefit**
- **lack of benefit** ***(or futility)***
- **established harm**
- or inability to reliably answer issues the trial was designed to address

End Stage Renal Disease

Results (Interim at 1/2 planned endpoints)

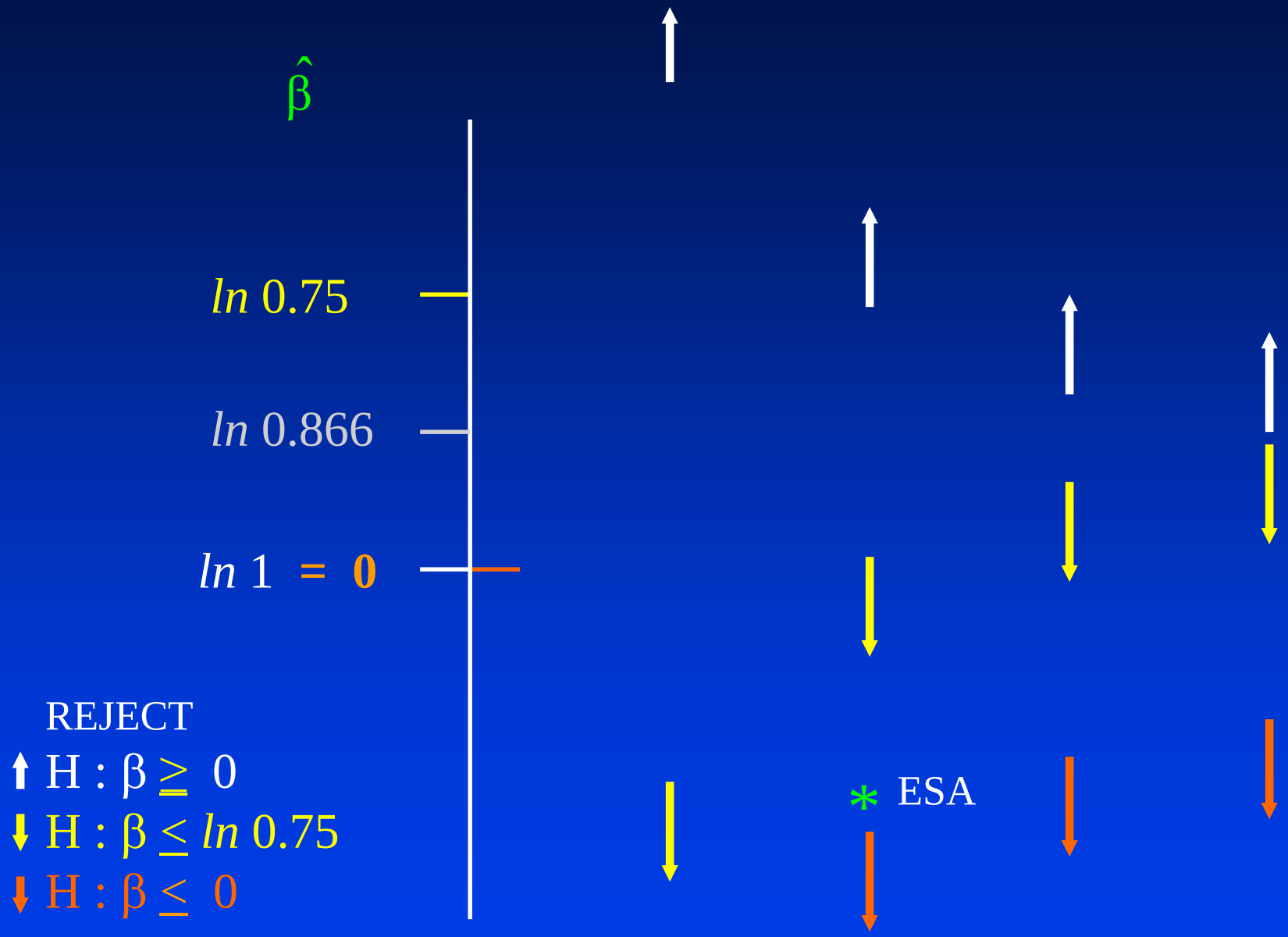
	n	Death/MI	Death
Standard Dose	615	**164**	**160**
High Dose	618	**202**	**195**

Death / MI relative risk: **1.30** (0.94, 1.79)

Besarab et al, NEJM 339:584-590, 1998:

"↑ **in incidence of thrombosis of vascular access sites**"

Symmetric O'Brien-Fleming Group Sequential Boundaries



Oversight Bodies in Ongoing Clinical Trials: Partnership of Responsibilities

- **Sponsors, Investigators, Care Givers**
  - Decision making responsibilities for design, conduct, & analysis of the trial
  - Primary patient care responsibilities
- **Institutional Review Boards & Regulatory Authorities**
  - Approval of ethics/science of the trial design
  - Ongoing monitoring of SUSARs & SAEs
- **Data Monitoring Committees (DMCs)**
  - Sole access during conduct of the clinical trial to:
    - Aggregated efficacy/safety data across the trial
    - Unblinded by treatment group

Summary:

An Opinion: The DMC process

for monitoring randomized clinical trials

is ***not*** better than it was 10 years ago !

In particular, ongoing and emerging challenges
threaten the DMC's *independence* and effectiveness…

Best practices and operating principles
for effective functioning of DMCs
have been proposed to address these challenges

Context for this Presentation

- An expert panel of representatives from academia, industry and government sponsors, and regulatory agencies met in June 2015 to discuss ongoing and emerging challenges potentially threatening DMC's independence and effectiveness

- A position paper was published in 2017 in *Clinical Trials* to summarize these discussions and to offer the authors' recommendations to improve the DMC process

- The authors of the *Clinical Trials* article:

  TR Fleming, DL DeMets, MT Roe, J Wittes, KA Carim, AN Vora, A Meisel, RP Bain, MA Konstam, MJ Pencina, DJ Gordon, KW Mahaffey, CH Hennekins, JD Neaton, GD Pearson, TLG Andersson, MA Pfeffer, SS Ellenberg

* Fleming TR et al. "Data monitoring committees: Promoting Best Practices To Address Emerging Challenges". *Clinical Trials* 2017; 14: 115-123

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Currentness of DMC data
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
  - ✓ DMC meeting format
  - ✓ Creating an effective DMC Charter
  - ✓ DMC recommendations through consensus, not by voting
  - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center

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Current Concerns: Expertise in DMC Processes

- DMC chairs and members
  - Only 8% of DMC members had training in DMC processes
    …nearly all indicated prior training would have been valuable
  - DMC chairs should realize they should take leadership:
    …in planning the DMC meeting,
    …*in the conduct of the DMC **Open** as well as **Closed** Session,*
    …in developing DMC Recommendations & Meeting Minutes
  - Rather than simply asking if anyone identified "any problems", the DMC chair should ensure the DMC is led through the key findings in the DMC ***Closed*** Report
- DMC Administrative Support Staff & the DMC Independent Statistician:
  - Should have meaningful expertise in DMC procedures obtained through proper training and previous experiences

Adequate Training/Experience in DMC Process

- Training options for those involved in the DMC process should be more widely developed and used
  - *DMC members, esp DMC chairs* and *DMC statisticians*
  - Sponsors & their designated '*DMC Meeting Coordinators*'
  - *Statistical Data Analysis Centers* supporting DMCs

✓ Didactic Instructions

Formal curriculum with textbooks, articles, web-based lectures, interactive courses, etc.

✓ Apprenticeship model for initial DMC service to provide real-world experiences

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Indemnification of the DMC

- DMC Indemnification
  - ✓ Multiple sources of possible liability from clin trial stakeholders
  - ✓ Sponsors/CROs often propose DMC members insure them
  - ✓ DMC concern about litigation could influence their performance
- DeMets et. al.; *Clinical Trials* 2004; 1: 525–531
  - ✓ Recommendations for indemnification of DMC members
  - ✓ DMC coverage without escape clauses: e.g., "negligence"
    vs. "willful misconduct or fraudulent acts"
- Tereskerz 2010; *Accountability in Research*
  - ✓ Recommendation for legislation requiring all sponsors:
    - To indemnify DMC members, and
    - To empower them to select and retain their own independent counsel

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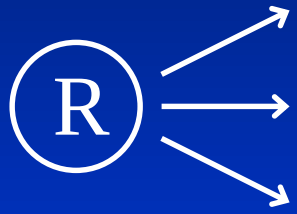
Current Concerns: Currentness of DMC Data

ACTG 019: Asymptomatic HIV+ Patients
CD4<500



Placebo		(428)
ZDV	500 mg	(453)
ZDV	1500 mg	(457)

Outcome:
Time to Advanced ARC, AIDS, or Death

Accrual initiation	July 1987
Interim analysis	August 1989

Current Concerns: Currentness of DMC Data

8/2/89 (Data freeze on 5/10/89)

Rx	# Prog	Prog* Rate	P-value vs. placebo
Placebo (428)	31	7.5	
500 mg (453)	8	2.1	.0008
1500 mg (457)	12	3.4	.015

* Failures per 100 person years of follow-up

Current Concerns: Currentness of DMC Data

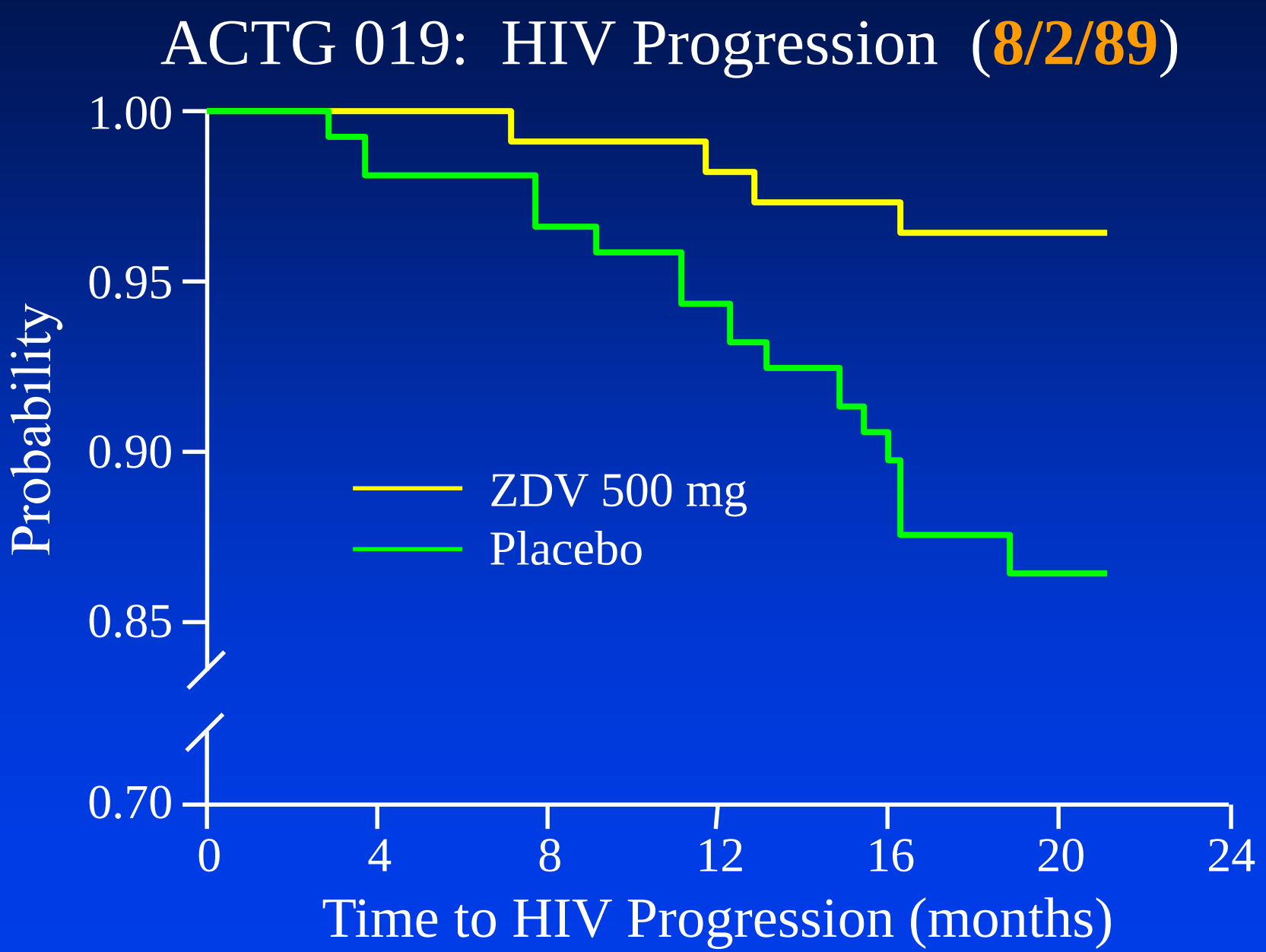
8/16/92 Updated Analysis

Rx	# Prog	Prog* Rate	P-value vs. placebo
Placebo (428)	38 = 31+**7**	7.6	
500 mg (453)	17 = 8+**9**	3.6	.0030
1500 mg (457)	19 = 12+**7**	4.2	.05

* Failures per 100 person years of follow-up

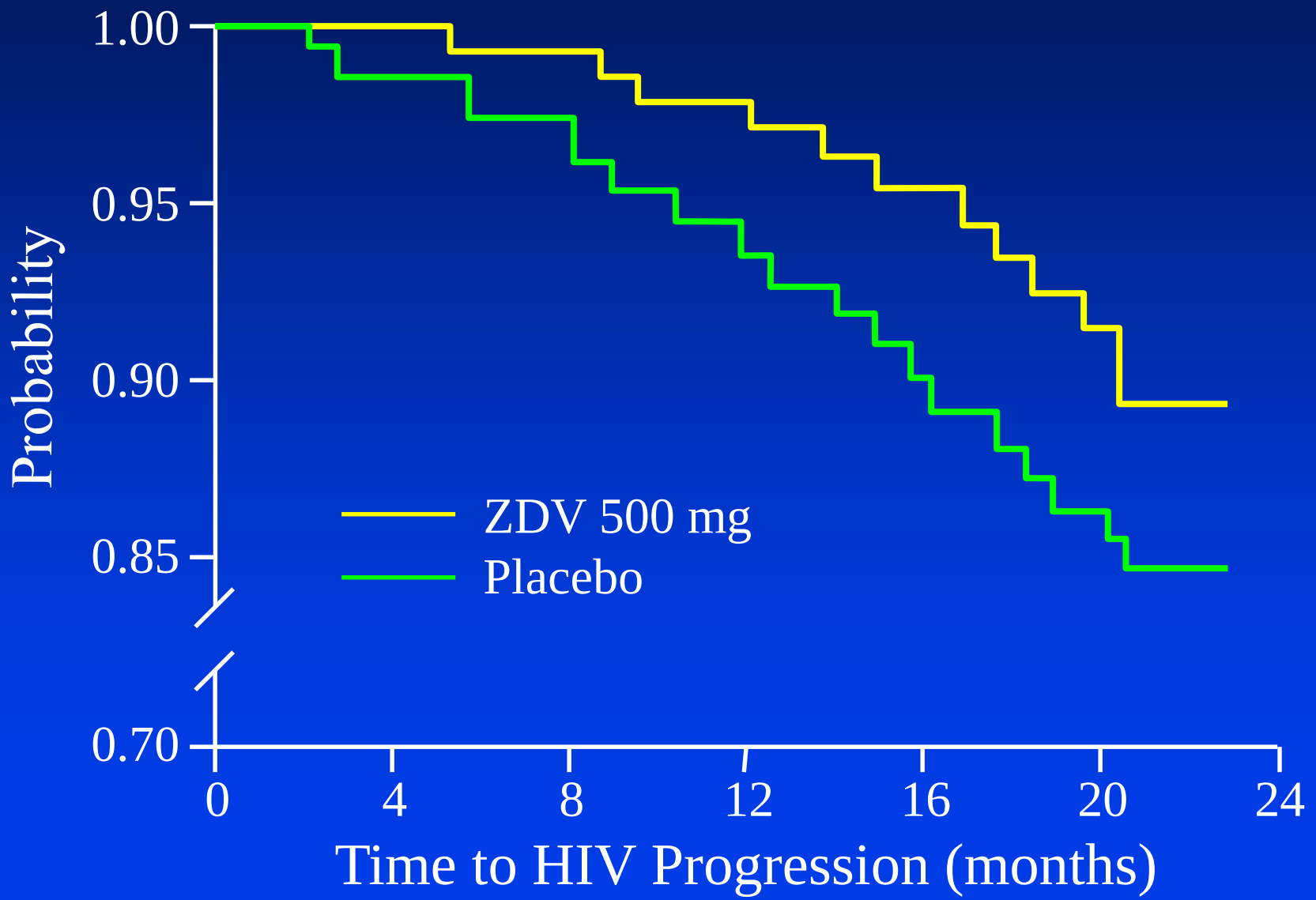
O'Brien-Fleming: .005

Current Concerns: Currentness of DMC Data



Current Concerns: Currentness of DMC Data

ACTG 019: HIV Progression (**8/16/89**)



Current Concerns: Currentness of DMC Data

In typical trials with duration 18 months to 4 years:

- '***Clinical Cut Date***' → DMC Meeting: 6 to 9 weeks

  5-6 weeks: Accuracy/Currentness issues

- '***Data Lock Date***' → DMC Meeting: about 3 weeks

  2 weeks: Analysis/Report generation
  1 week: Reports to DMC for their review

- Also SAE data & non-validated key endpoint data should be current to the '*Data Lock Date*'

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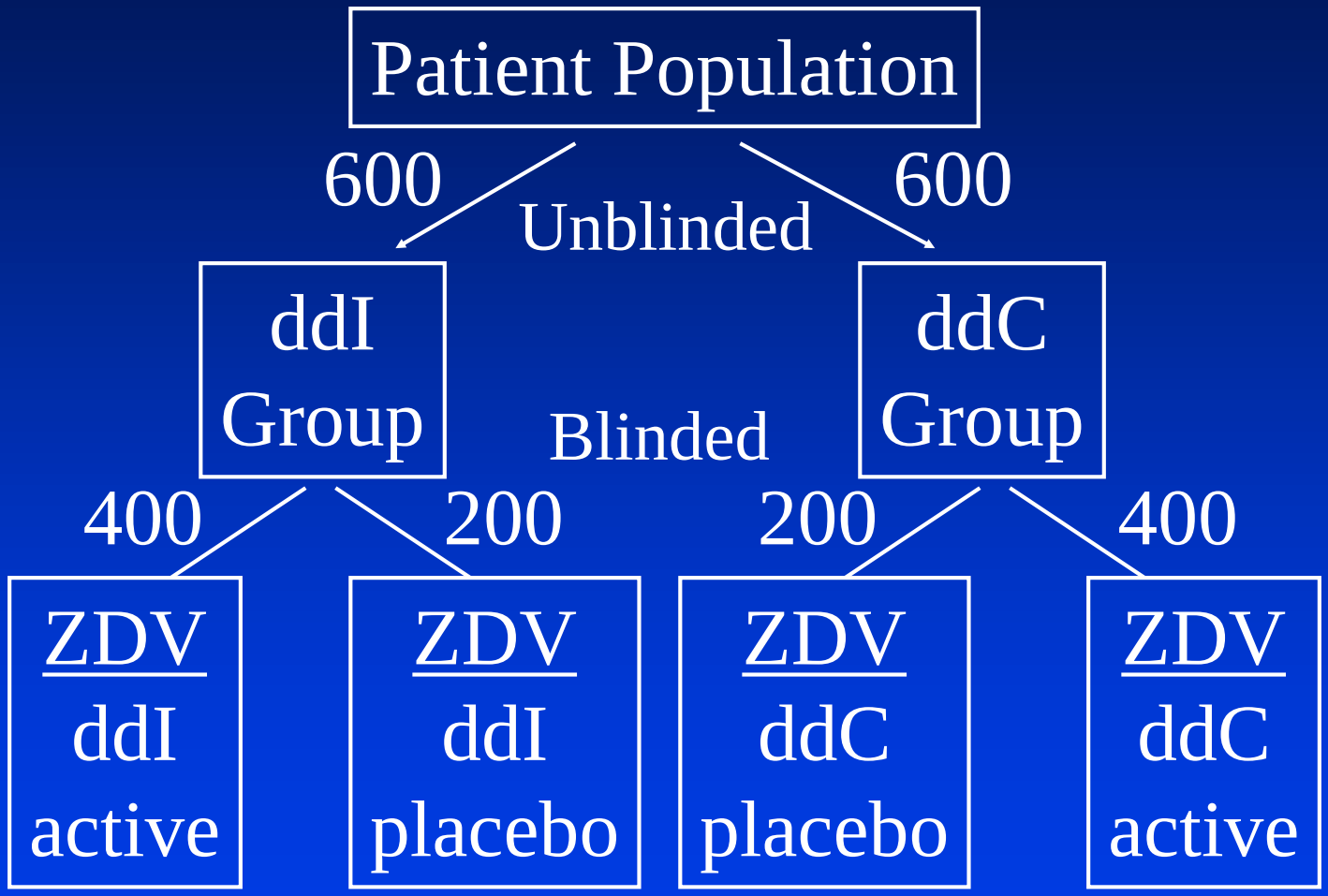

Issues & Controversies: DMC ↔ DMC Data Sharing

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Some Important Questions Regarding Early Release of Interim Data

Will early release of interim data increase enthusiasm of participating investigators?

Will early release of data provide more timely access to reliable insights?

Will Release of Data from a Concurrent Companion Trial render other Trials Non-influential?

Confidentiality of Interim Data

DAMOCLES*:

"*The current prevailing view is that the trial investigators should not see the unblinded interim results,*

and the argument that releasing interim results would aid enthusiasm and accrual is false."

* The United Kingdom NHS Health Technology Assessment Program commissioned the '*Data Monitoring Committees: Lessons, Ethics, Statistics Study Group*' (DAMOCLES):

- to investigate existing processes of monitoring accumulating data
- to identify ways of improving the DMC process.

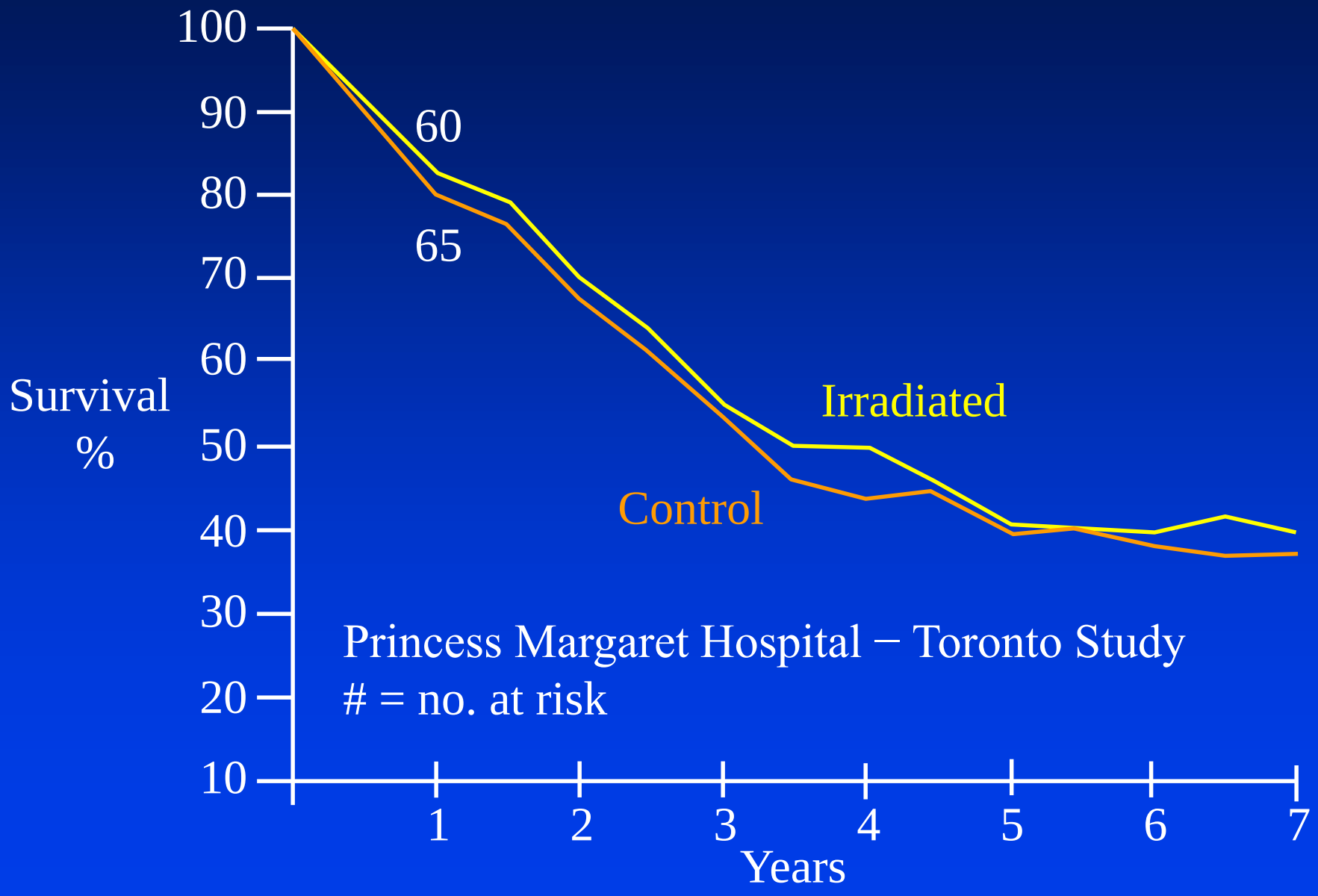
Grant, Altman, Babiker, et al. *Health Technology Assessment* 2005

Evidence from NIH Cancer Cooperative Group Studies

Maintaining Confidentiality ⇒ ↓ Pre-judgment ⇒ ↑ Trial Integrity

NIH Cancer Cooperative Group	NCCTG	SWOG
Interim Data shown only to DMCs:	YES	NO
Declining accrual rate	**0**/10	**5**/10
Number closed	9/10	9/10
Full accrual	8	6
Term early appropriately	1	1
Term early inappropriately	**0**	**2**
Completed studies with current results inconsistent with early published results	**0**/9	**2**/9

Survival of Patients with Rectal Carcinoma in Control and Irradiated Groups



Enhancing Trial Integrity by Maintaining Confidentiality

Maintaining Confidentiality of Emerging Data
from Ongoing Clinical Trials:

- Reduces the Risk of Pre-judgment,
  correspondingly *increasing* the ability to achieve:
  - ✓ Timely Enrollment
  - ✓ Targeted levels of Adherence & Retention
  - ✓ Timely Trial Completion with Reliable Results
- Reduces the Risk for Early Release of Misleading Results
- Protects the Flexibility to Modify Trial Design
  Based on Insights from Emerging External Data

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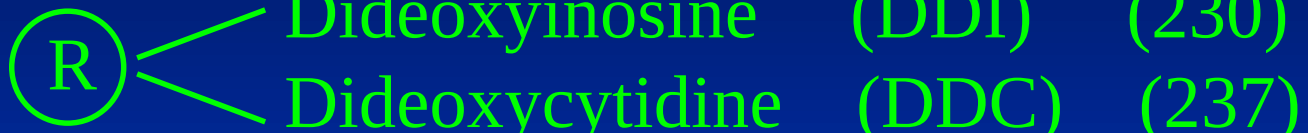
CPCRA #002 HIV Infected Patients who are AZT Intolerant/AZT Failures



Outcome:

Survival Time, Time to AIDS/Death

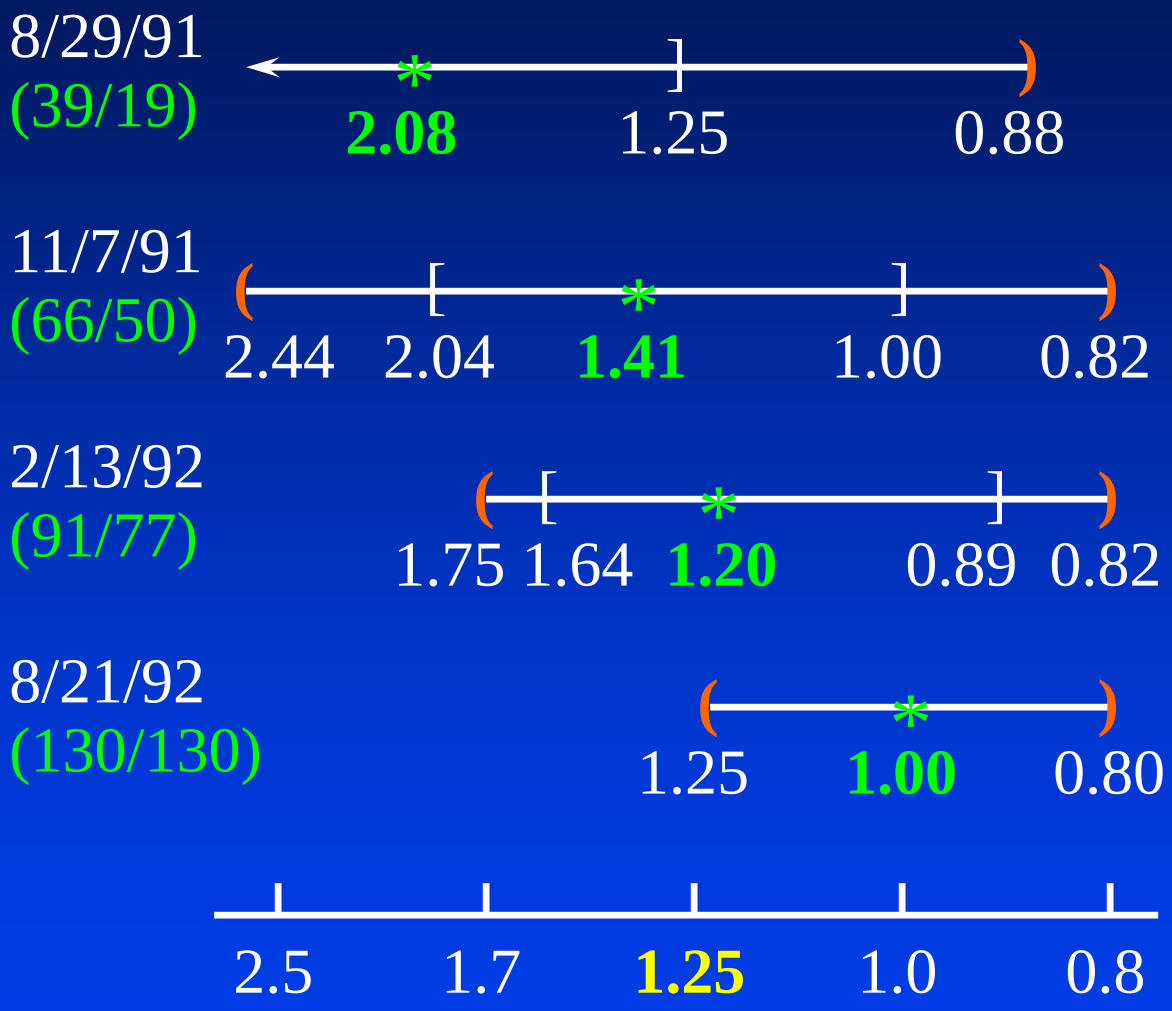
Enrollment: 12/90 - 9/91

DMC Efficacy Interim Analyses:

Approximately at increments of 60 events

(Protocol: Follow-up until 243 events)

ddC/ddI: Rate of Progression to AIDS/Death



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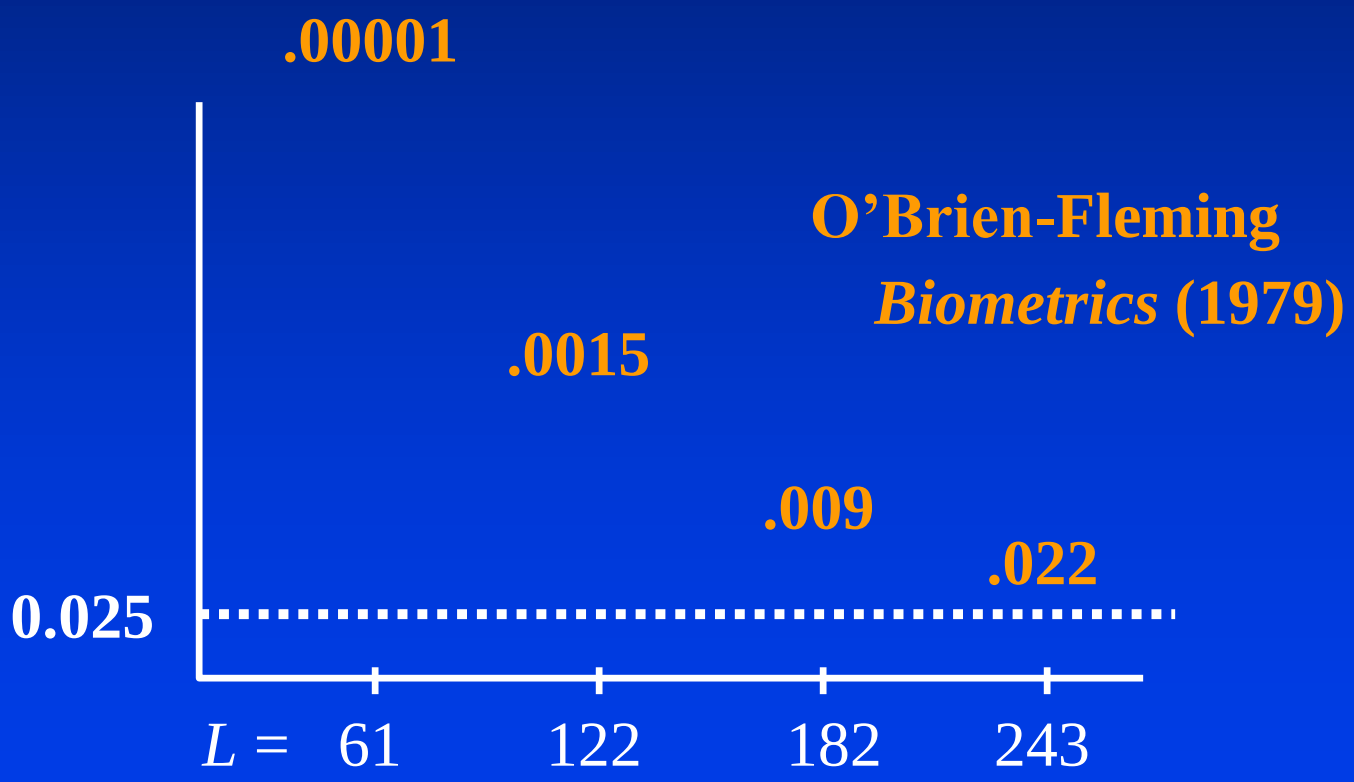
Goal: With 4 analyses, preserve the (1-sided) false positive error rate: 0.025



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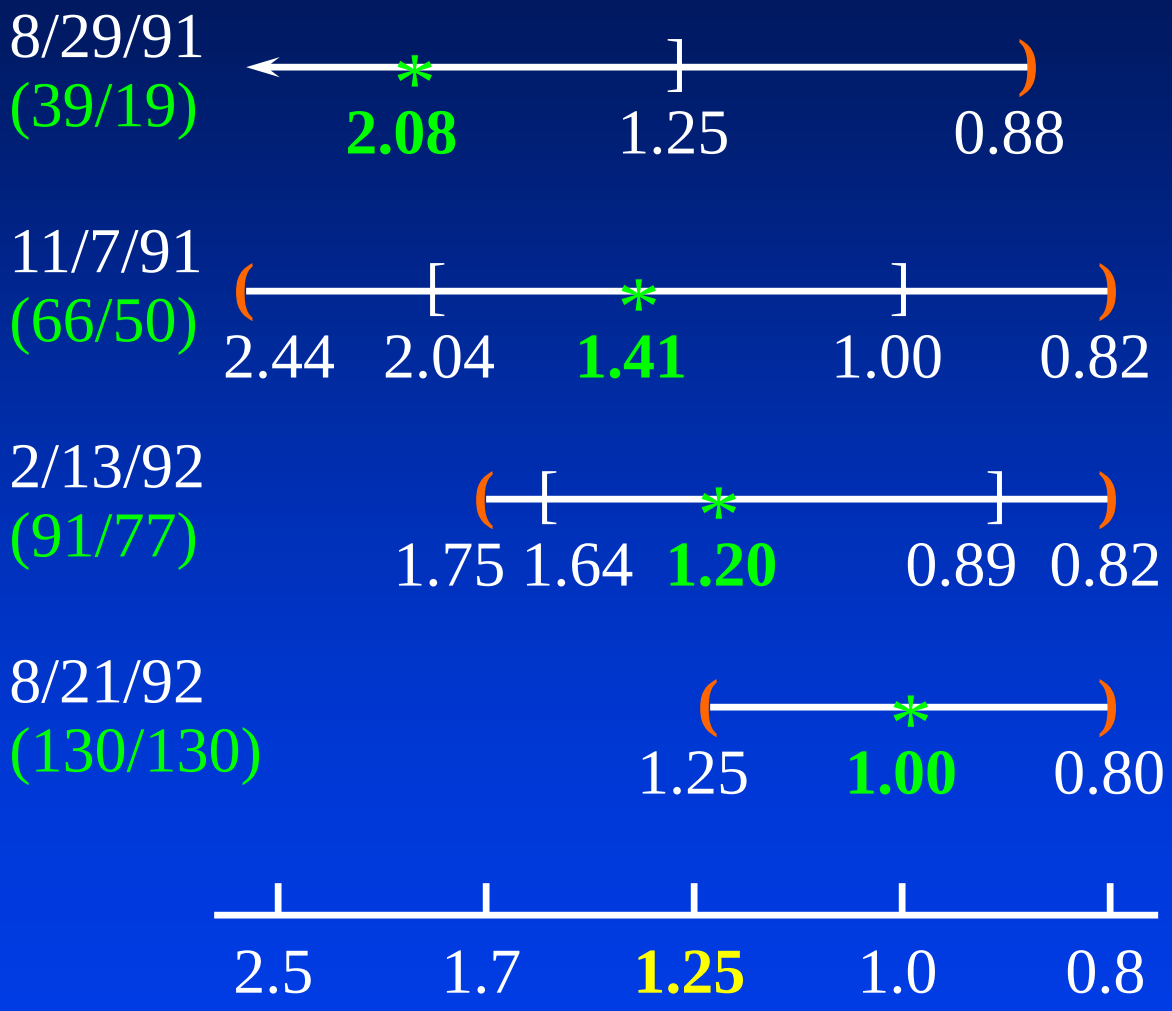

"VALUE Trial"
Hypertensive Patients at High Cardiovascular Risk

Events on Valsartan / Amlodipine ; Relative Risk

Outcome Measure	May '98 to August '00 (n = 15,290)	May '98 to December '03 (n = 15,245)
Death	178/141; 1.253	841/818; 1.021
M.I.	102/76; 1.332	369/313; 1.171
Stroke	124/92; 1.338	322/281; 1.138
H.F. Hosp	104/112; 0.922	354/400; 0.879
Diabetes	No data	690/845; 0.811

"LIGHT Trial"

Naltrexone SR/Bupropion SR:
"Contrave"
CV risks in Overweight/Obese Subjects
With CV Risk Factors

Key Design Objectives:

At 90 events: ***2.0*** Margin for CVDeath / Str / MI
At 378 events: ***1.4*** Margin for CVDeath / Str / MI

…FDA's Part 15 Open Public Hearing, 8/11/2014…
"*Confidentiality of Interim Results in Cardiovascular Outcome Safety Trials*"

	CVD Stroke MI	Overall Deaths CV Non-CV		Total	Stroke	MI	D Stroke MI
"1st Quadrant": Up to *11/23/2013*							
Contrave	35	5	5	10	7	24	40
Placebo	59	19	3	22	11	34	62
HR	**0.59**						**0.64**

✓ DMC rec: '*Release data to FDA per Data Access Plan*'

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"2nd Quadrant": Between *11/23/2013* and *3/3/2015*

Contrave	55	12	21	33	15	31	74
Placebo	43	15	14	29	10	23	57
HR	**≈1.29**						**≈1.30**

✓ On *3/3/2015, DMC recommended trial continuation…*

	CVD Stroke MI	Overall Deaths CV	Non-CV	Total	Stroke	MI	D Stroke MI
"1st Quadrant": Up to *11/23/2013*							
Contrave	35	5	5	10	7	24	40
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Placebo	43	15	14	29	10	23	57
HR	**≈1.29**						**≈1.30**

✓ On *3/3/2015, DMC recommended trial continuation…*

That day, sponsor released "1st Quadrant" in Patent Filing

⇒ Steering Committee recommends trial termination

	CVD Stroke MI	Overall Deaths CV Non-CV		Total	Stroke	MI	D Stroke MI
"1st Quadrant": Up to *11/23/2013*							
Contrave	35	5	5	10	7	24	40
Placebo	59	19	3	22	11	34	62
HR	**0.59**						**0.64**
***JAMA 3/8/2016* Final 64%: 'End of Study' Results**							
Contrave	119	26	39	65	31	69	156
Placebo	124	42	29	71	23	71	151
HR	**0.95**						**1.02**

Key insights:

- ✓ Potential unreliability of interim data
- ✓ Breaches in confidentiality provide potential for:
  - ⇒ Dissemination of misleading results
  - ⇒ Risks to irreversibly bias subsequent trial conduct

Principles & Insights

"It isn't so much
The Things we Don't Know
That get us into Trouble.
It's the Things we Know
That Aren't So."

Artemus Ward

Some Important Questions Regarding Early Release of Interim Data

Will early release of interim data increase enthusiasm of participating investigators?

Will early release of data provide more timely access to reliable insights?

Will Release of Data from a Concurrent Companion Trial render other Trials Non-influential?

Release of Data from a Concurrent Companion Trial

CPCRA 023 Trial: April 1993 – July 1995
Oral Gancyclovir: Prevention of CMV Symptoms

	July 1994 SYNTEX #1654		July 1994 CPCRA #023	
	Rx	PLA	Rx	PLA
n	486	239	646	327
CMV	76	72	40	23
(RR/p)	(0.45 /0.0001)		(0.87 / 0.60)	
Death	109	68	58	23
(RR/p)	(0.71/ 0.052)		(1.27 / 0.34)	

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	Rx	PLA	Rx	PLA	Rx	PLA
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CMV	76	72	40	23	101	55
(RR/p)	(0.45 /0.0001)		(0.87 / 0.60)		(0.92 / 0.60)	
Death	109	68	58	23	222	132
(RR/p)	(0.71/ 0.052)		(1.27 / 0.34)		(0.83 / 0.09)	

Betaseron in Secondary-Progressive MS Patients

Berlex North America (NA) Trial: 2/96 - 2/00
Number & Percent with Confirmed EDSS Progression

	October 1998 EU Trial		October 1998 NA Trial	
	Rx	PLA	Rx	PLA
n	360	358	631	308
Number	148	178	119	57
Percent	38.9	49.7	18.9	18.5
(OR/ 2p)	(0.644/ 0.005)		(1.027/ 0.90)	

Betaseron in Secondary-Progressive MS Patients

Berlex North America (NA) Trial: 2/96 - 2/00
Number & Percent with Confirmed EDSS Progression

	October 1998 EU Trial		October 1998 NA Trial		February 2000 NA Trial	
	Rx	PLA	Rx	PLA	Rx	PLA
n	360	358	631	308	631	308
Number	148	178	119	57	227	106
Percent	38.9	49.7	18.9	18.5	36.0	34.4
(OR/ 2p)	(0.644/ 0.005)		(1.027/ 0.90)		(1.071/ 0.64)	

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Opposing Views

- Lilford et. al.: "Why should data arising in a trial be secret… setting up a system that perpetuates ignorance violates Kant's injunction that people should not be used as a mere ends to a mean."

- Fleming et. al.: "This opinion does not recognize that clinical trials must be conducted in a manner to address both collective and individual ethics. Addressing collective ethics includes achieving the goal of a timely and reliable evaluation of the overall benefits and risks of an intervention for the benefit of all patients. Furthermore, many patients join clinical trials in part due to altruistic interests in achieving this same goal, so failure to maintain trial integrity violates individual as well as collective ethics."

…the second principle of clinical equipoise…

Confidentiality of Interim Data

- DAMOCLES:

  "*There is near unanimity*
  that the interim data and the deliberations of the DMC
  should be absolutely confidential…

  …Breaches of confidentiality
  are to be treated extremely seriously"

- Formal statements of concordance have been issued by NIH, WHO, EMA and FDA*

*Fleming et al. Maintaining confidentiality of interim data to enhance trial integrity and credibility. *Clinical Trials* 2008; 5: 157–167

Canadian Institutes of Health Research
Aspirin +/- Warfarin in Peripheral Arterial Disease

- Anand, Wittes, Yusef, et. al. "What information should a sponsor of a randomized trial receive during its conduct?"
- Survey of "experienced clinical trialists":

"*Do you think that in a large randomized clinical trial, in which there is an independent DMC, made up of reputable clinical trialists and biostatisticians who carefully monitor the trial, interim data such as conditional power should be given to the sponsor when requested?"*

Response: Yes: No: (EU, US, Australia, Canada)

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Response: Yes: **0** No: **28** (EU, US, Australia, Canada)

Current Concerns: Confidentiality of Interim Data

Another Illustration:

- Potential Registration Endpoint:
  e.g: '*Validated' Biomarker* or *Symptom Measure*
- Clinical Endpoint of Principal Interest:
  e.g: *Overall Survival (OS)*

…For subsequent labeling or other regulatory authority…

Approach to maintain integrity of *Overall Survival* data:

When data on the '*Registration Endpoint*' are complete, and if the monitoring boundary for *OS* is not crossed:

- Release data on the Registration Endpoint
- Maintain confidentiality of *OS* data until the boundary is crossed or target # of events is achieved

Current Concerns: Sponsor Access to Pooled Data

- Availability of Interim Safety and Efficacy Data on a "*Need to Know Basis*"

  E.g:
  - Medical Monitors for Reporting SUSARs & SAEs
  - Caregivers in Unblinded Trials
  - Pooled data to modify sample size

- Open access (e.g., in DMC Open Reports) to pooled data on efficacy and safety measures readily may provide insights into treatment effects

DMC **Open** Report: An Outline

- Enrollment rate, by time and by institution
- Baseline characteristics
- Eligibility violations
- Adherence to randomized study medications
- Retention rates
- Currentness of data capture & adjudication of key events

…All information is pooled across treatment groups…

N.B.: The DMC **Open** Report does NOT provide safety or efficacy data, even pooled by treatment regimen

DMC **Closed** Report: An Outline

- Repeat of the DMC Open Report information, in greater detail by treatment group
- Analyses of primary and secondary efficacy endpoints
- Analyses of lab values, including basic summaries and longitudinal analyses
- Analyses of adverse events and overall safety data

…The DMC is provided information to allow *unblinded* review by treatment groups…

Current Concerns: Blinding DMC Members

E.g: DAIDS Therapeutic DMC

′86-′06	About 50 clinical trials
′86-′88	DMC Blinded: Safety (A/B); Efficacy (X/Y)
′88-Present	DMC Unblinded

DMC Unblinding facilitated the Timely/Efficient detection of:

- ✓ risk/benefit issues
- ✓ trial integrity issues

Current Concerns: Blinding DMC Members

Eg: Cardiology Pre-Trial Organizational Meeting

- **Blind**
  - leaks: Data falls in wrong hands
  - leaks: By DMC Membership
  - overreaction to something "not real"
- **Don't Blind**
  - Timely & informed integration of complex patterns …including risk (A/B) / benefit (X/Y)
  - Earlier detection of something "real" using evidence that does exist

Current Concerns: Blinding DMC Members?

E.g.: The CAST Trial

- DMC blinded through X/Y coding
  for: Class IC antiarrhythmics vs. placebo
- First DMC Meeting:
  - ***19*** vs. ***3*** sudden deaths

  …The "blinded" DMC recommended continuation
- Emergency DMC Meeting:
  - ***33*** vs. ***9*** sudden deaths;
  - ***56*** vs. ***22*** overall deaths

  …DMC recommended immediate termination

Addressing Confidentiality Issues

- Preserving confidentiality of interim clinical trial data is essential to trial integrity by reducing risks of prejudgments
- DMC review of *'unblinded'* efficacy as well as safety data throughout the trial facilitates timely/efficient detection of:
  - ✓ benefit/risk issues
  - ✓ trial integrity issues
- In rare settings in which the DMC believes the sponsor's dissemination or lack of dissemination of information has led to serious scientific or ethical concerns, some type of mediation process could be useful

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Currentness of DMC data
- Addressing confidentiality issues
- **Implementing procedures to enhance DMC independence**
  - ✓ **DMC meeting format**
  - ✓ Creating an effective DMC Charter
  - ✓ DMC recommendations through consensus, not by voting
  - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center

DMC Meeting Format

DMC Meeting Format, as evolved in the 1980s:

- **Closed Session**
- **Open Session** { Sponsor, Regulators; Lead Investigators
- **Closed Session**

E.g: Fluconazole: Serious Fungal Infections

✓ Preserves confidentiality
while maximizing opportunities for interaction

✓ Allows for more efficient use of the Open Session

✓ Enhances DMC chair leadership of the DMC meeting

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DMC Charter

- Primary Responsibilities of the DMC
- Membership of the DMC
- Timing and Purpose of the DMC Meetings
- Procedures to Maintain Confidentiality
  - ✓ **Open** and **Closed** Sessions
  - ✓ **Open** and **Closed** Reports
  - ✓ **Open** and **Closed** Session Minutes
  - ✓ DMC Recommendations to the Steering Committee
- Statistical Monitoring Guidelines

The DMC shares responsibility to finalize the DMC Charter

Creating an Effective DMC Charter: Avoid Rigid Procedures

- DMC Charters should articulate *principles*
  that provide *guidance* to the DMC process
  rather than providing a *rigid set of requirements*…
  DMCs need flexibility to deal with unexpected challenges
- Sponsor's should avoid excess control: such as
  '*limiting # of looks at outcome data*', or saying
  '*just review safety data to avoid spending alpha*', etc.
- Budgets should allow flexibility in meeting frequency
  and in the format/content of DMC reports
- DMC Recommendations through *consensus*, not *voting*
- Proper focus: empowering the DMC regarding its mission
  rather than a compulsion about documentation

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
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- Currentness of DMC data
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- **Implementing procedures to enhance DMC independence**
  - ✓ DMC meeting format
  - ✓ Creating an effective DMC Charter
  - ✓ DMC recommendations through consensus, not by voting
  - ✓ **DMC contracting process**
- Defining the role of the Statistical Data Analysis Center

DMC Contracting Process and COI

- Real/Perceived Conflicts of Interest should be identified and procedures should be followed to avoid creating them
  - Criteria for achieving independence of DMC members
  - Selection of venues for meetings, avoiding pre-meeting dinners
  - Rather than using generic consulting agreements, develop "independent scientist" agreements to engage DMC members… that recognize DMC members as independent scientists having primary focus to protect patient safety and trial integrity
  - If possible, 'independent entity' should engage DMC members, such as academic leadership of study steering committee

Clinical guideline committees

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Currentness of DMC data
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
  - ✓ DMC meeting format
  - ✓ Creating an effective DMC Charter
  - ✓ DMC recommendations through consensus, not by voting
  - ✓ DMC contracting process
- **Defining the role of the Statistical Data Analysis Center**

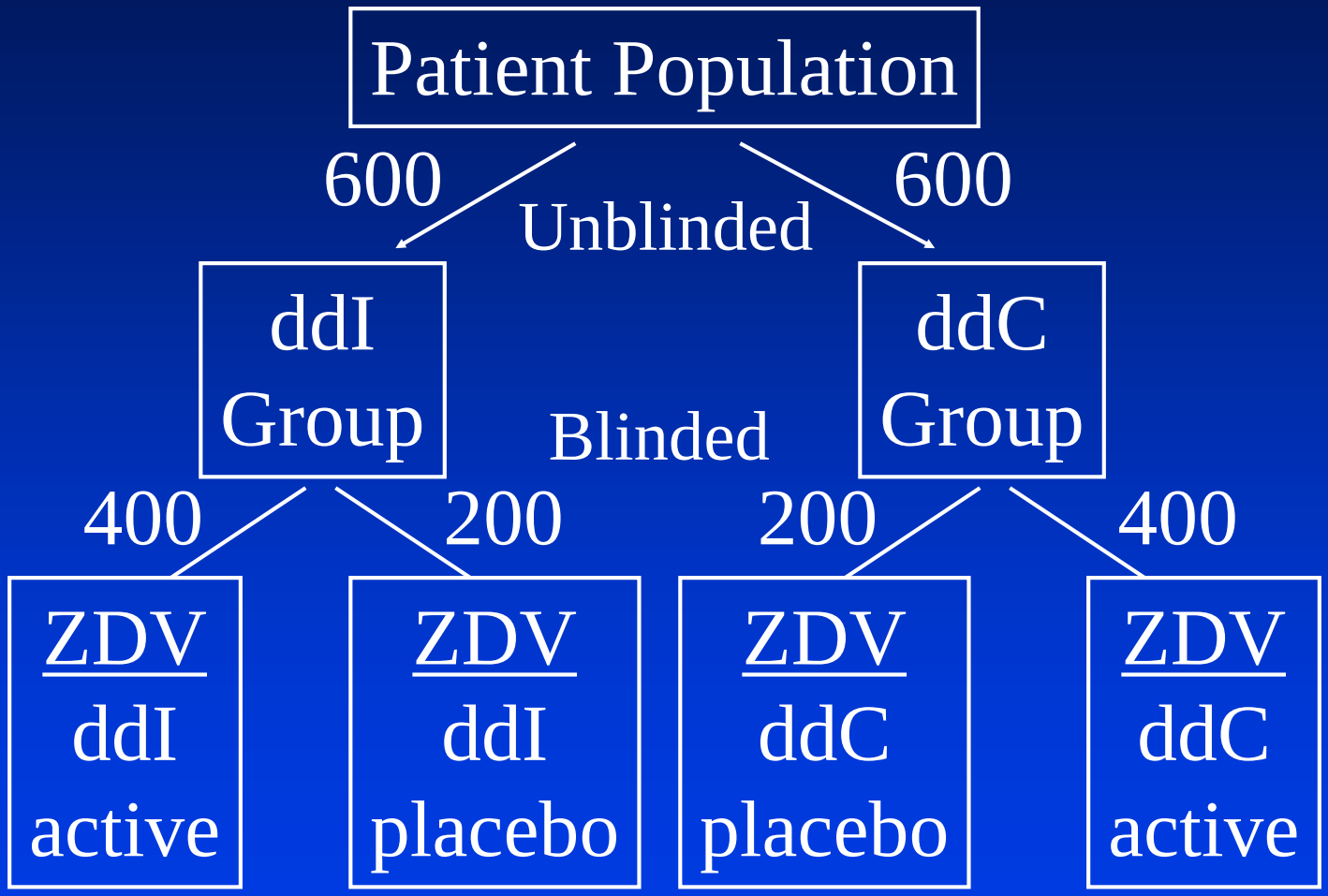
Defining the Role of the Statistical Data Analysis Center

- The DMC relies on the DMC Open and Closed Reports, generated by independent statistician at the SDAC, for timely & accurate data on efficacy, safety, & quality of trial conduct
- The independent statistician at the SDAC should have *sufficient depth of knowledge* about the study at hand and *experience with trials* in general to ensure the DMC has access to timely, reliable, and readily interpretable insights about emerging evidence in the clinical trial
- DMC Reports should be thoughtfully developed concise documents, with optimally informative figures and tables
- The SDAC independent statistician should routinely have access to all unblinded efficacy and safety data… …permission from the sponsor should not be required to address DMC requests for additional information

Proposed Best Practices and Operating Principles for Effective Functioning of Contemporary DMCs

- DMC chairs and members need better training opportunities
- DMC members should be protected against legal liability
- DMCs should review *'unblinded'* efficacy and safety data
- Overly rigid procedures can compromise DMC independence
  - ✓ DMC Charters: providing principles to guide DMC process, rather than listing a rigid set of requirements
  - ✓ Developing DMC recommendations: consensus, not voting
  - ✓ Beginning DMC meeting with Closed Session may enhance independence and establish the DMC Chair's leadership
  - ✓ DMC contracts should recognize DMC as independent scientists
- The SDAC needs experience, access, and flexibilities
- Regulatory scientists would benefit from direct involvement

CPCRA #007: Study Design



Issues & Controversies: DMC ↔ DMC Data Sharing

CPCRA #007:

11/93	ZDV ddI Active	ZDV ddI Placebo	ZDV ddC Placebo	ZDV ddC Active
n	337	172	168	344
Prog/Death	55	42	28	62
Death	18	17	2	18
All Events	92	73	37	102

Issues & Controversies: DMC ↔ DMC Data Sharing

CPCRA #007:

	11/93		5/95	
	ZDV ddI Placebo	ZDV ddC Placebo	ZDV ddI Placebo	ZDV ddC Placebo
n	172	168	188	187
Prog/Death	42	28	100	95
Death	17	2	75	66
All Events	73	37	210	202