Summer Institute in Statistics for Clinical Research

Data Monitoring Committees

July 28, 2016

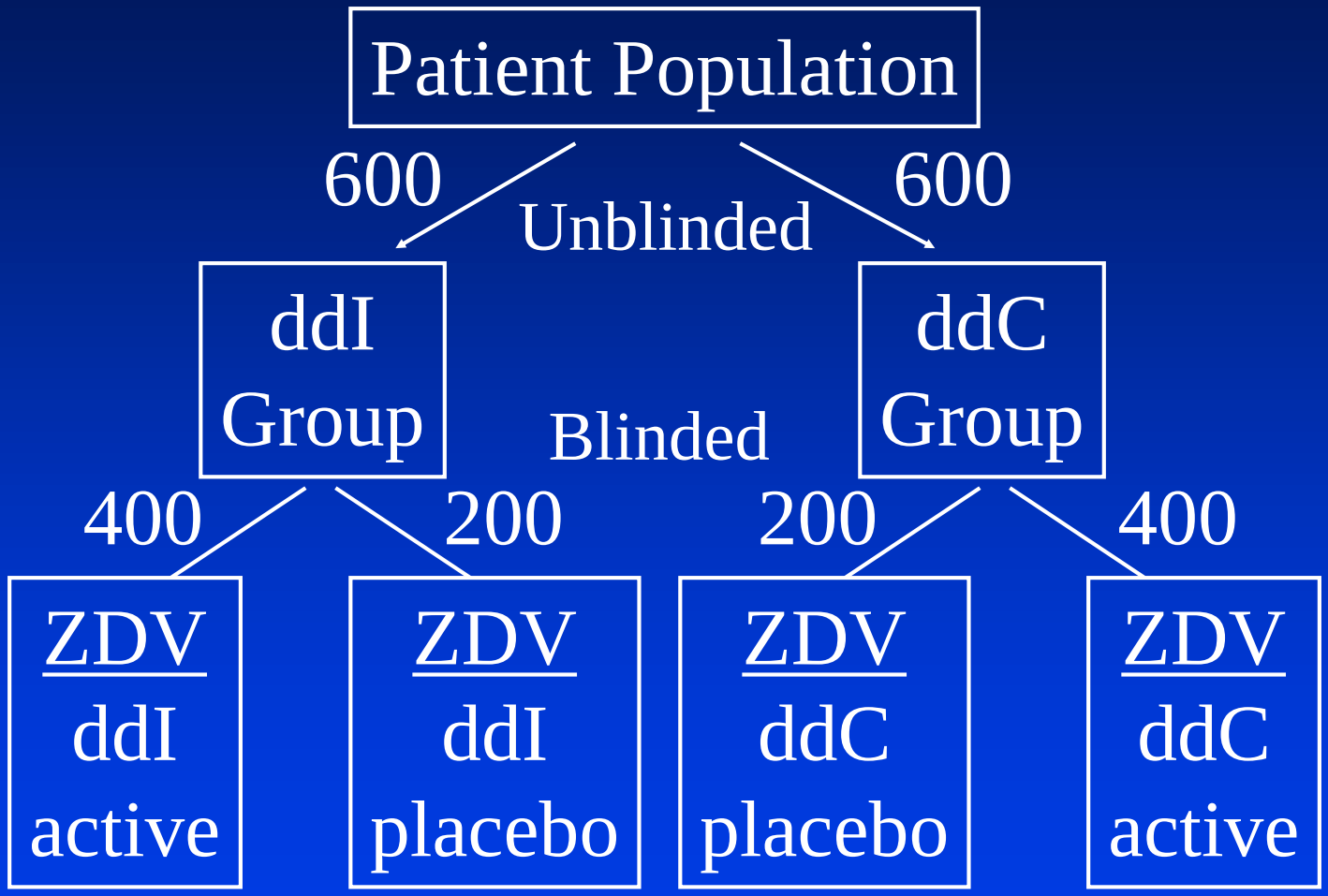
Thomas R. Fleming, Ph.D.
Professor, Dept. of Biostatistics
University of Washington

Ellenberg SS, Fleming TR, and DeMets DL: *"Data Monitoring Committees: A Practical Approach"*, John Wiley & Sons, 2002

Fleming TR et. al. "Maintaining Confidentiality of Interim Data to Enhance Trial Integrity & Credibility". *Clinical Trials* 2008; 5: 157-167

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

While a DMC is reviewing data from ongoing clinical trials, to achieve this 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 composition and functioning

Some Fundamental Principles
(re. DMC composition & functioning)

- 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

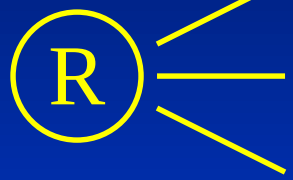
  …Guided by *recommendations of outside consultants*

  …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

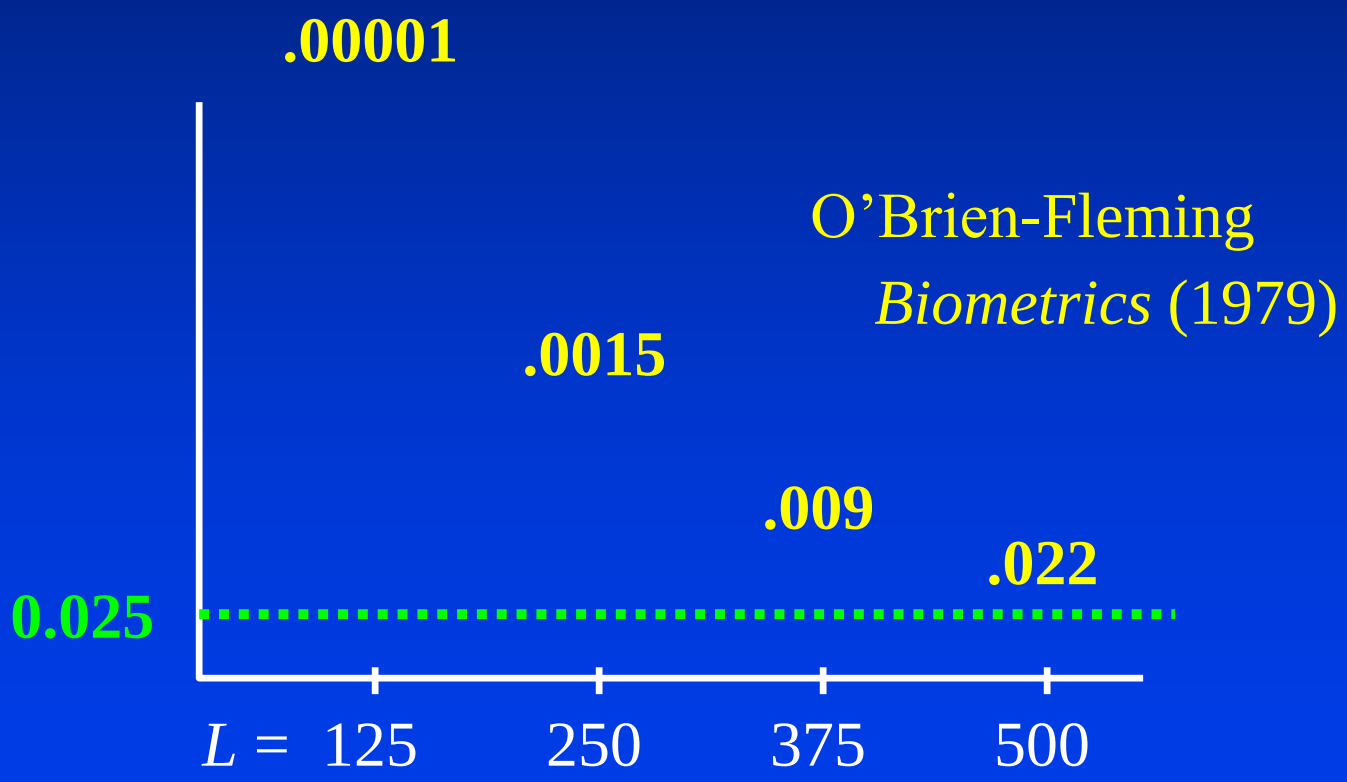
Follow-up to 500 deaths

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

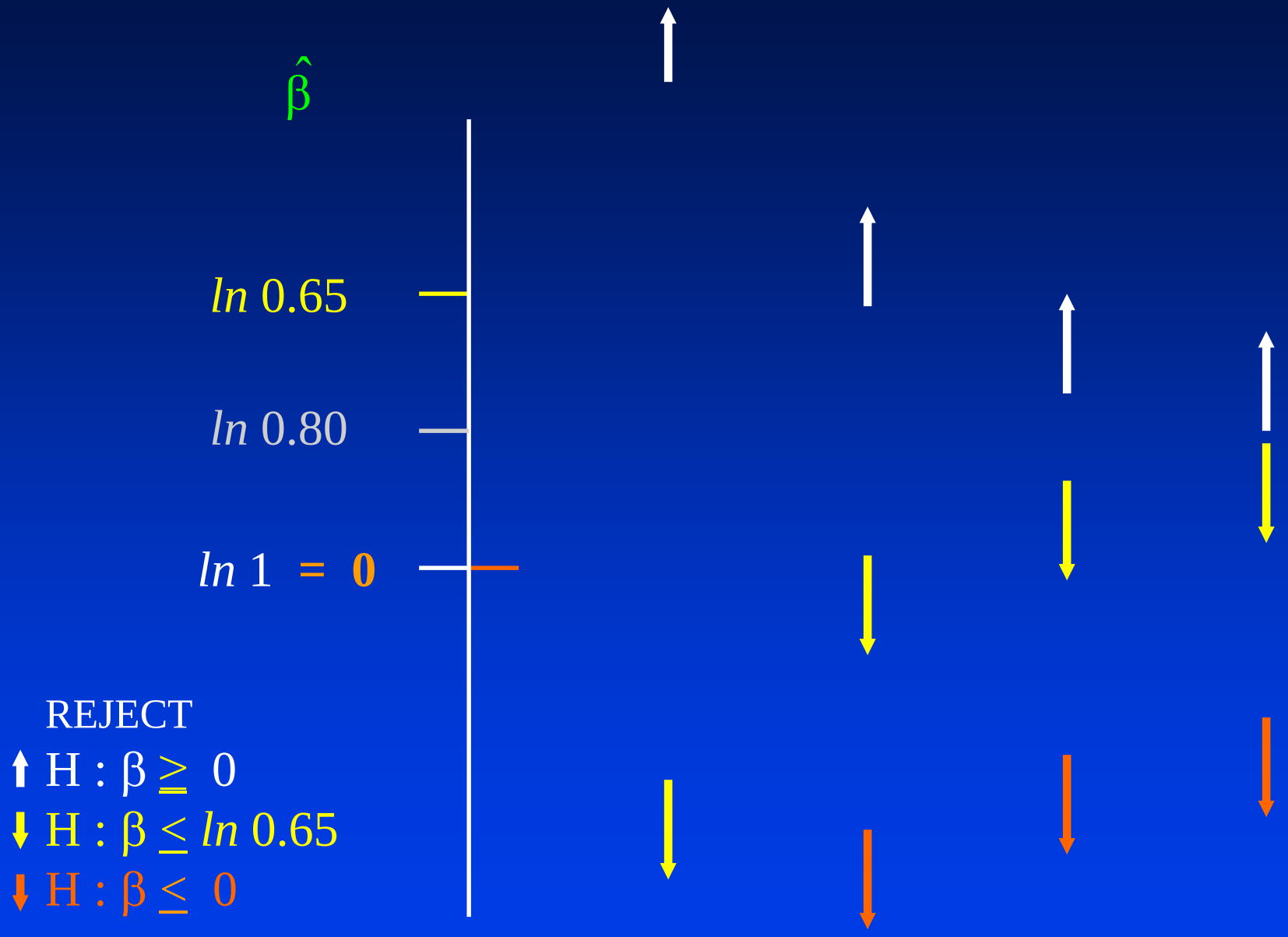
- How the O'Brien-Fleming guideline works:
  Arriving at recommendations about
  early termination of clinical trials

  ~ 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

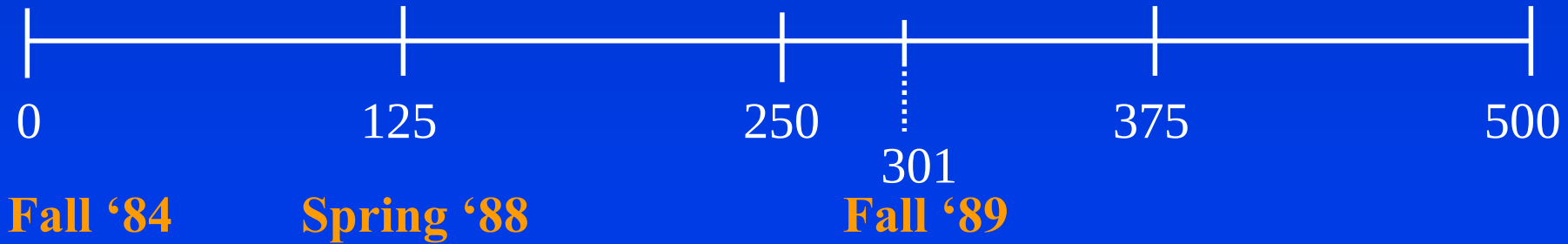
Fall '89
Survival: p = .003 < .005
Recurrence: p = .0001

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

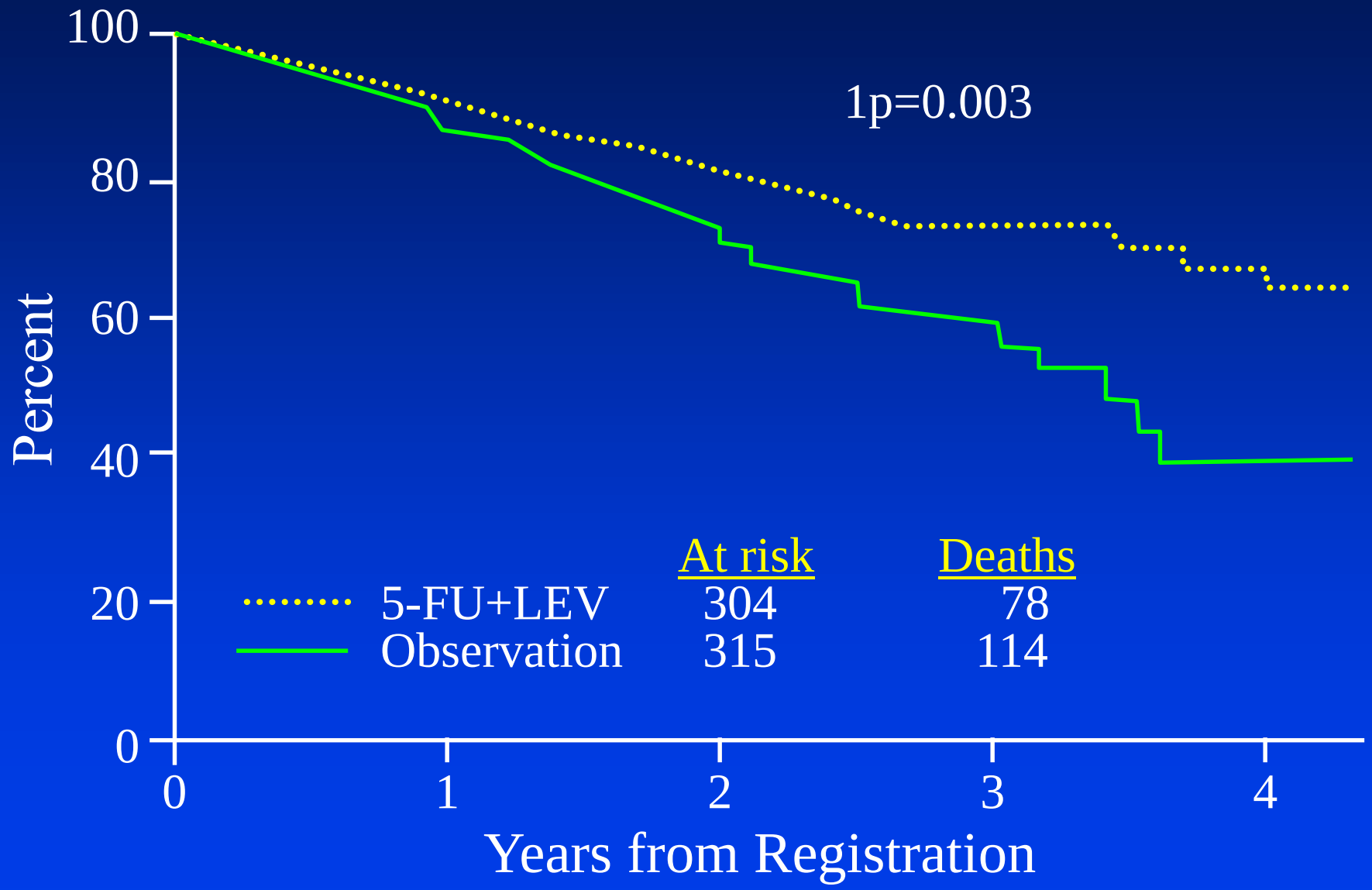
AFTER

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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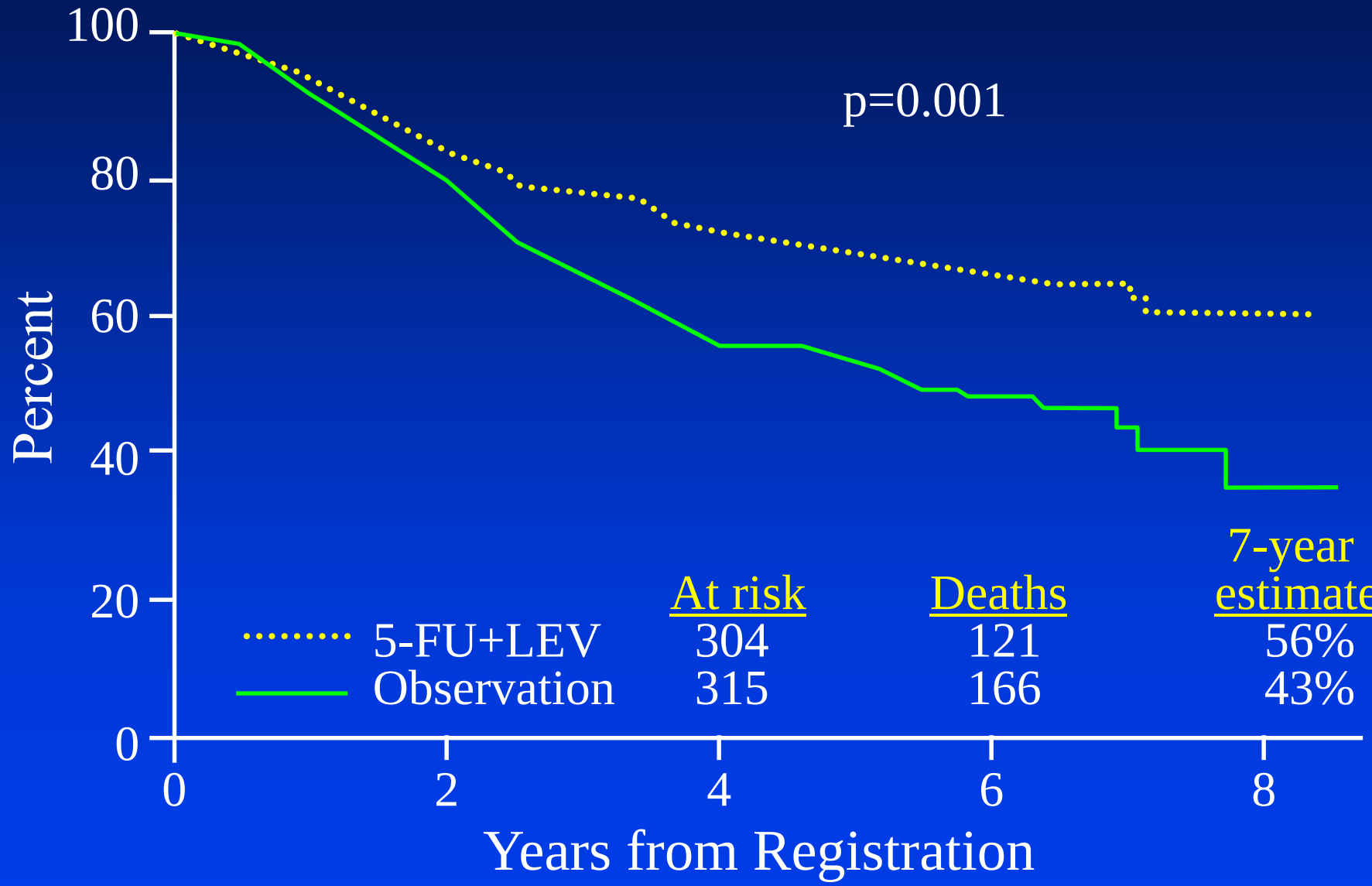

Types of Meetings of the Data Monitoring Committee

- **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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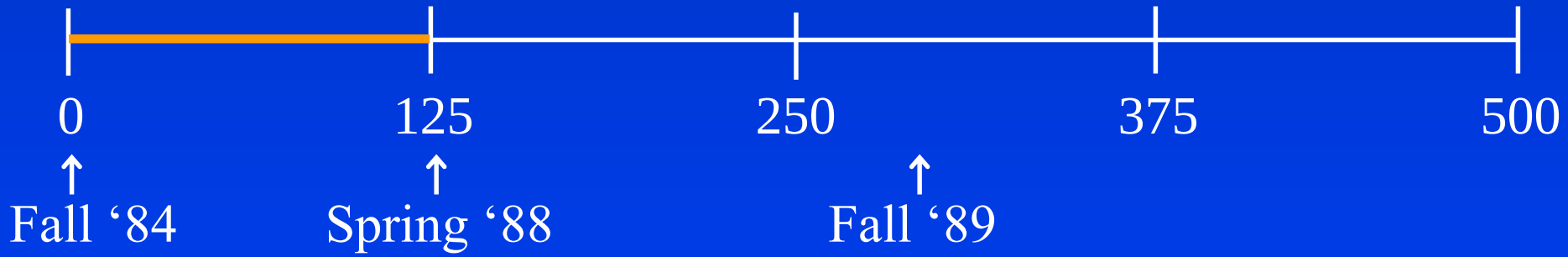
Follow-up to 500 deaths

Four look O'Brien-Fleming design

≈ 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
- Early Safety/Trial Integrity Reviews
- **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

DMCs and other Oversight Bodies: Relative Responsibilities and Relationships

- **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
  - Real time Monitoring of SUSARs & SAEs
- **Data Monitoring Committees**
  - Sole access during conduct of the clinical trial to:
    - Aggregated efficacy/safety data across the trial
    - Unblinded by treatment group

An Opinion:

The DMC process

for monitoring randomized clinical trials

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

…The Emergence of Some Common Myths
can adversely impact DMC Independence…

A Dozen Common 'Myths' that can Adversely Impact DMC Independence

- DMCs procedures must rigidly follow the DMC Charter
- DMCs use '*stopping rules*', not '*monitoring guidelines*'
- The # & timing of DMC meetings are fixed in advance
- Content of DMC reports is rigidly pre-specified
- The DMC chair & statistician needn't have DMC experience
- DMC meetings always should begin with an **Open** Session
- The sponsor or CRO should lead the DMC **Open** Session
- DMC members are consultants for the trial's sponsor
- DMC members should indemnify the trial's sponsor & CRO
- Currentness of DMC reports is based on passive procedures
- DMCs should review '*blinded*' efficacy and safety data
- DMCs '*vote*' when developing their recommendations

Addressing Threats to the Independence of DMCs: An Outline of Topics to be Discussed

- **DMC Meeting Format**
- DMC Charter
- Currentness of DMC Data
- Training & Experience in the DMC Process
- Maintaining Confidentiality of Interim Data
- Blinding DMC Members
- DMC Member Contracts & Conflict of Interest
- Avoiding Conflict of Interest
- Indemnification of the DMC
- Conclusion: What should be done?

Current Concerns: 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 has lead responsibility to finalize the DMC Charter

Current Concerns: DMC Charter

- DMC Charters should be a set of *guidelines* and *principles*, not a *legal contract*; they are getting longer…
- Sponsor's control: '*limit # of looks at outcome data*', saying '*don't spend any alpha*', '*just review safety*', etc.
- Some sponsors budget for fixed number of meetings, & don't allow flexibility in format/content of DMC reports
- Some refer to *voting* rather than *consensus development*
- Sponsor compulsion about documentation, rather than empowering the DMC regarding its main mission
  - Frequent updated and signed CVs
  - Constantly changing the DMC Charter

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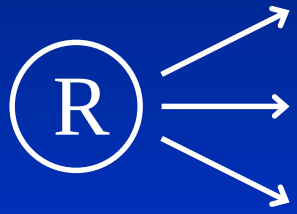
Current Concerns: Currentness of DMC Data

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

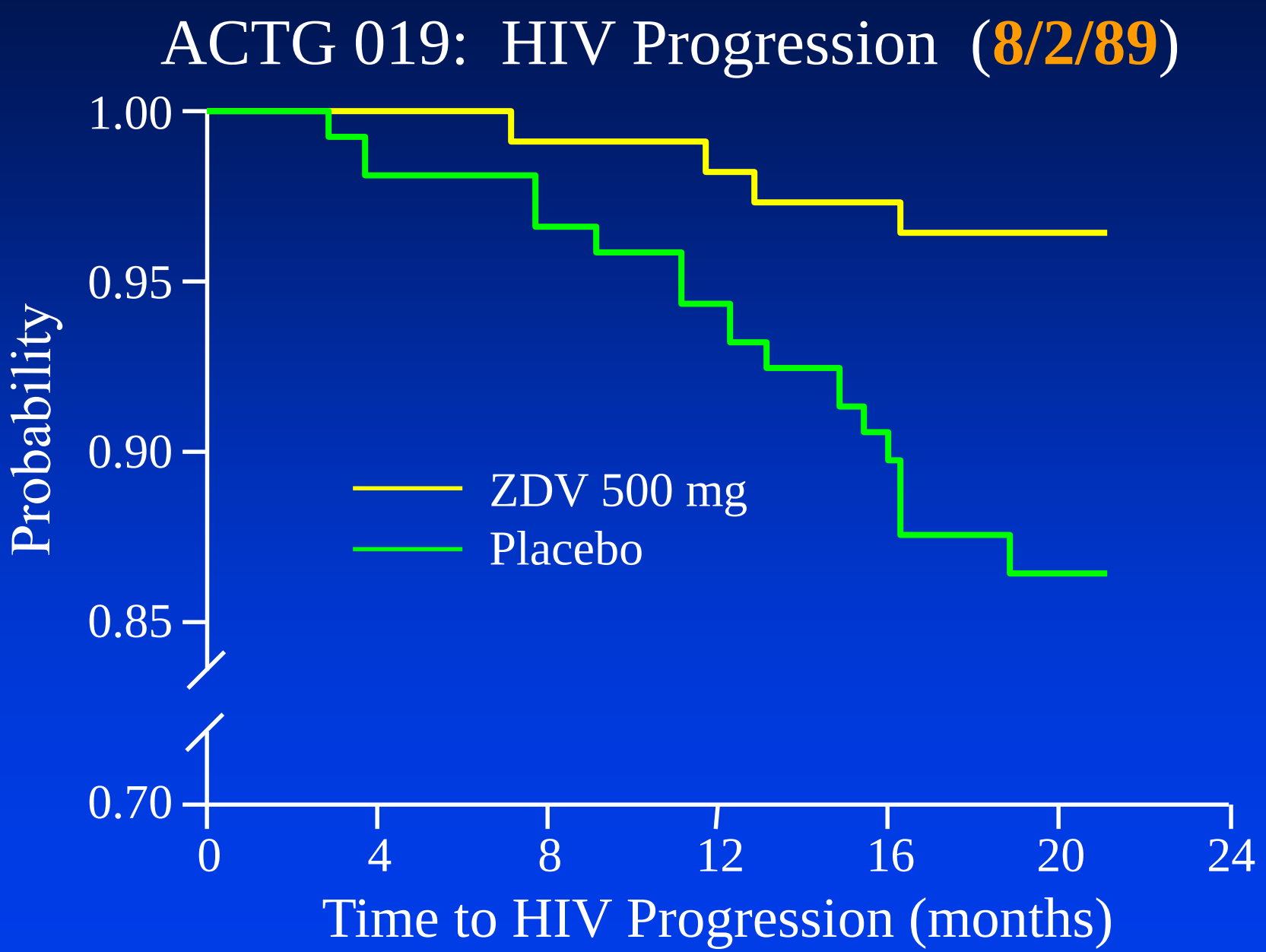
8/16/92 Updated Analysis

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

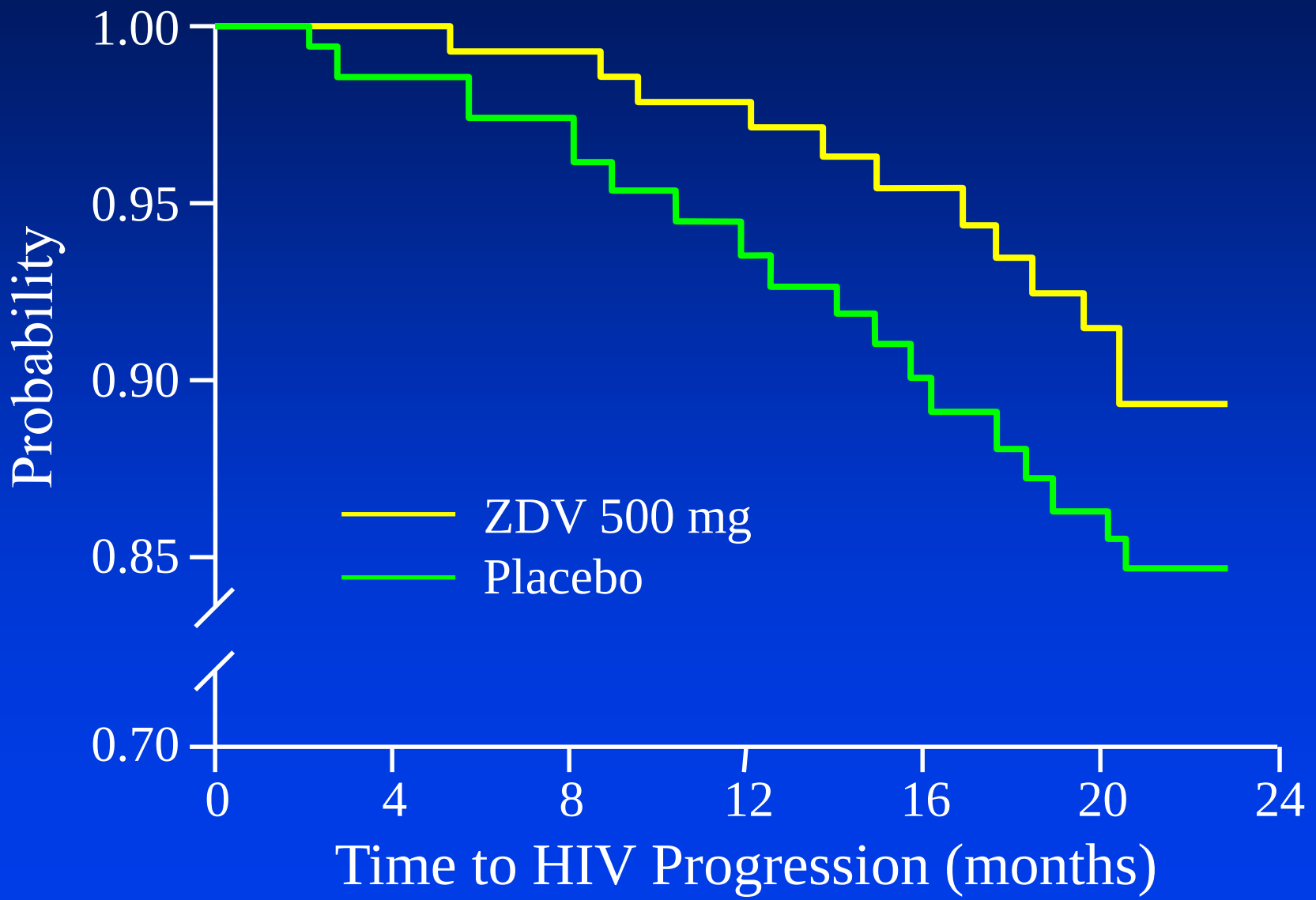
O'Brien-Fleming: .005

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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Current Concerns: Expertise in DMC Processes

- DMC chairs
  - Some DMC chairs don't realize they should take leadership:
    …in planning the DMC meeting,
    …*in the conduct of the DMC **Open** as well as **Closed** Session,*
    …in developing and finalizing the DMC Recommendations & DMC 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

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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):

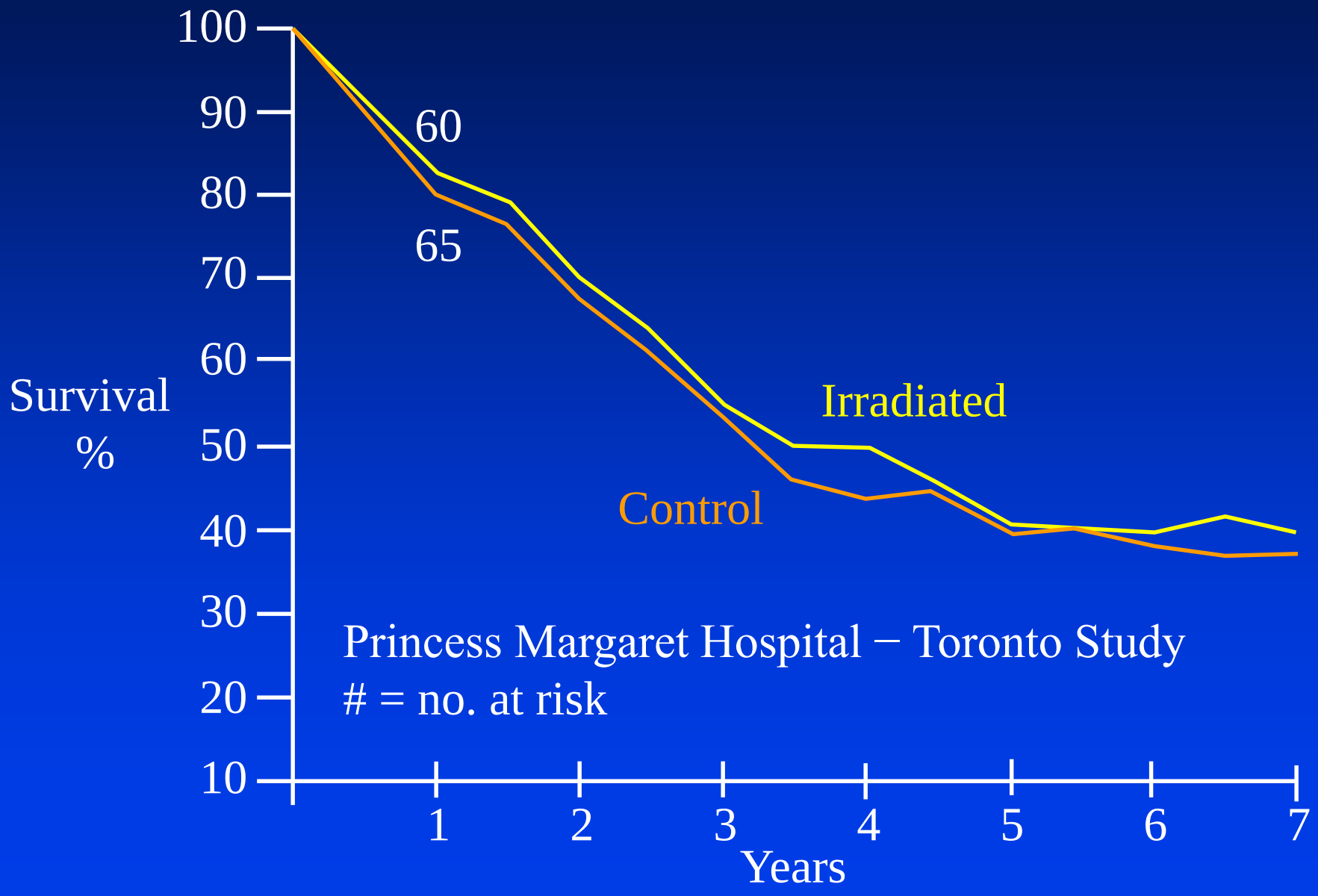
- to investigate existing processes of monitoring accumulating data
- to identify ways of improving the DMC process.

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

Evidence from Cooperative Group Studies

Cooperative Group DMCs	NCCTG YES	SWOG 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 Preventing Breaches in Confidentiality

- Reduce Risk of Pre-judgment
- Reduce Risk of Declining Enrollment
- Reduce Risk of Altered Adherence
- Maintain Commitment to Capturing Outcome Data and Maintain Integrity of Subsequent Data Evaluation
- Protect Flexibility to Modify Trial Design Based on Insights from Emerging External Data
- Reduce Risk of Early Release of Misleading Results

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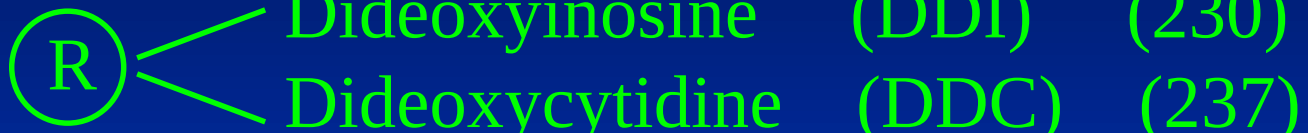
CPCRA #002 HIV Infected Patients who are AZT Intolerant/AZT Failures



Outcome:

Time to AIDS/Death

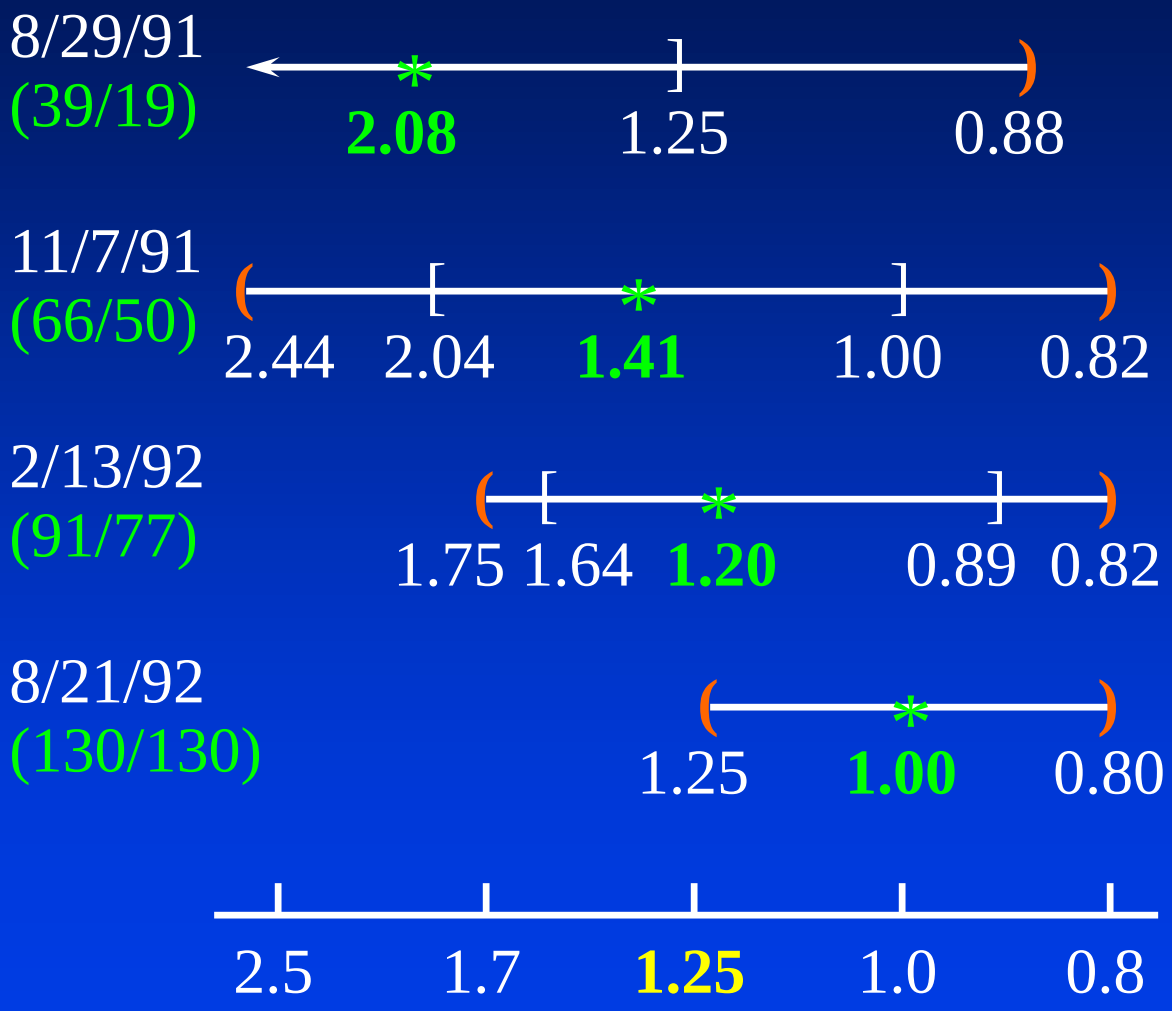
Enrollment: 12/90 - 9/91

DMC Efficacy Interim Analyses:

Approximately at increments of 60 events

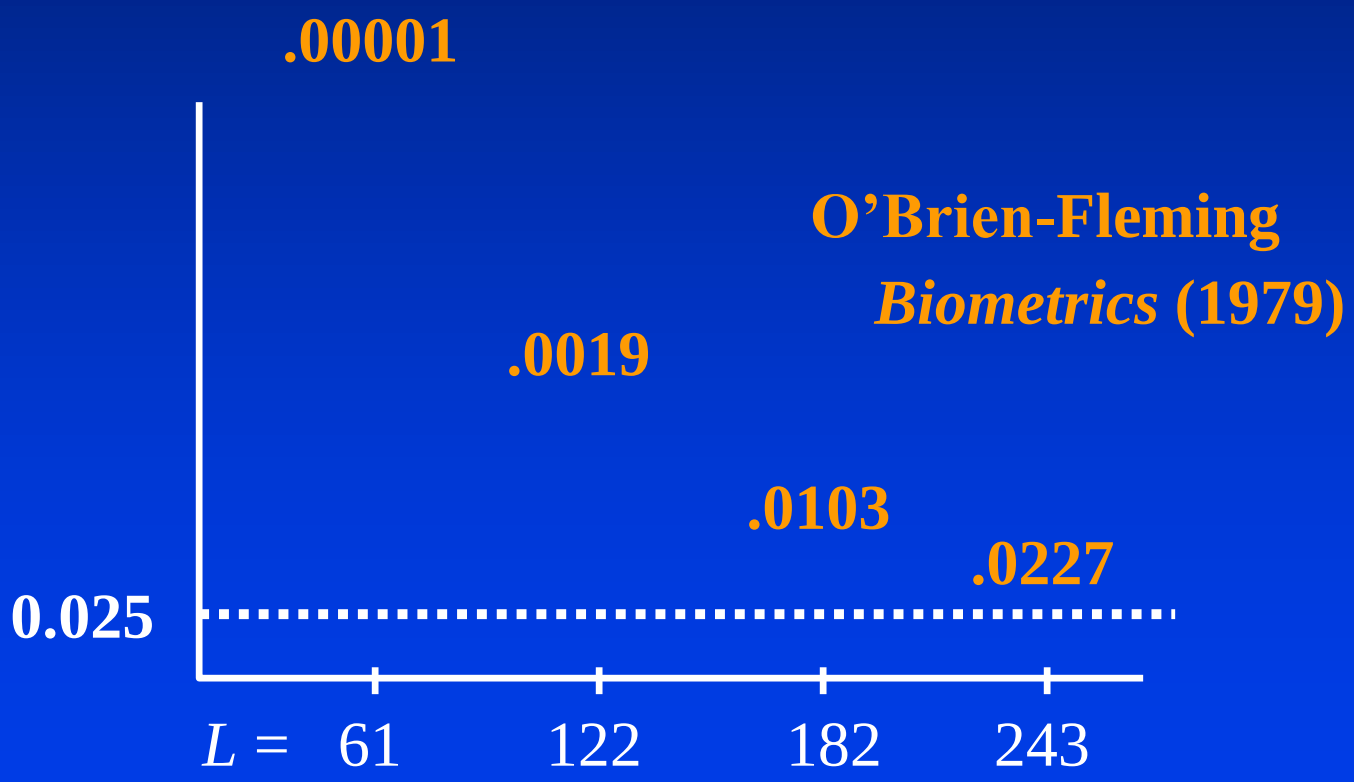
(Protocol: Follow-up until 243 events)

ddC/ddI: Rate of Progression to AIDS/Death

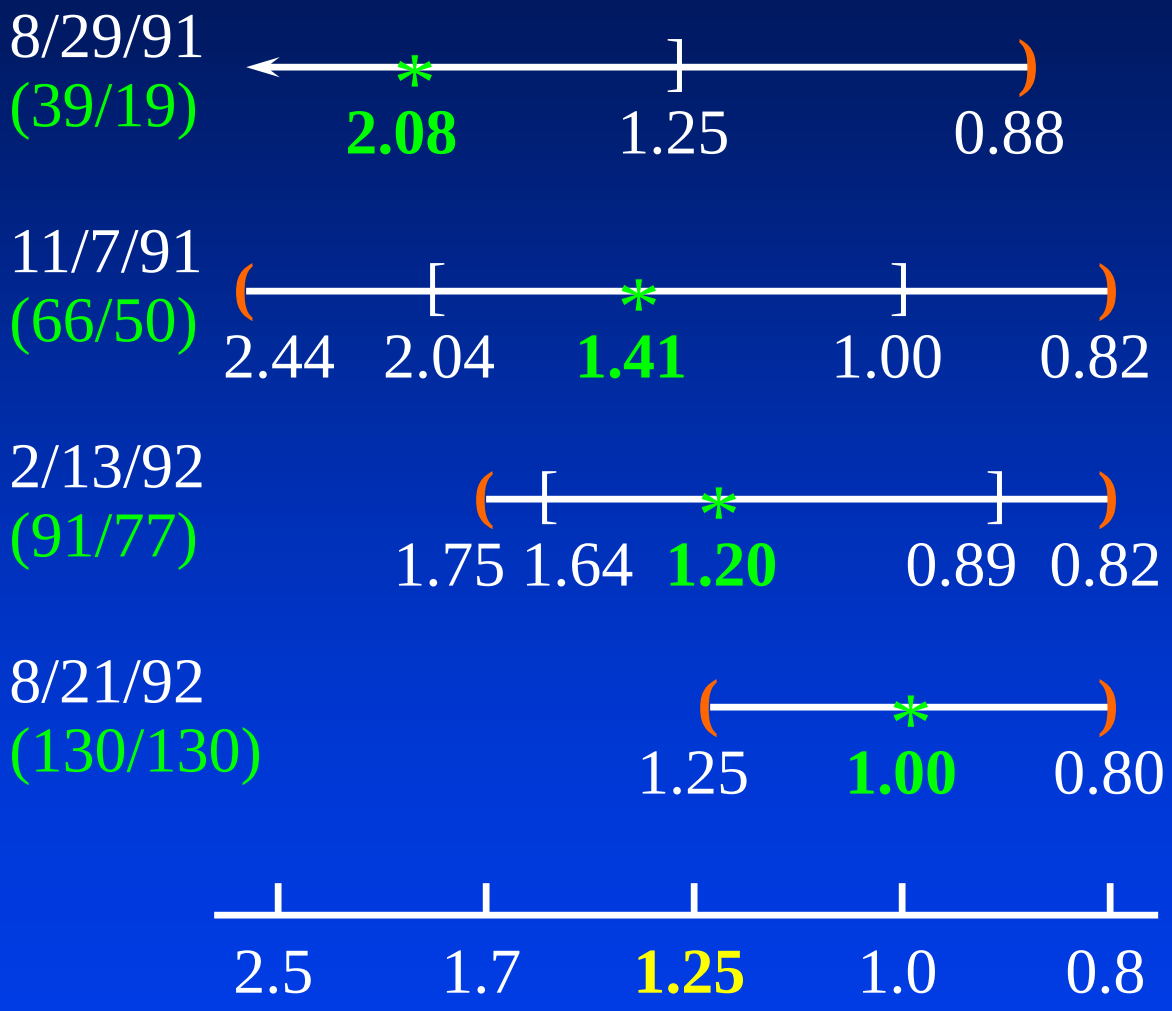


O'Brien-Fleming Group Sequential Boundary

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



ddC/ddI: Rate of Progression to AIDS/Death



"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 CVD/S/MI
At 378 events: ***1.4*** Margin for CVD/S/MI

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

	CVD S MI	CVD	Non CV D	D	S	MI	D S 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**

	CVD S MI	CVD	Non CV D	D	S	MI	D S 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**
"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**

	CVD S MI	CVD	Non CV D	D	S	MI	D S 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**
***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**

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

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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)	

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		July 1995 CPCRA #023	
	Rx	PLA	Rx	PLA	Rx	PLA
n	486	239	646	327	662	332
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)	

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?

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…

Addressing Threats to the Independence of DMCs: An Outline of Topics to be Discussed

- DMC Meeting Format
- DMC Charter
- Currentness of DMC Data
- Training & Experience in the DMC Process
- Maintaining Confidentiality of Interim Data
- **Blinding DMC Members**
- DMC Member Contracts & Conflict of Interest
- Avoiding Conflict of Interest
- Indemnification of the DMC
- Conclusion: What should be done?

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

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

  …DMC recommended immediate termination

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Current Concerns: DMC Contracts and COI

- To avoid creating unnecessary Conflicts of Interest,
  (e.g, re. developing treatment guidelines, serving on FDA ACs)

  …DMC members do not work for the sponsor…

  DMC members should be engaged by an entity that is independent from the trial sponsor

- DMC member contracts are becoming very long and legal looking – very one sided – should be simple without needing a lawyer to review – should cover:

  - Confidentiality
  - Intellectual Property
  - Consulting Rate
  - Indemnification

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- **Avoiding Conflict of Interest**
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- Conclusion: What should be done?

Current Concerns: Avoiding Conflicts of Interest

- To further avoid creating unnecessary Conflicts of Interest:

  - ✓ DMC members should not socialize with the sponsor or study investigators, (e.g., pre meeting dinners)
    - "loose lips" and "body language"
  - ✓ DMC meetings should not be in resorts or exotic locations
    - Chicago O'Hare Hilton is good enough
      - perception of independence

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- Avoiding Conflict of Interest
- **Indemnification of the DMC**
- Conclusion: What should be done?

Current Concerns: Indemnification of the DMC

- DMC Indemnification
  - ✓ Sponsors/CROs often propose the DMC insure them
  - ✓ DMCs cannot function if worried about litigation
- 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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- Avoiding Conflict of Interest
- Indemnification of the DMC
- **Conclusion: What should be done?**

What Should Be Done?

- Turn the tide on making the DMC process more complicated than it needs to be…

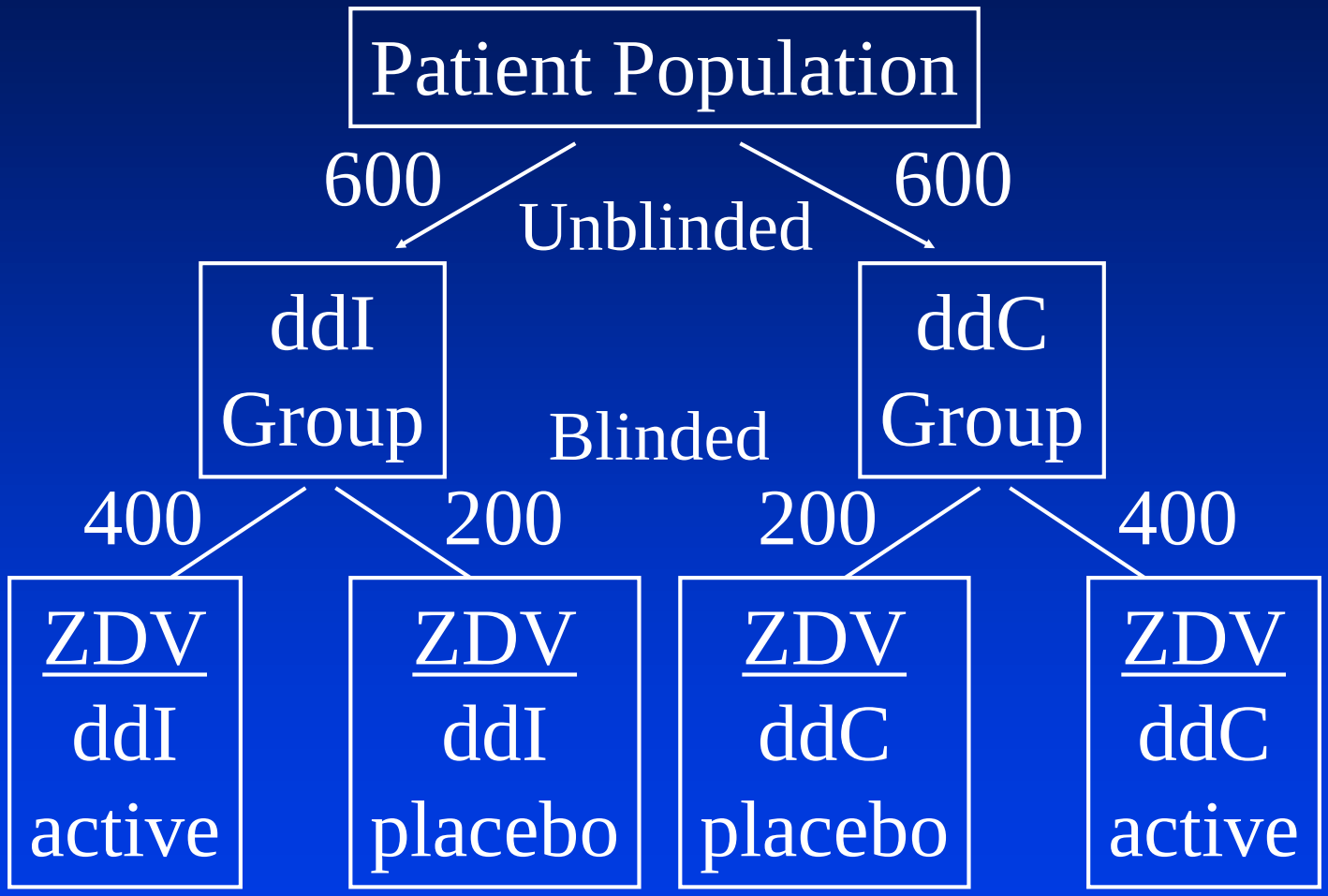
  Implementing rigid and legalistic procedures isn't consistent with the proper objective of protecting the integrity of independent oversight

- Training, training, training…
  - ✓ Textbooks, articles, courses etc.
  - ✓ Apprentice approach to train future DMC members
    - ➢ *DMC chairs* and *DMC statisticians*
    - ➢ Sponsors & their designated '*DMC Meeting Coordinators*'
    - ➢ *Statistical Data Analysis Centers* supporting DMCs
    - ➢ *Regulators*…Seek opportunities for membership on DMCs

What Should Be Done?

- Implement Creative Approaches & Current Best Practices
  - Consider beginning DMC meetings with **Closed** Sessions
  - The DMC Chair should lead the DMC **Open** Sessions
  - When possible, have independent entities engage DMC members
  - Reduce Conflict of Interest when planning meeting venues/events
  - DMC members should have proper indemnification
  - Active (not passive) approaches are needed for data capture and adjudication to ensure currentness to the '*clinical cut date*'
  - The DMC should be unblinded in its review of **Closed** Reports
  - DMC Recommendations: '*consensus development*', not '*voting*'
  - Regulators should ensure confidentiality of interim data on primary endpoints if obtained from ongoing clinical trials
  - Regulators should provide co-leadership in ensuring necessary steps are taken to protect DMC independence.

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