

# Summer Institute in Statistics for Clinical Research

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## Data Monitoring Committees

July 28, 2017

**Thomas R. Fleming, Ph.D.**

*Professor, Dept. of Biostatistics*

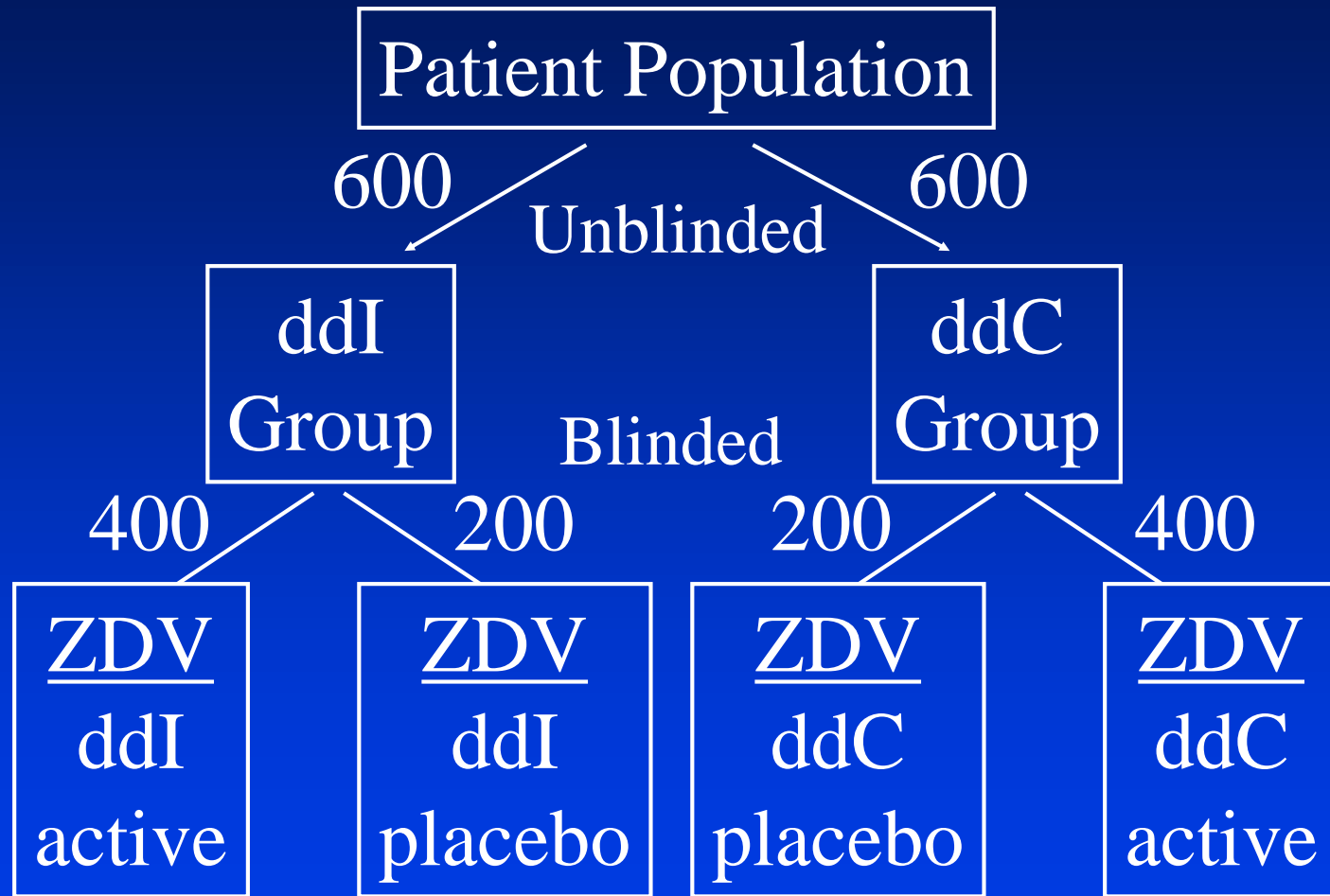
*University of Washington*

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

# Mission of the DMC

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# CPCRA #007: Study Design



# CPCRA #007: 5/92 - 5/95

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

# CPCRA #007:

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

---

	<u>ZDV</u> ddI Active	<u>ZDV</u> ddI Placebo
n	337	172
Prog/Death	55	42
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All Events	92	73

# Mission of the DMC

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- 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

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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

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- 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

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- 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

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Duke's C

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

Outcome:

Survival Time, Time to Recurrence

Follow-up to 500 deaths

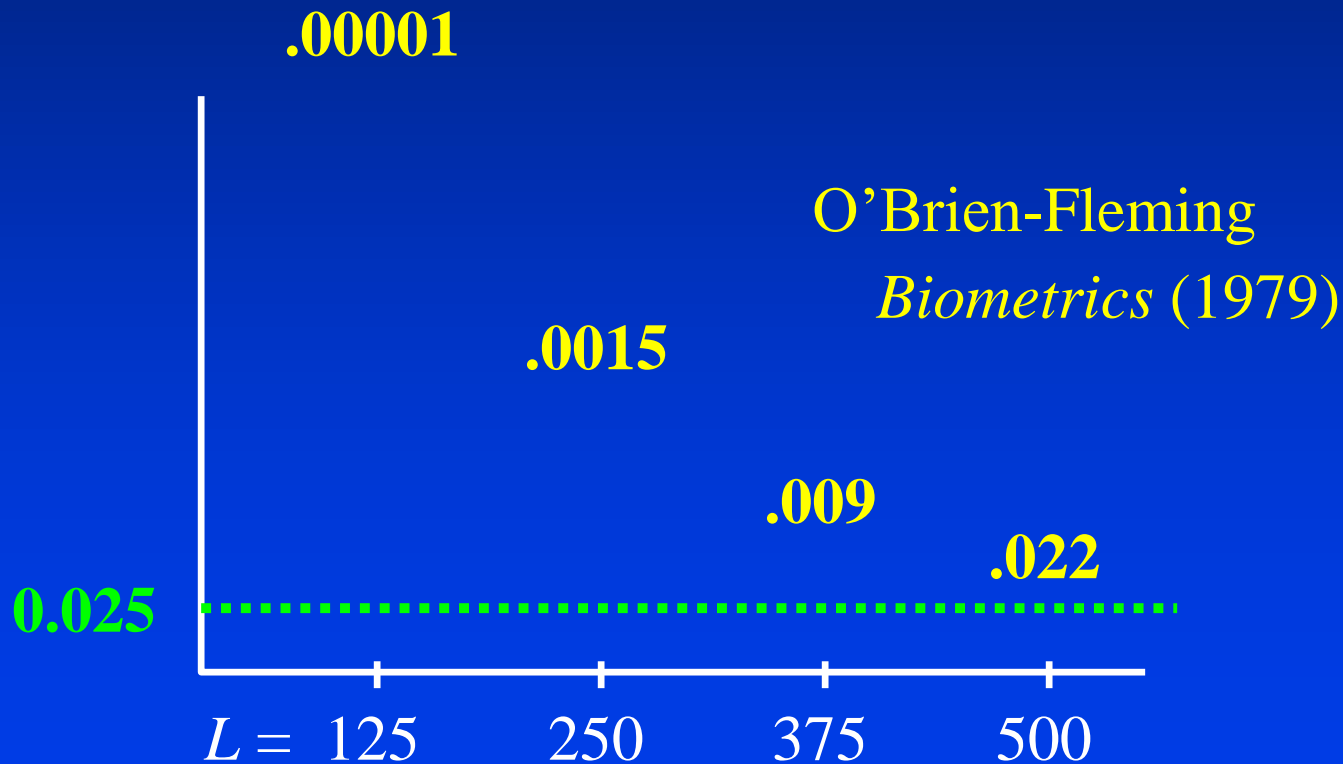
**Four look O'Brien-Fleming design**

**... one every 125 deaths**

# O'Brien-Fleming Boundary

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

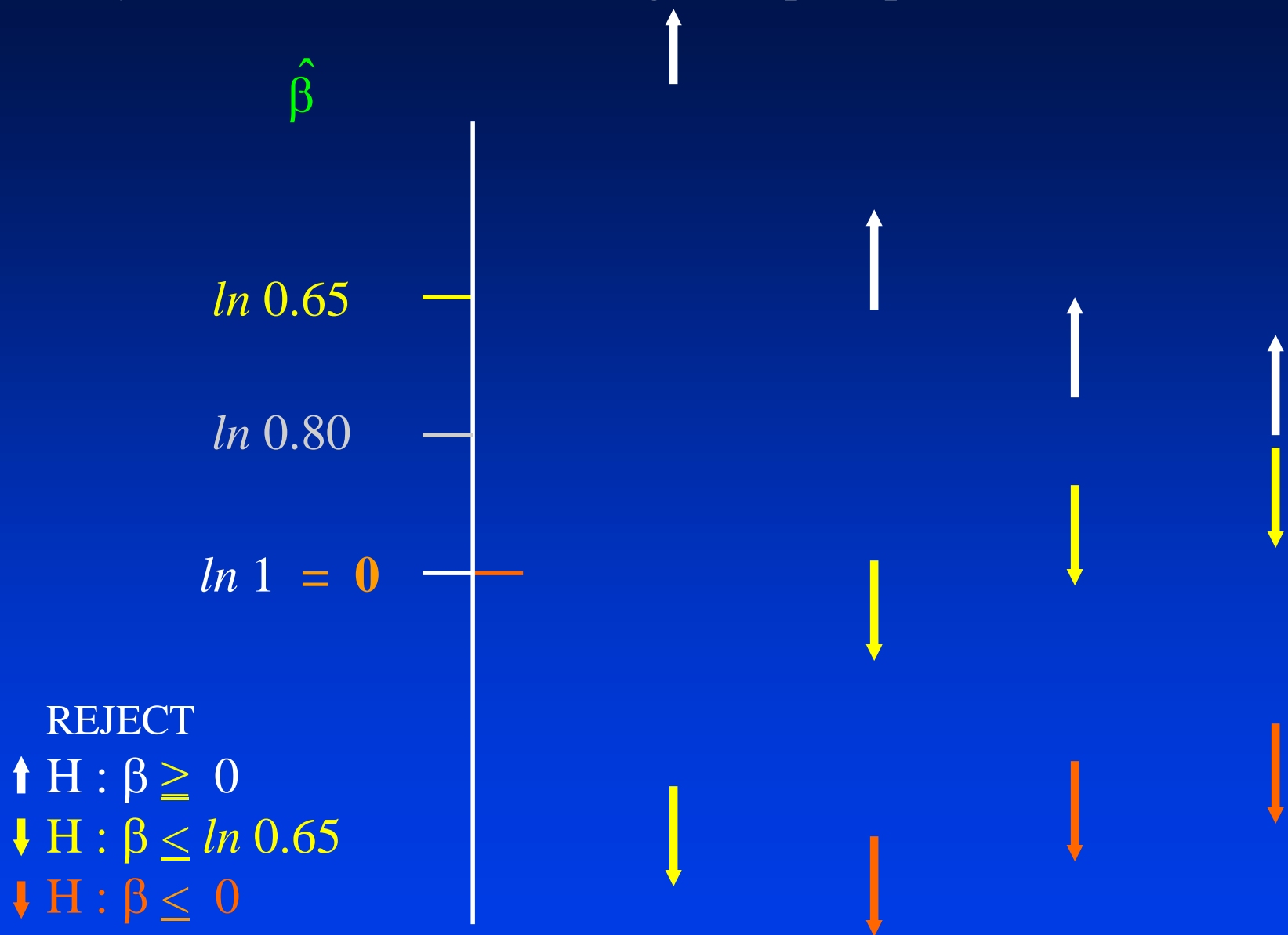


# Monitoring Clinical Trials

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- 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**



**Fall '84**

**Spring '88**

**Fall '89**

# Consequences of Fall 1989 Release of Results:

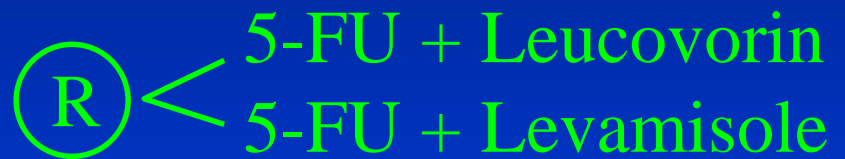
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- Immediate re-design of next generation  
Colon Adjuvant Trial

BEFORE



AFTER

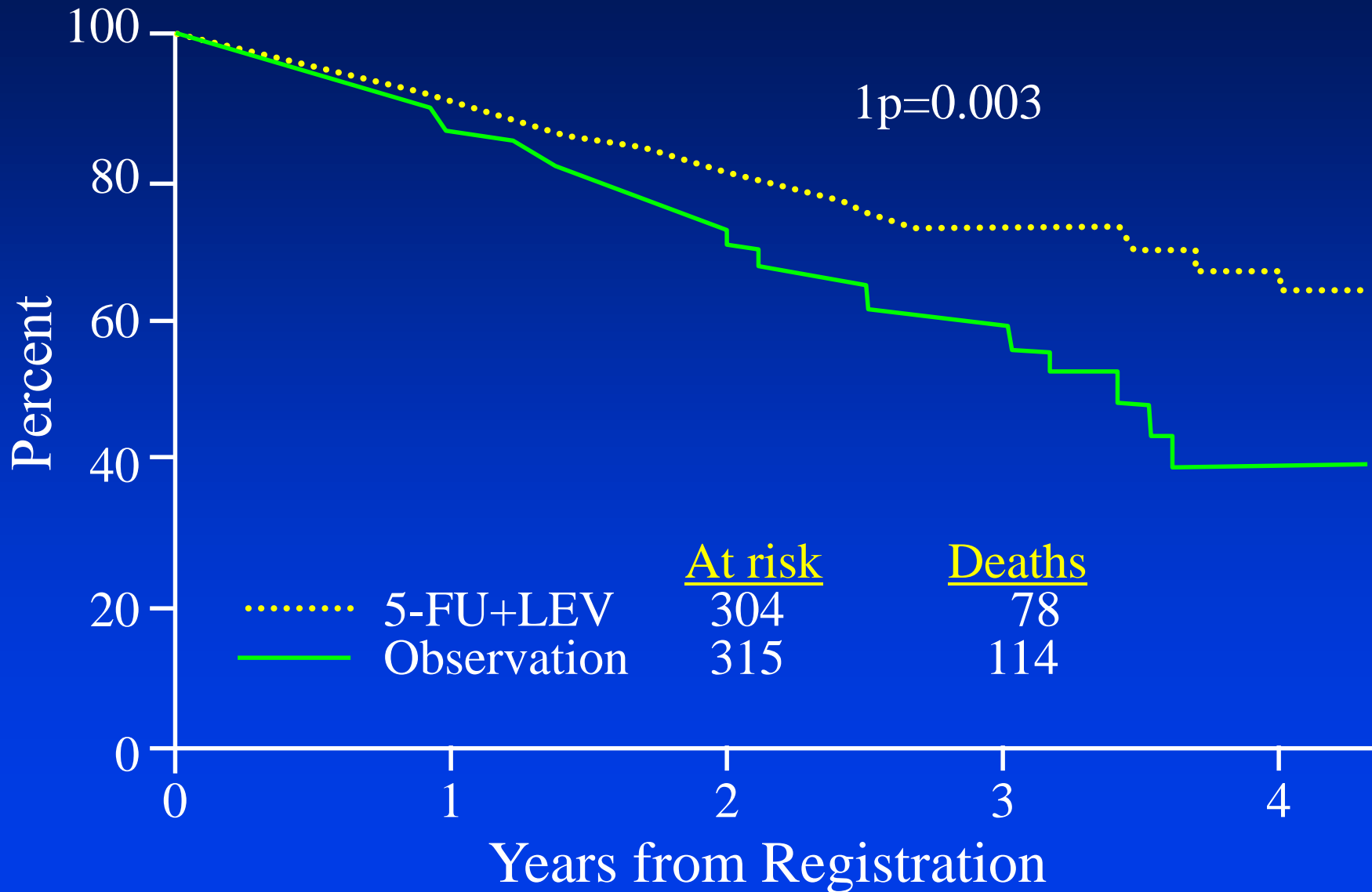


- 1990 FDA Approval of Levamisole NDA

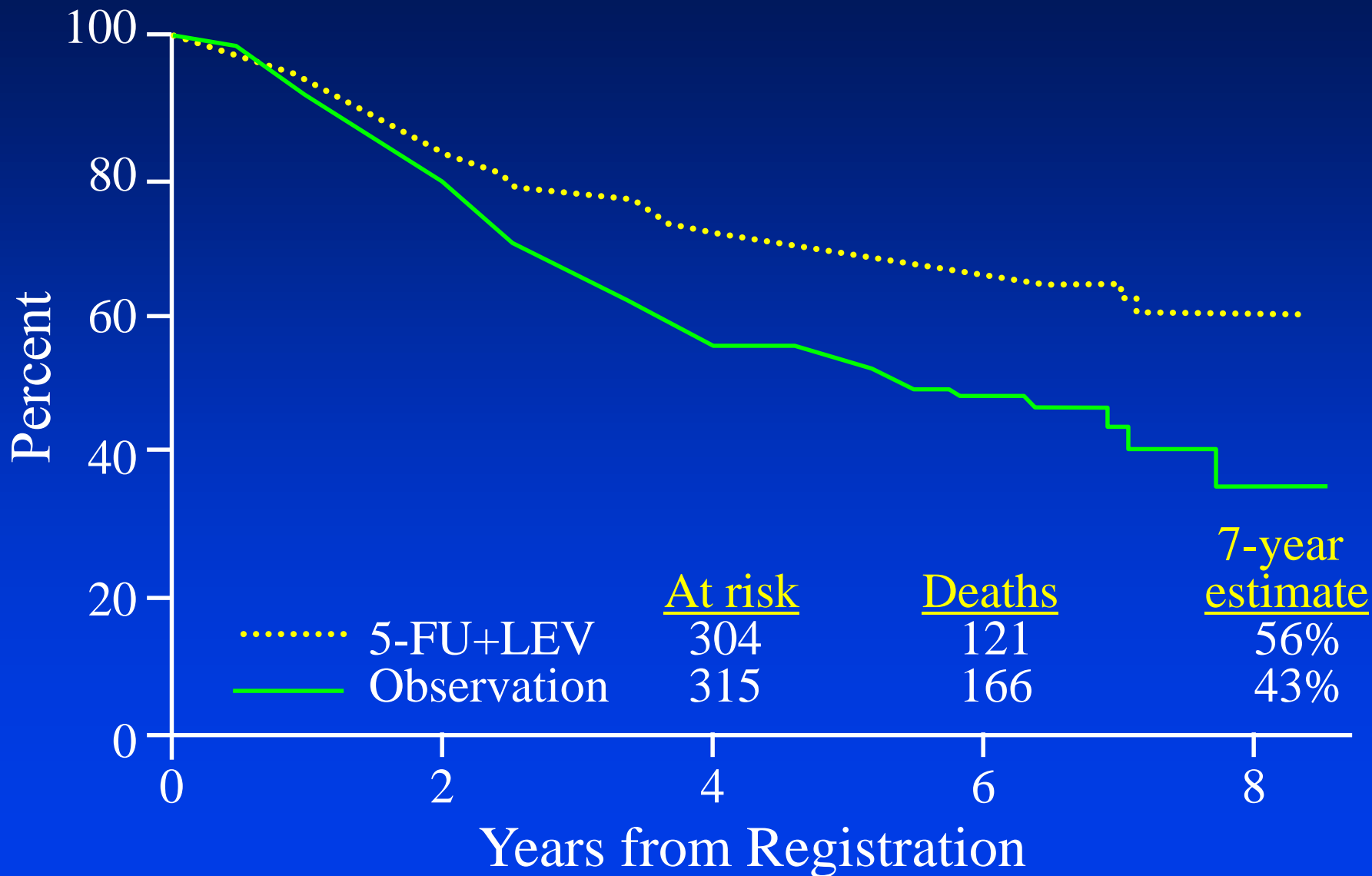
Follow-up continued through March, 1993  
Median follow-up increased  
from 3 years to > 6 years



# Duke's C Colon Cancer Overall Survival



# Duke's C Colon Cancer Overall Survival



# Types of Meetings of the Data Monitoring Committee

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

# Organizational Meeting

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## 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)

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## 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

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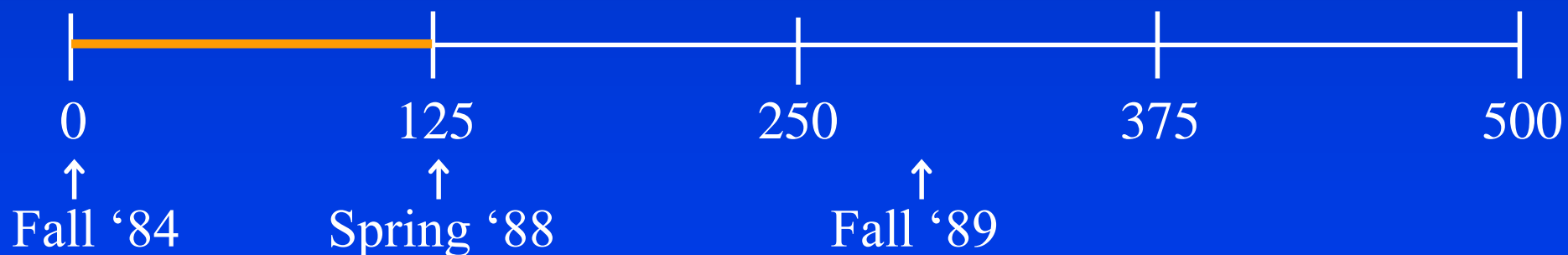
Eg. Cancer Intergroup # 0035: Colon Adjuvant

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Follow-up to 500 deaths

Four look O'Brien-Fleming design

≈ every 125 deaths





# Safety/Trial Integrity Reviews

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- 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

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

# Formal Interim Analyses

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- **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

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- **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

## Summary:

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*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

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- 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 Hennekens, JD Neaton, GD Pearson, TLG Andersson, MA Pfeffer, SS Ellenberg

# Proposed Best Practices and Operating Principles

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- 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

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- 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

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- 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

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- 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

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## ACTG 019: Asymptomatic HIV+ Patients CD4<500



Outcome:

Time to Advanced ARC, AIDS, or Death

Accrual initiation

July 1987

Interim analysis

August 1989

# Current Concerns: Currentness of DMC Data

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

<u>Rx</u>	<u>#</u> <u>Prog</u>	<u>Prog*</u> <u>Rate</u>	<u>P-value</u> <u>vs. placebo</u>
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

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

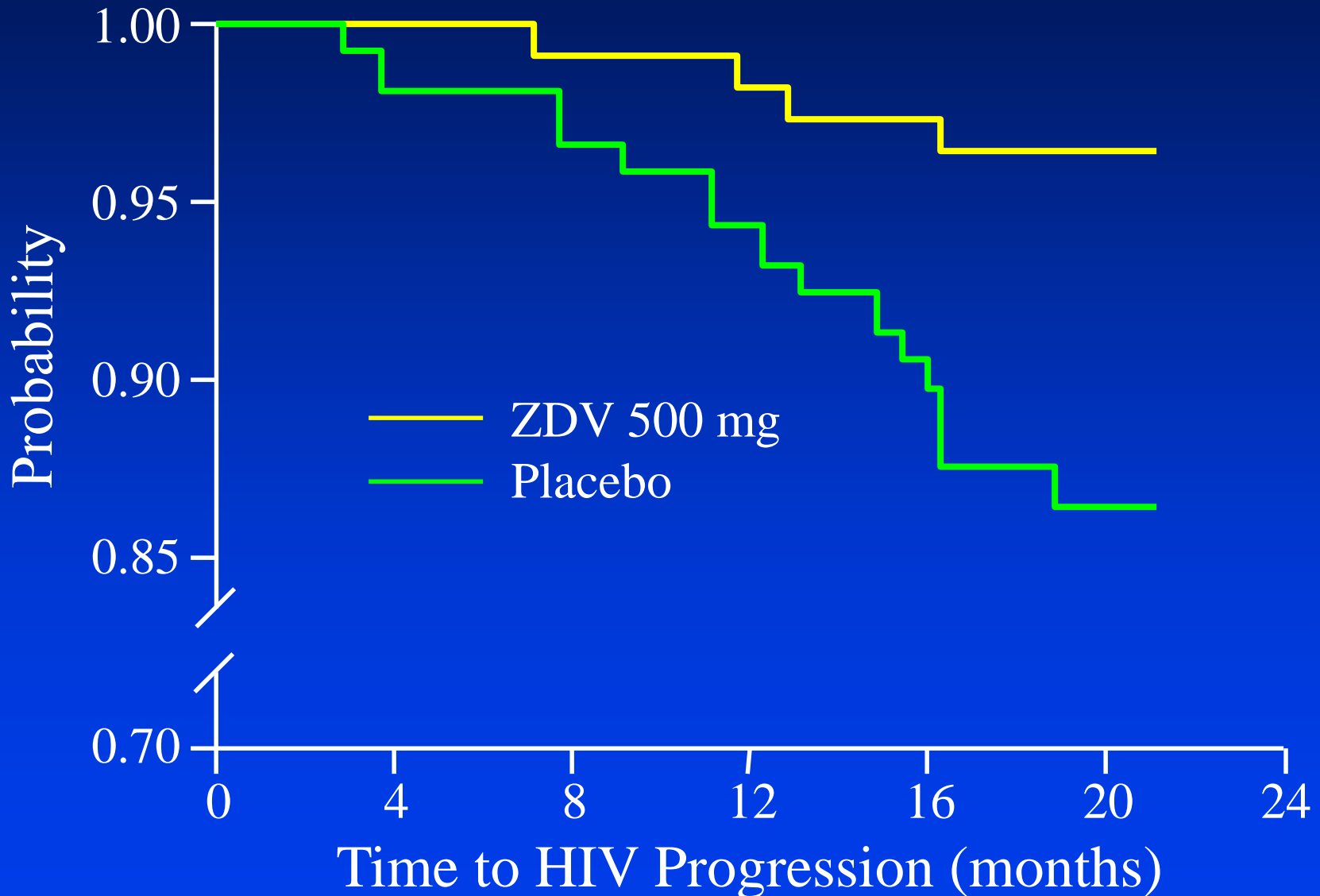
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O'Brien-Fleming: .005



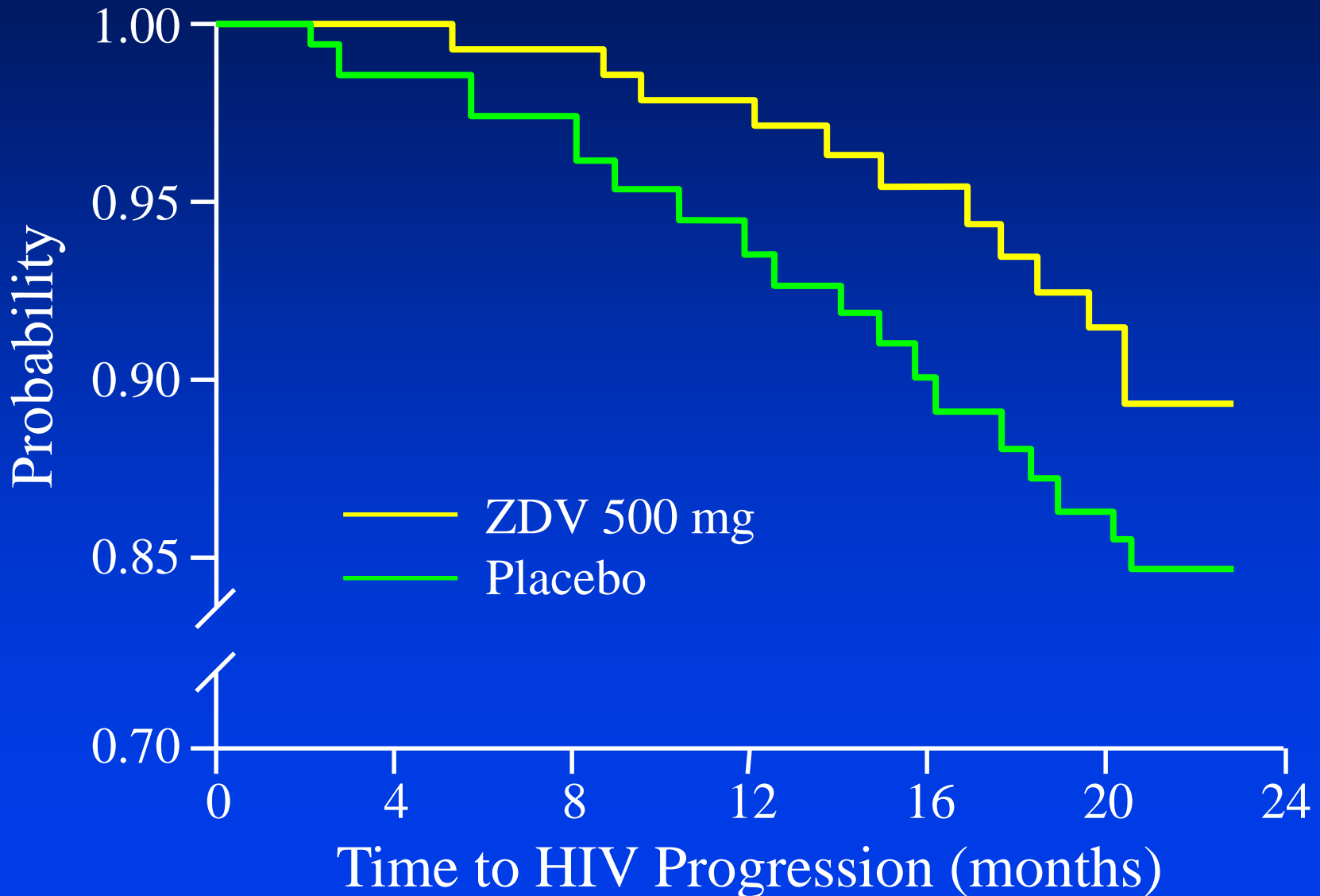
# Current Concerns: Currentness of DMC Data

## ACTG 019: HIV Progression (8/2/89)



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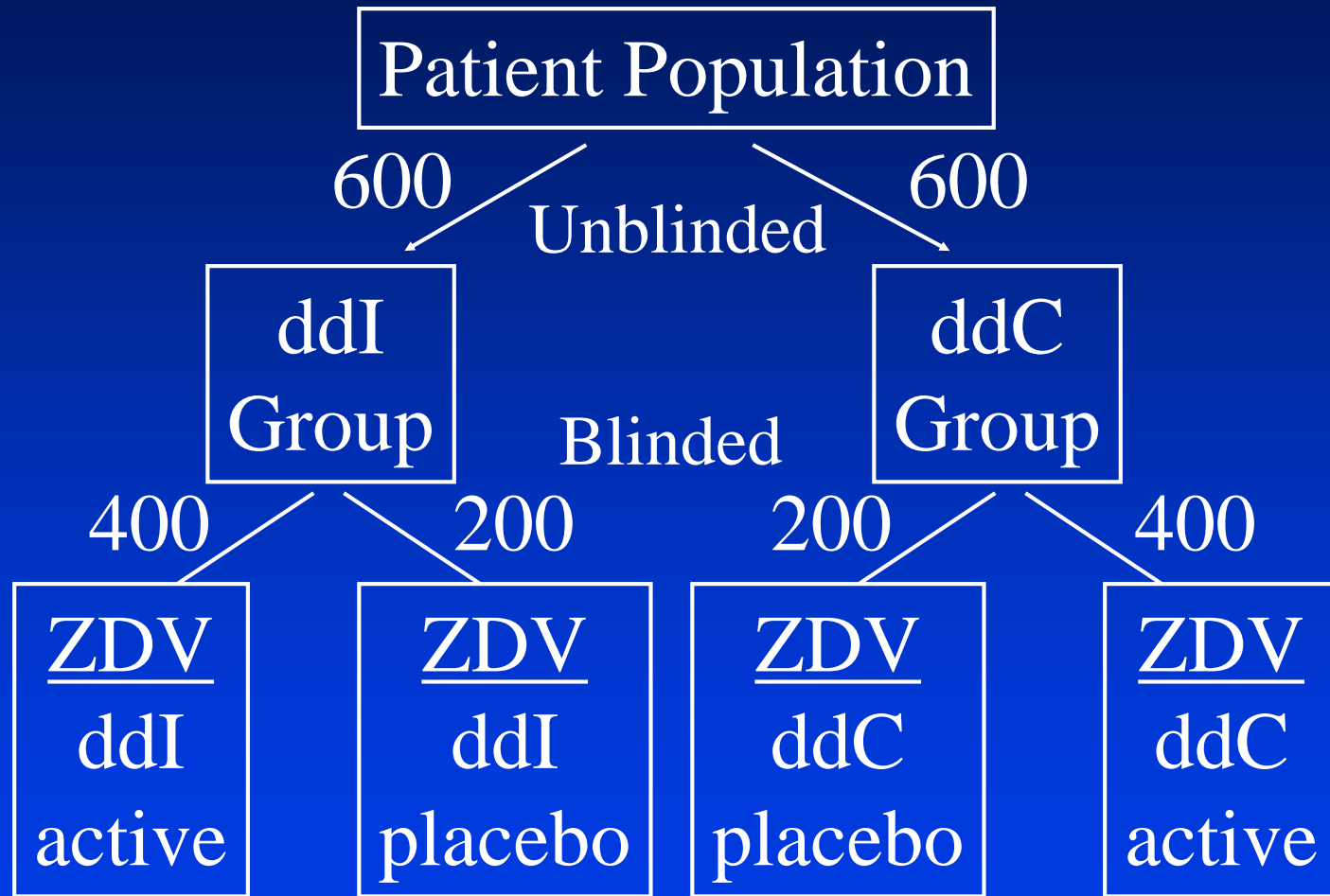
# Current Concerns: Currentness of DMC Data

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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*’

# CPCRA #007: Study Design



# Issues & Controversies: DMC ↔ DMC Data Sharing

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CPCRA #007:

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

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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

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## 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.

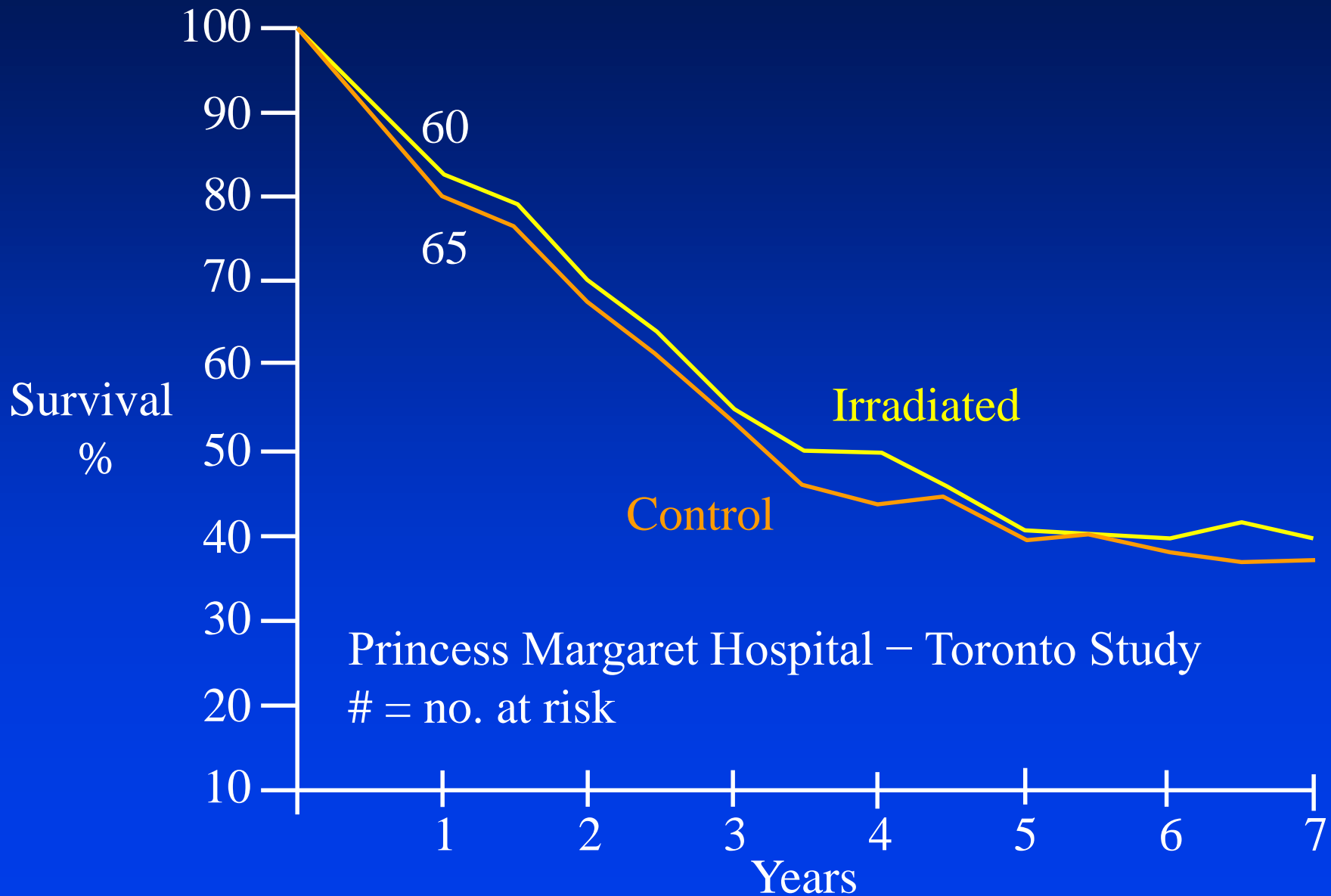
Grant, Altman, Babiker, et al. *Health Technology Assessment* 2005

# Evidence from NIH Cooperative Group Studies

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

# Survival of Patients with Rectal Carcinoma in Control and Irradiated Groups





# Enhancing Trial Integrity

## By Preventing Breaches in Confidentiality

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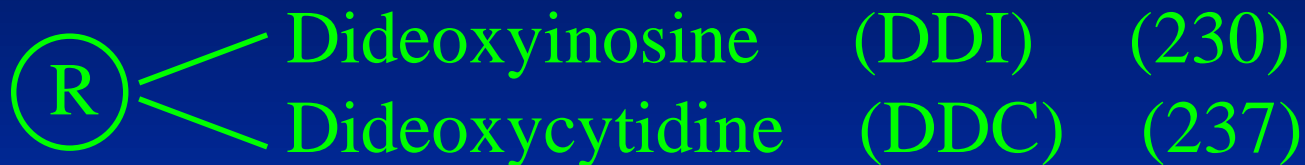
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# CPCRA #002 HIV Infected Patients who are AZT Intolerant/AZT Failures

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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



# “VALUE Trial”

## Hypertensive Patients at High Cardiovascular Risk

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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”

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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
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**“1<sup>st</sup> Quadrant”: Up to *11/23/2013***

Contrave	35	5	5	10	7	24	40
Placebo	59	19	3	22	11	34	62
HR	<b>0.59</b>						<b>0.64</b>

	CVD S MI	CVD	Non CV D	D	S	MI	D S MI
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**“2<sup>nd</sup> 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	<b>≈1.29</b>						<b>≈1.30</b>



	CVD S MI	CVD	Non CV D	D	S	MI	D S MI
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**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	<b>0.95</b>						<b>1.02</b>

# Principles & Insights

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"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

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

	<u>July 1994</u> <u>SYNTEX #1654</u>		<u>July 1994</u> <u>CPCRA #023</u>	
	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

	<u>July 1994 SYNTEX #1654</u>		<u>July 1994 CPCRA #023</u>		<u>July 1995 CPCRA #023</u>	
	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

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

	<u>October 1998 EU Trial</u>		<u>October 1998 NA Trial</u>	
	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 <u>EU Trial</u>		October 1998 <u>NA Trial</u>		February 2000 <u>NA Trial</u>	
	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

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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

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- 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

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- 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

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- 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

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## 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

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- 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

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- 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

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- 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

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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

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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?

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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

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- 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

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- 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

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*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

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- 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

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- 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

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- Currentness of DMC data
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- **Implementing procedures to enhance DMC independence**
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  - ✓ **DMC contracting process**
- Defining the role of the Statistical Data Analysis Center

# DMC Contracting Process and COI

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- 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

# Proposed Best Practices and Operating Principles

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- Indemnification
- Currentness of DMC data
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
  - ✓ DMC meeting format
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  - ✓ 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

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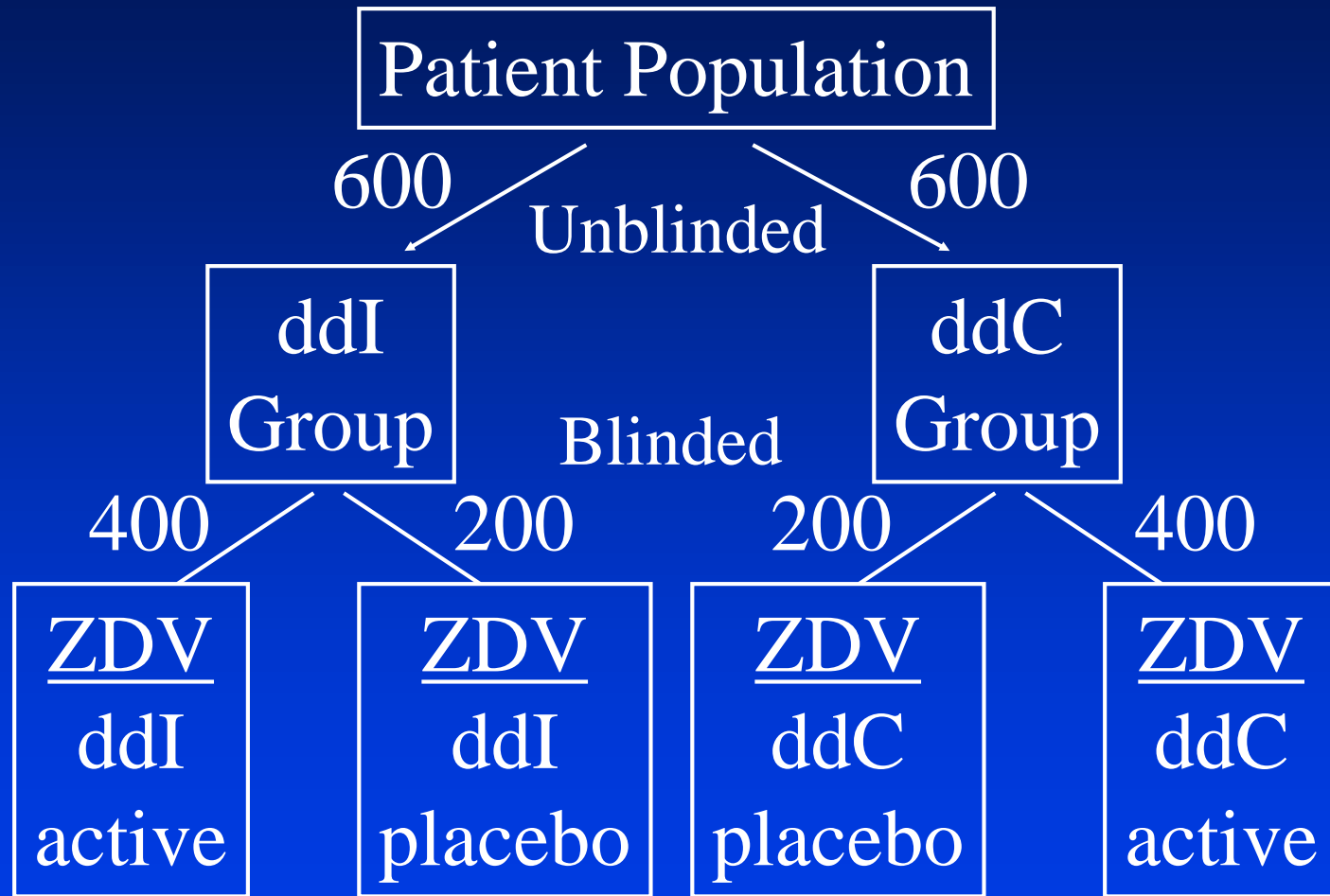
- The DMC relies on the DMC Open and Closed Reports, generated by independent statistician at the SDAC, for timely & accurate data on efficacy, safety, & quality of trial conduct
- The independent statistician at the SDAC should have *sufficient depth of knowledge* about the study at hand and *experience 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

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- 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

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CPCRA #007:

<u>11/93</u>	<u>ZDV</u> ddI Active	<u>ZDV</u> ddI Placebo	<u>ZDV</u> ddC Placebo	<u>ZDV</u> 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

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CPCRA #007:

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

