HPTN
HIV Prevention
Trials Network

Workshop on Clinical Trials

Monitoring Guidelines, Adaptive Methods & Data Monitoring Committees

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October 18, 2017

South Africa
Workshop on Clinical Trials

Obtaining insights

to recognize and effectively address scientifically challenging issues in

- Design
- Conduct
- Analysis/Reporting

of clinical trials

Workshop on Clinical Trials
October 16-17: Durban & Johannesburg

- Design of Clinical Trials
  - ***Biomarkers and Replacement Endpoints***
  - ***Designs using Active Controls:***
    Non-inferiority (NI) Trials
  - *Monitoring Guidelines & Adaptive Methods*
- Conduct of Clinical Trials
  - ***Addressing Missing Data in Clinical Trials***
  - *Data Monitoring Committees: Current Issues*
- Analysis/Reporting of Clinical Trials
  - ***Exploratory Analyses:***
    Why do we need particular caution?

Workshop on Clinical Trials
October 18: HPTN African Regional Meeting

- Design of Clinical Trials
  - *Biomarkers and Replacement Endpoints*
  - *Designs using Active Controls: Non-inferiority (NI) Trials*
  - ***Monitoring Guidelines & Adaptive Methods***
- Conduct of Clinical Trials
  - *Addressing Missing Data in Clinical Trials*
  - ***Data Monitoring Committees: Current Issues***
- Analysis/Reporting of Clinical Trials
  - *Exploratory Analyses: Why do we need particular caution?*

Workshop on Clinical Trials

- **Group Sequential Guidelines**

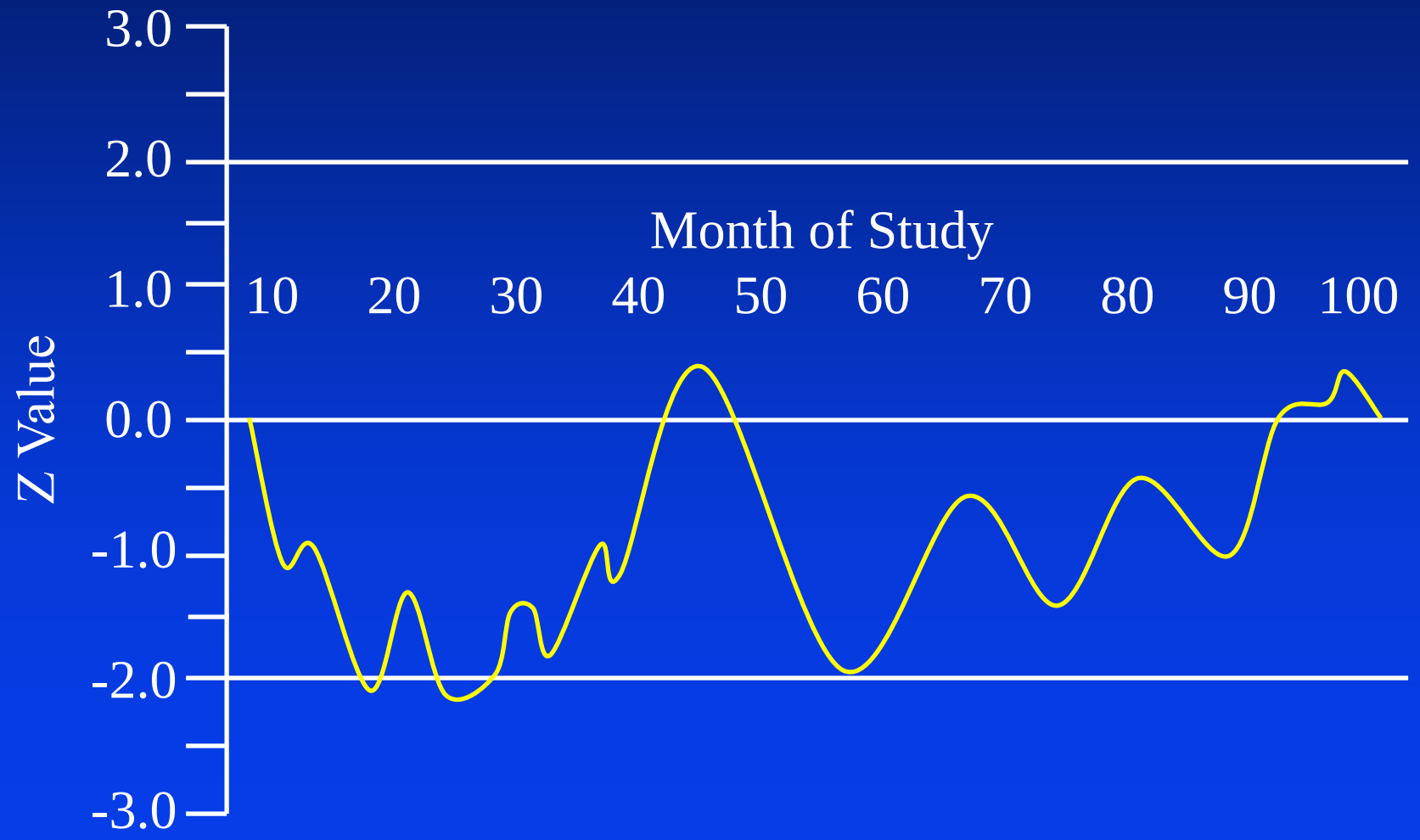
  Moertel's Query

- Adaptive Methods

- Data Monitoring Committees

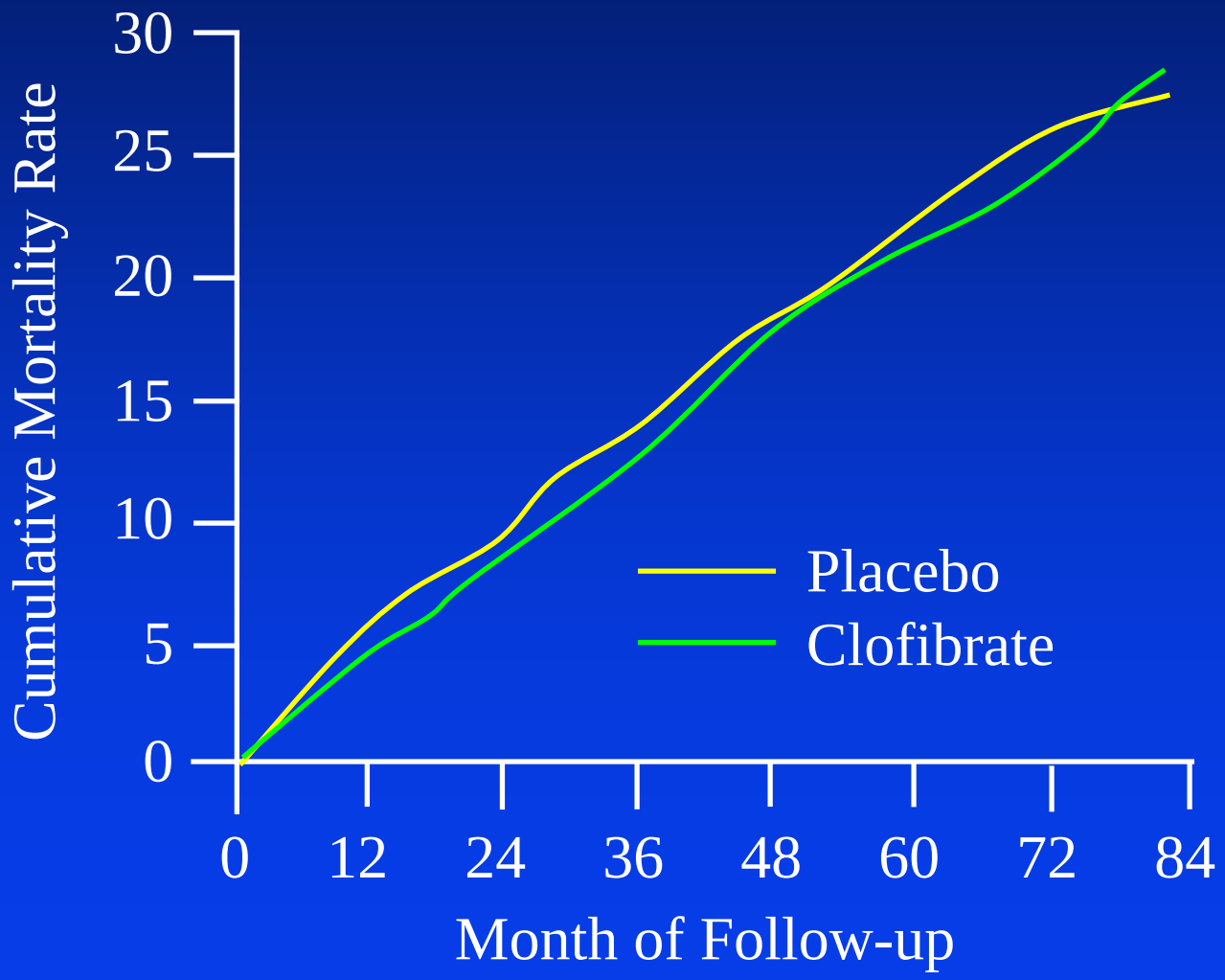
Coronary Drug Research Project Group

Z Values for Clofibrate - Placebo Differences



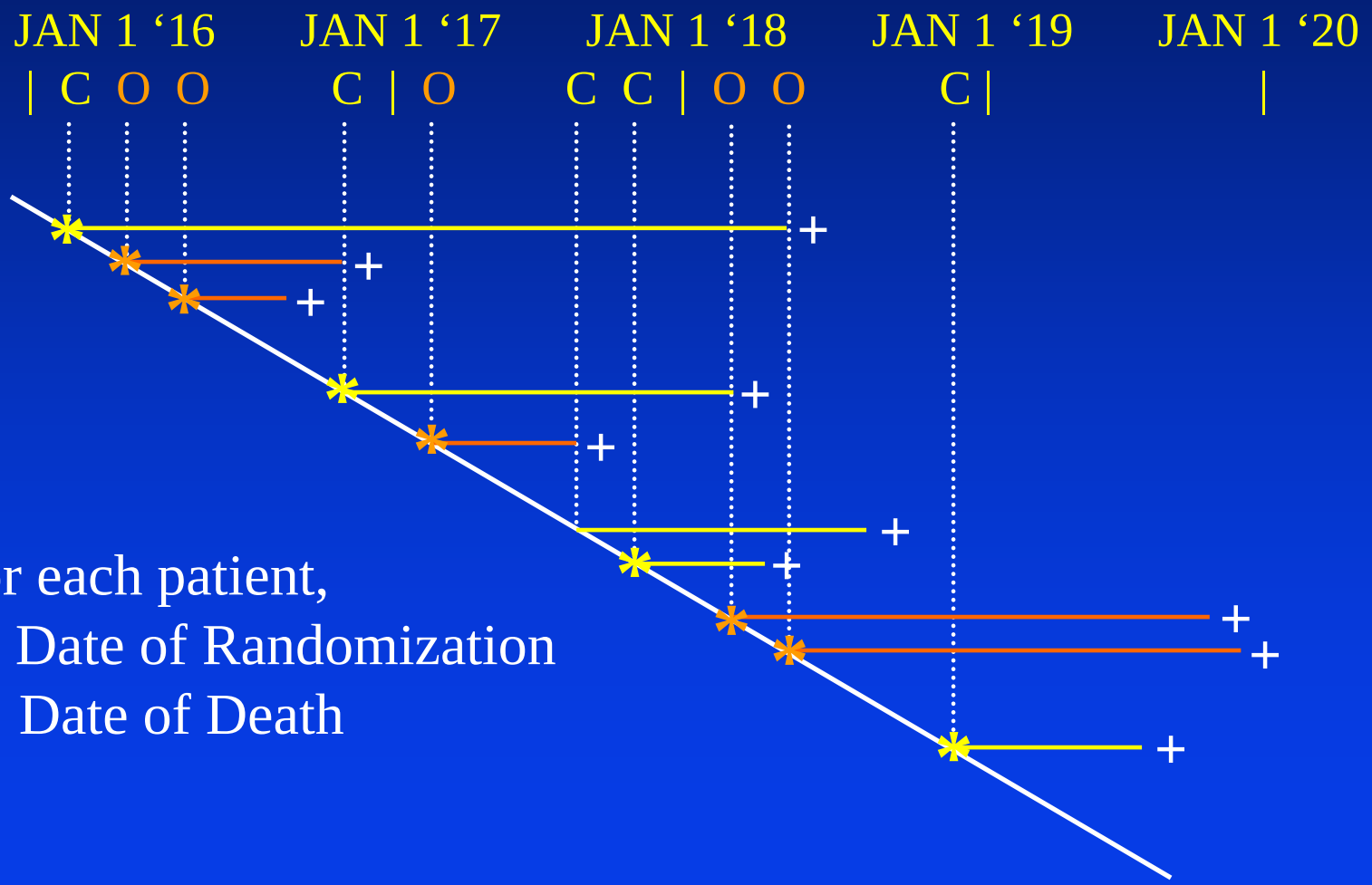
Coronary Drug Research Project Group

Life-table Cumulative Mortality Rates



Suppose we want to compare the survival of patients randomized to chemotherapy *vs* observation

Assume it is planned to accrue patients into the study from 1/1/16 to 1/1/19, with final analysis on 1/1/20



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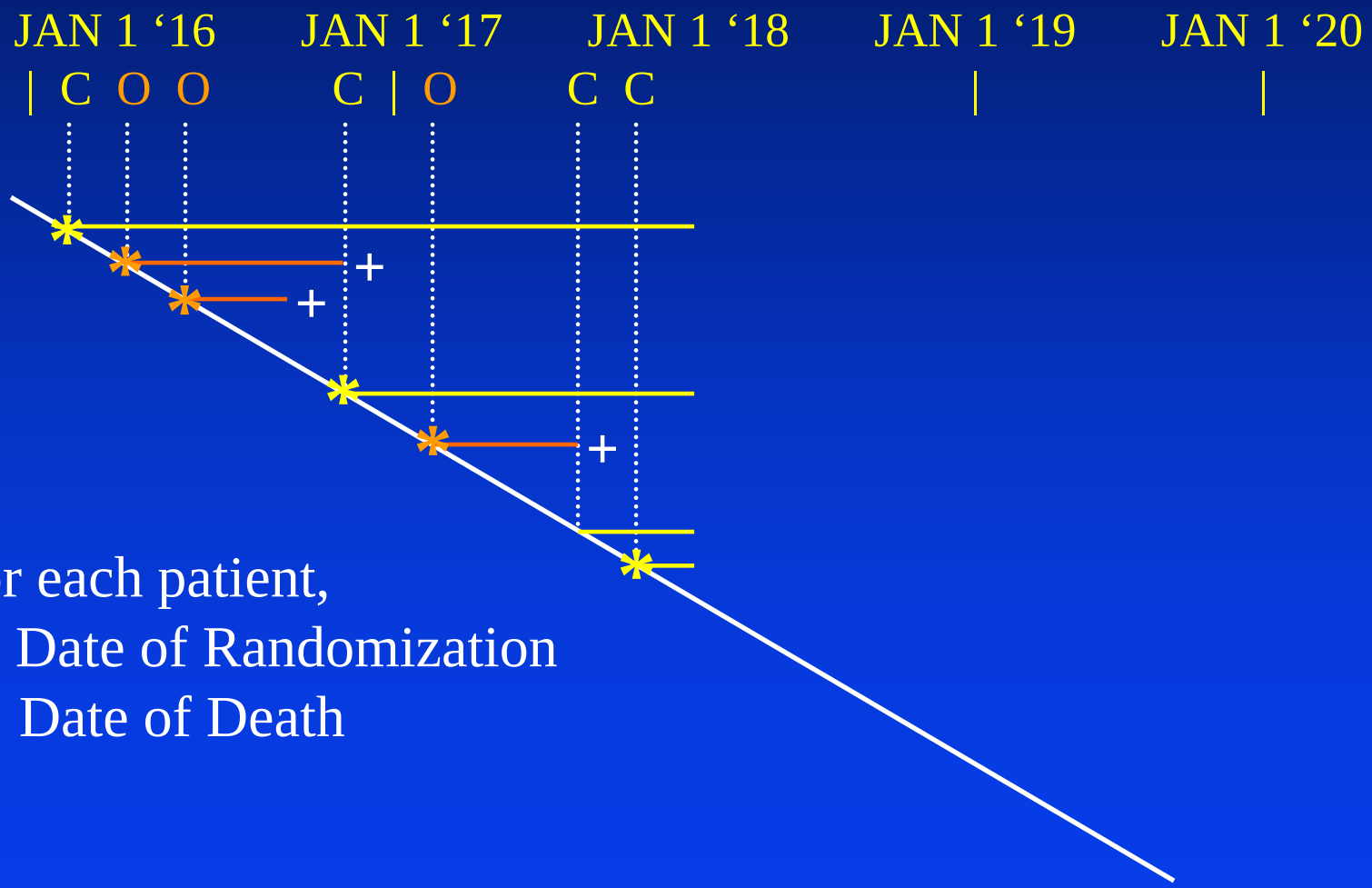


For each patient,

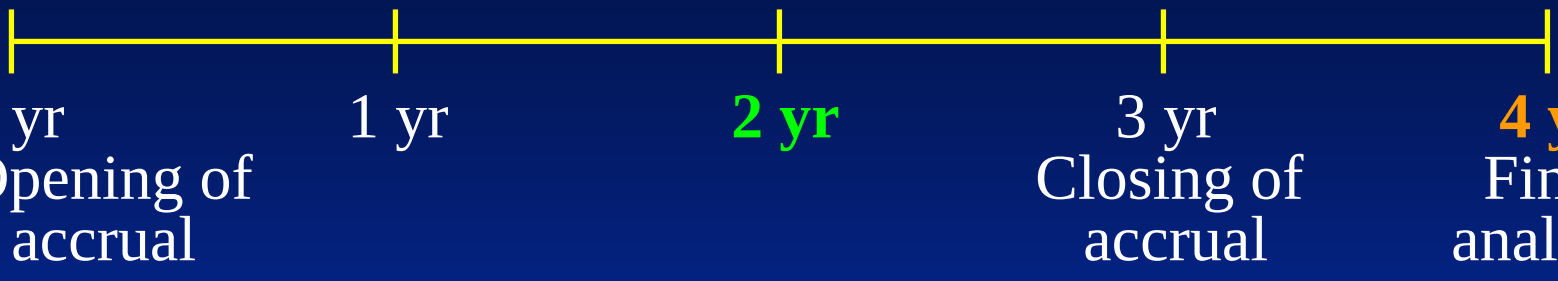
* : Date of Randomization

\+ : Date of Death

Results of Simulations

LR P-value < 0.05 at **4 years** in of 100 studies

LR P-value < 0.05 at **2 years** in of 100 studies



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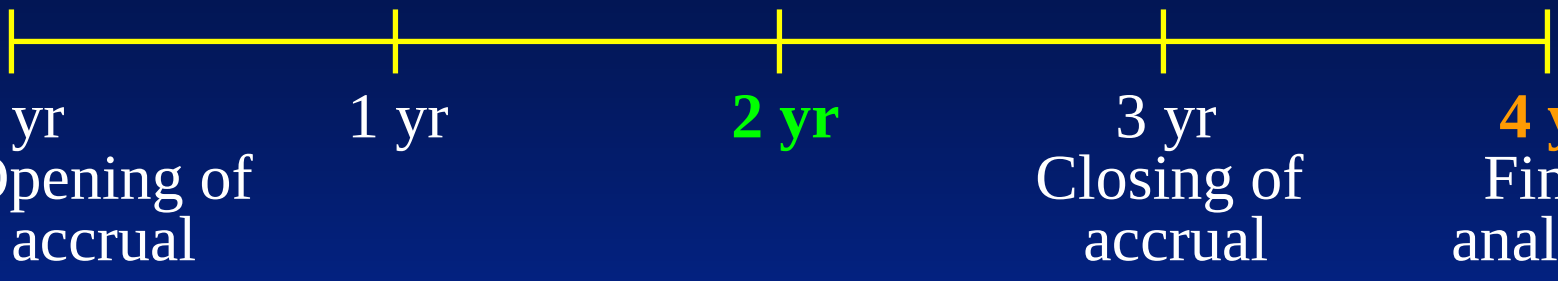
LR P-value < 0.05 at **4 years** in **5** of 100 studies

LR P-value < 0.05 at **2 years** in of 100 studies



Results of Simulations

LR P-value < 0.05 at **4 years** in **5** of 100 studies

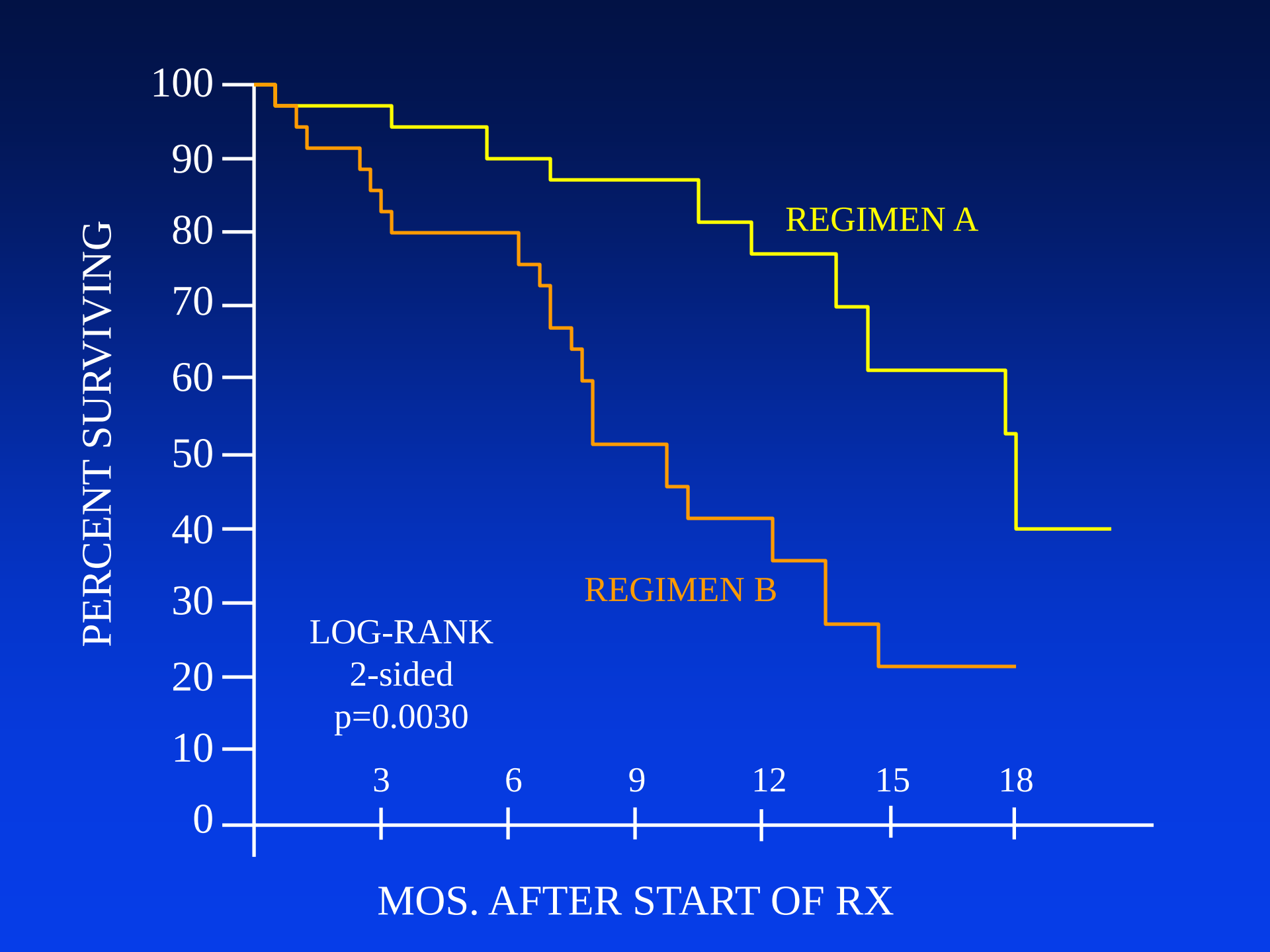
LR P-value < 0.05 at **2 years** in **5** of 100 studies

Were these the same studies?

NO

None of the studies with P < 0.05 at **2 years** had P < 0.05 at **4 years**

P values at		P values at	
2 yr	4 yr	2 yr	4 yr
0.1194	**0.0349**	**0.0220**	**0.8255**
0.4417	**0.0274**	**0.0205**	**0.5253**
0.7104	**0.0227**	**0.0165**	**0.1318**
0.3704	**0.0310**	**0.0086**	**0.2118**
0.0734	**0.0147**	**0.0110**	**0.1697**


100
90
80
70
60
50
40
30
20
10
0
PERCENT SURVIVING
REGIMEN A
REGIMEN B
LOG-RANK
2-sided
p=0.0030
3
6
9
12
15
18
MOS. AFTER START OF RX

RESULTS

THE LOG-RANK P VALUE WAS LESS THAN 0.05 AT

The final test; i.e. at 4 years	in	**5** of 100 studies
Either the 2- or 4-year test	in	**10** of 100 studies
At least 1 of 4 yearly tests	in	of 100 studies
At least 1 of 8 semi-annual tests	in	of 100 studies
At least 1 of 16 three-month tests	in	of 100 studies

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Either the 2- or 4-year test	in **10** of 100 studies
At least 1 of 4 yearly tests	in **17** of 100 studies
At least 1 of 8 semi-annual tests	in **21** of 100 studies
At least 1 of 16 three-month tests	in **26** of 100 studies

GOAL

Develop a design
for repeated data analyses

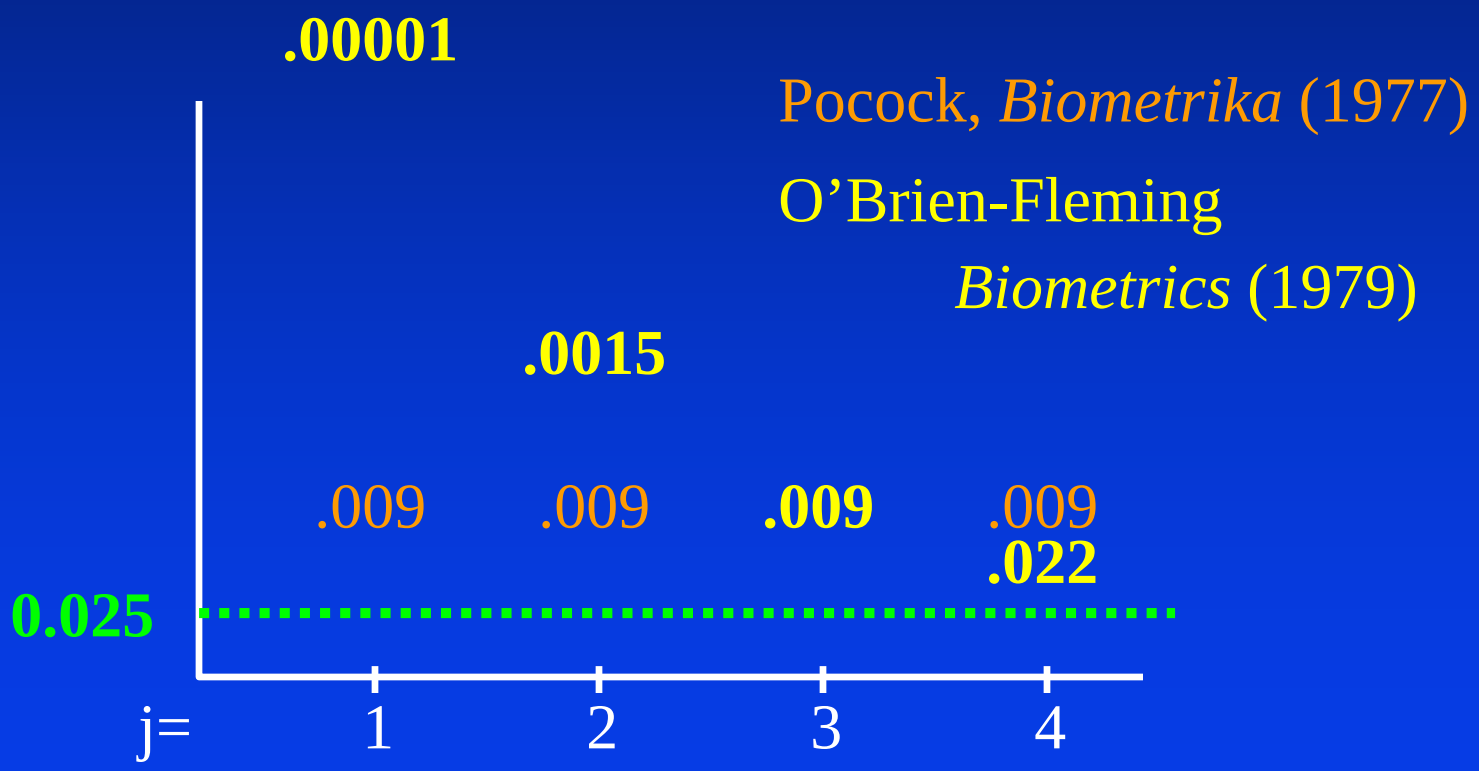
- which satisfies
the ethical need for early termination
if initial results are extreme

- while not increasing
the chance of false conclusions

Illustration: 4 Analyses

(1-sided) false positive error rate: 0.025

At analysis j, compute the p value P_j



Monitoring Clinical Trials

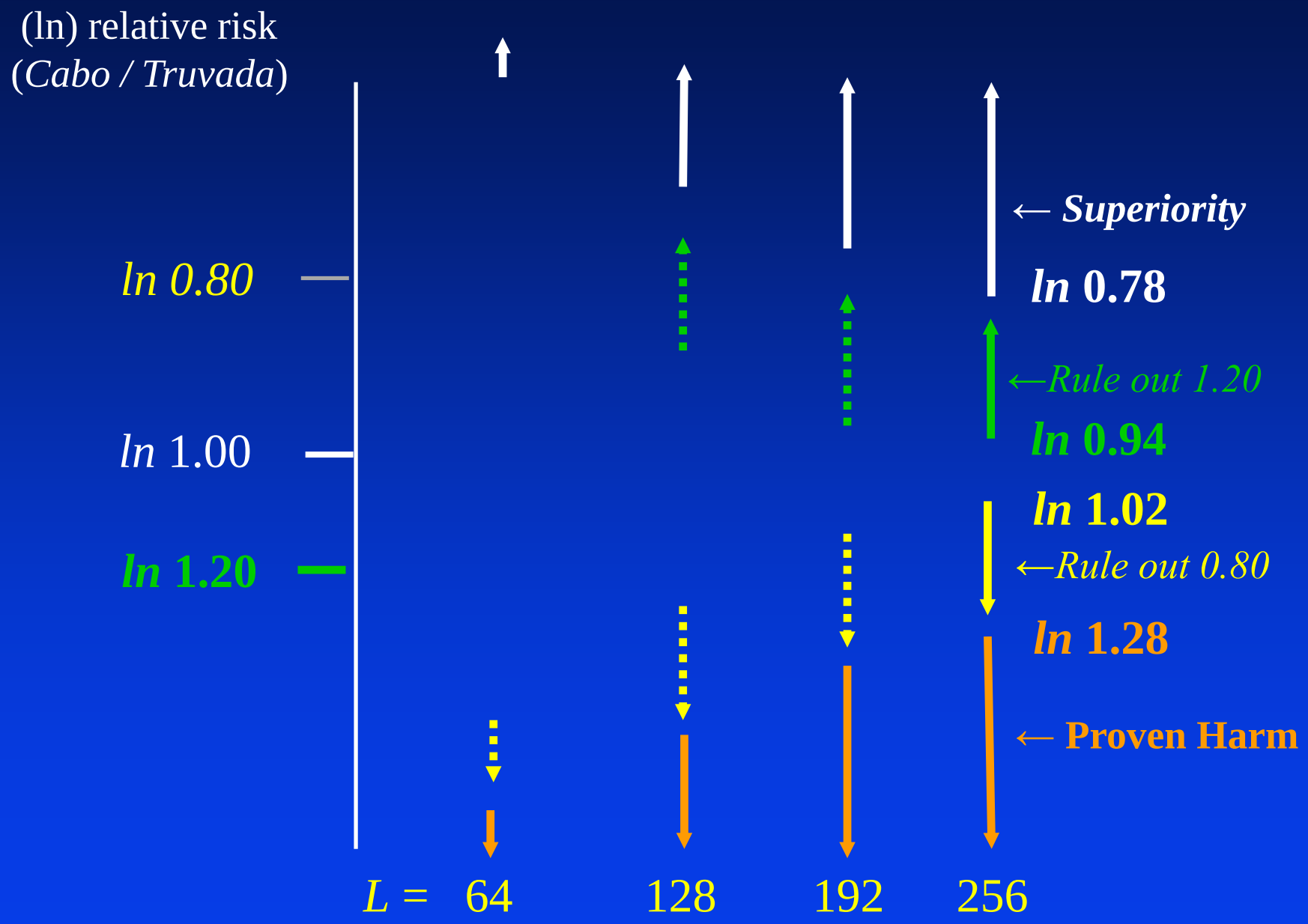
- How the O'Brien-Fleming guideline works: Arriving at recommendations about early termination of clinical trials

  ~ that establish benefit

  ~ that rule out benefit

  ~ that establish harm

O'Brien-Fleming Group Sequential Boundaries



Workshop on Clinical Trials

- Group Sequential Guidelines
- **Adaptive Methods**
- Data Monitoring Committees

Adaptive Designs

~ The objective of adaptive design usually is to improve flexibility and efficiency by folding the discovery process into confirmatory trials…

"*These methods use unblinded data regarding measures of treatment effect to make:*

- *adaptive selection / modification of treatments,*
- *adaptive selection of primary endpoints (Bauer and Kohne, 1994),*
- *adaptive modification of maximal sample size (Proschan and Hunsberger, 1995; Muller and Schafer, 2001; Shi, 2003; Jennison and Turnbull, 2006; Tsiatis and Mehta, 2003),*
- *adaptive modification of randomization ratios (Berry and Eick, 1994; Yao and Wei, 1996), and*
- *adaptive enrichment, i.e., adaptive modification of target populations (Freidlin and Simon, 2005; Jiang et al., 2007).*"

(Ellenberg, Fleming, DeMets, 2nd Edition, 2017)

Adaptive Designs

~ When conducting discovery or exploratory analyses,
it is critical to properly distinguish *noise* from *signal*

Eg: In pursing genetic signatures for enrichment,
discovery is performed using a "*training data set*"

Then confirmation is pursed by evaluating these discoveries in a "*validation data set*" firewalled away during the discovery process

~ When using the same data to generate and then confirm hypotheses,
it is critical to address these multiplicity issues…

– to avoid random high bias in estimates of effects and
– to provide an interpretable sampling context for inference
(such as p-values)

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Efficiency and Interpretability Issues: Standard vs. Adaptive Monitoring Procedures

Illustration: δ = 6-week Drop in HAM-D depression Score

$\delta = 4$, $(n_1+n_2 = 267)$, vs. $\delta = 2$, $(n_1+n_2^* \approx 1100)$

Adaptive Approach: $n_1 = 200$; $n_2 = 67$

Interim Analysis at $n_1 = 200$: $\hat{\delta} = 1.8$

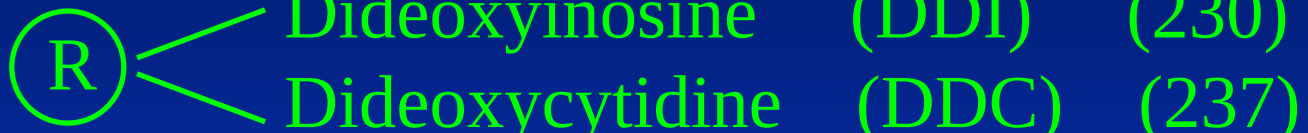
Enroll additional $n_2^* = 900$

Monitoring Proc:	Standard		Adaptive	
Cohort (i=1, 2)	200	900	200	(67)900
Weights for Z_i	.426	.905	.865	.501
Weights for $\hat{\delta}_i$	.182	.818	.449	.551
n_1 vs $\sqrt{(n_2\, n_2^*)}$				
Relative Efficiency	1.0		0.676	

Key Issues: Outline

- Efficiency
- Interpretability
- **Reliability of Interim Results**
- Maintaining the Integrity of the Monitoring Process:
  Scientific and Ethical Considerations
- Conclusions:
  Clinical vs. Statistical Significance

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



Outcome:

Time to AIDS/Death

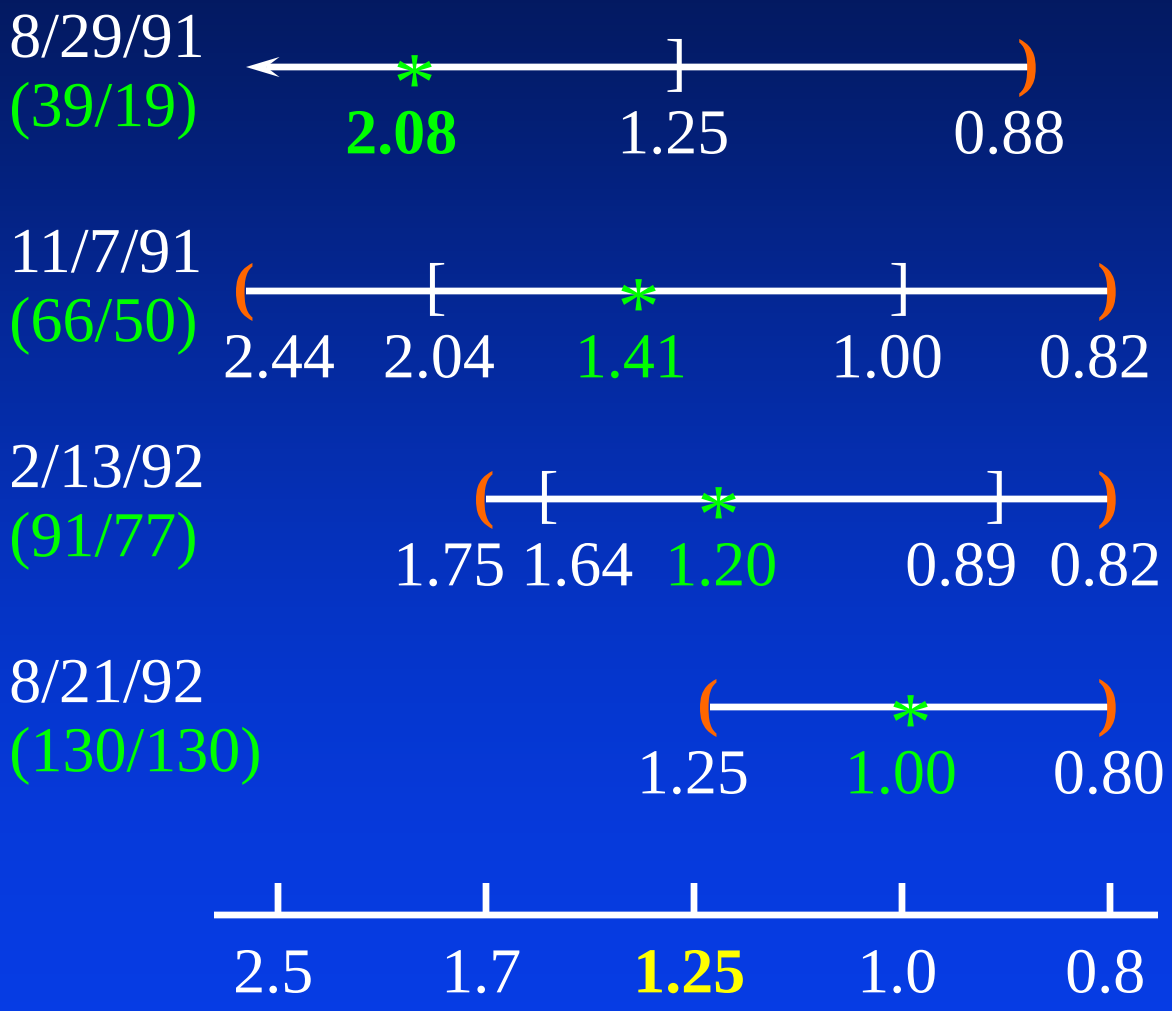
Enrollment: 12/90 - 9/91

DMC Efficacy Interim Analyses:

Approximately at increments of 60 events

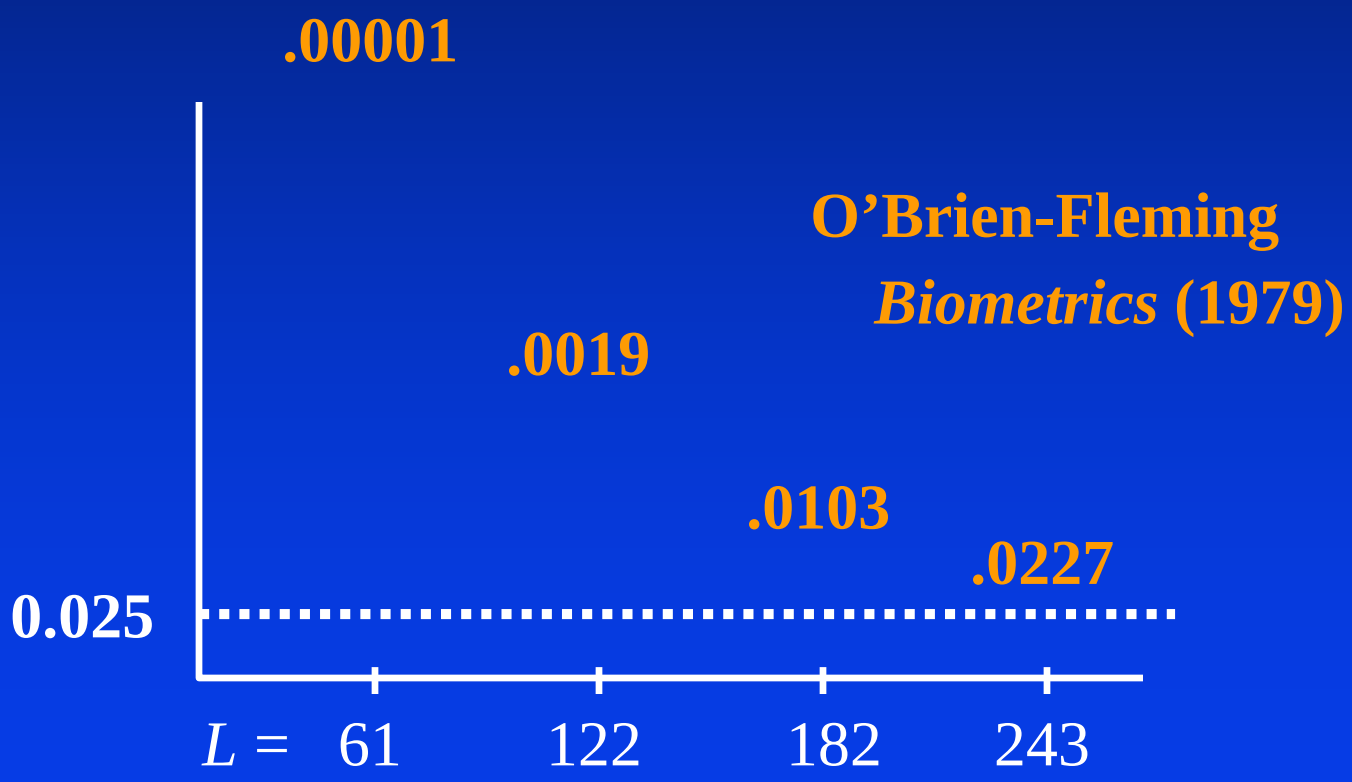
(Protocol: Follow-up until 243 events)

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



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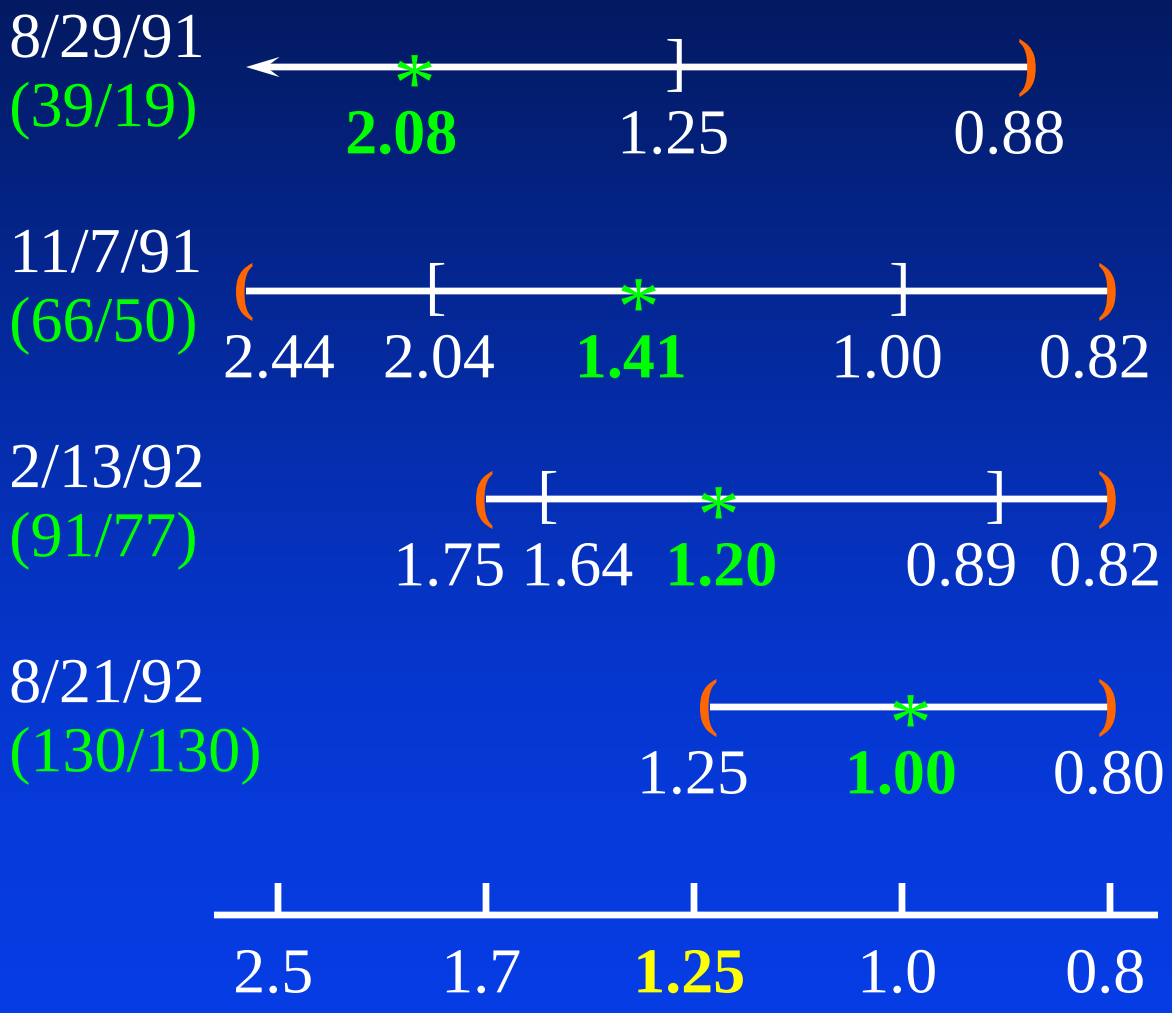

Key Issues: Outline

- Efficiency
- Interpretability
- Reliability of Interim Results
- **Maintaining the Integrity of the Monitoring Process: Scientific and Ethical Considerations**
- Conclusions:
  Clinical vs. Statistical Significance

Key Issues: Outline

- Efficiency
- Interpretability
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- Maintaining the Integrity of the Monitoring Process:
  Scientific and Ethical Considerations
- **Conclusions:**
  Clinical vs. Statistical Significance

Primary Goal of Clinical Trials

- Not:

  "To obtain a statistically significant result"

- Rather:

  "To obtain a statistically reliable evaluation regarding whether the experimental intervention is safe and provides clinically meaningful benefit."

  Fleming, Statistics in Medicine, 2006

Clinical Significance as well as Statistical Significance

Mehta E.g. $\delta = 1.8$

Adaptive Designs

~ Proper adaptive procedures:

– should be specified in detail before unblinding the personnel who would implement them

– have the potential for having less favorable operating characteristics than more conventional study designs

▪ FDA Guidance for Industry on "*Adaptive Design Clinical Trials*"

⇒ Adaptive methods may have

✓ reduced efficiency & interpretability (Emerson: Costs of planning to not plan)

✓ imbalanced weighting of statistical versus clinical significance

✓ reduced flexibility to address emerging external information if adaptive method provides insights about interim results.

▪ Tsiatis and Mehta, 2003; ▪ Bauer and Posch, 2004; ▪ Emerson, 2006;
▪ Fleming, 2006; ▪ Jennison and Turnbull, 2006; ▪ Emerson and Fleming (2010);
▪ Emerson, Levin and Emerson (2011); ▪ Levin, Emerson and Emerson (2013)

~ Preferred role for Adaptive Design may be Exploratory Stages of Development

Principles & Insights

"Thomas Edison once said,
'Opportunity is missed by most people because it is dressed in overalls and looks like work.'
In clinical science, it is
the steady, incremental steps
that are likely to have the greatest impact."

* Emerson SS, Fleming TR. Adaptive Designs: Telling 'The Rest of the Story'. 2010; *Journal of Biopharmaceutical Statistics*.

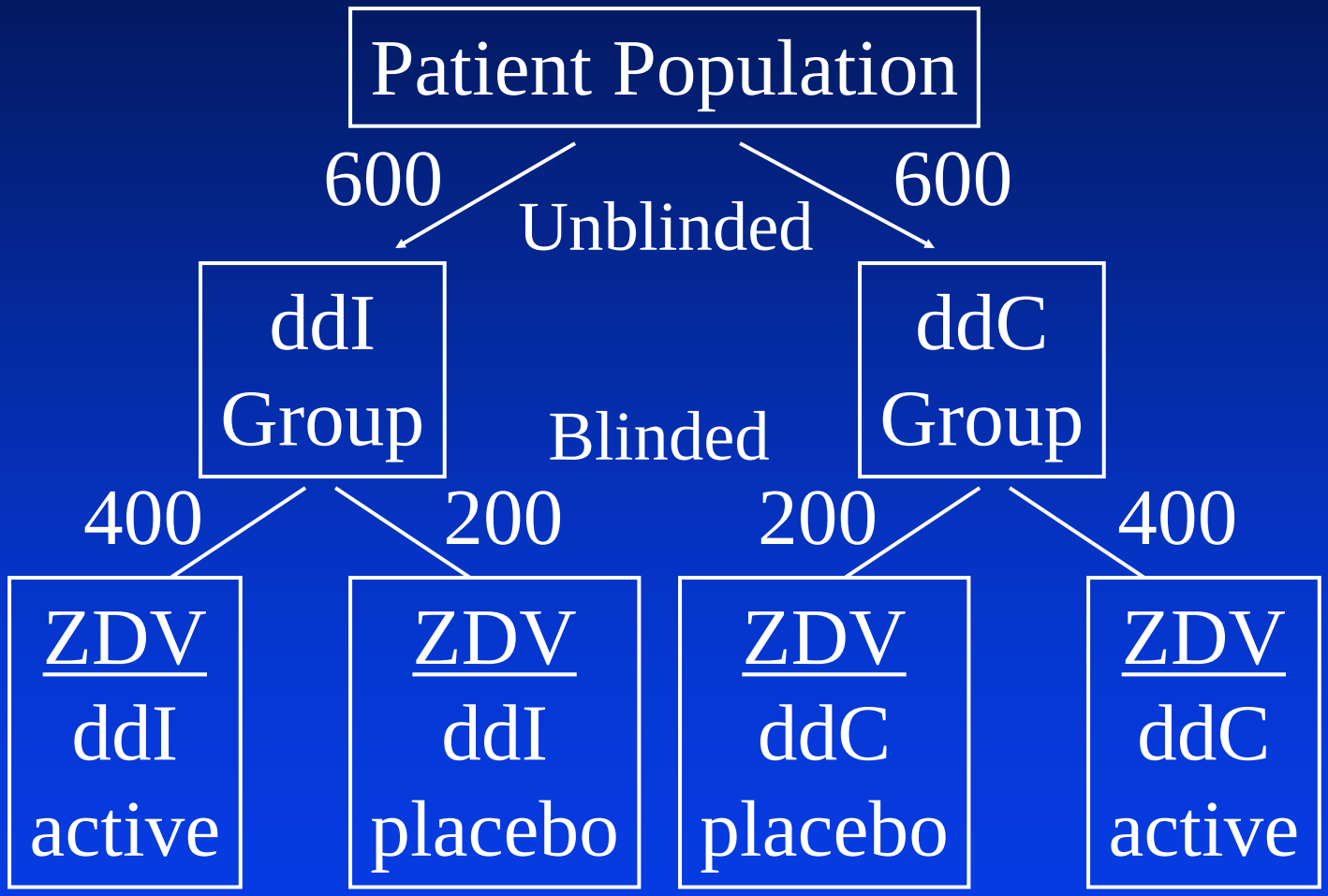
Fleming TR "Standard vs. Adaptive Monitoring Procedures" *Statistics in Medicine* 2006; 25:3305-3312

Workshop on Clinical Trials

- Group Sequential Guidelines
- Adaptive Methods
- **Data Monitoring Committees**

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

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

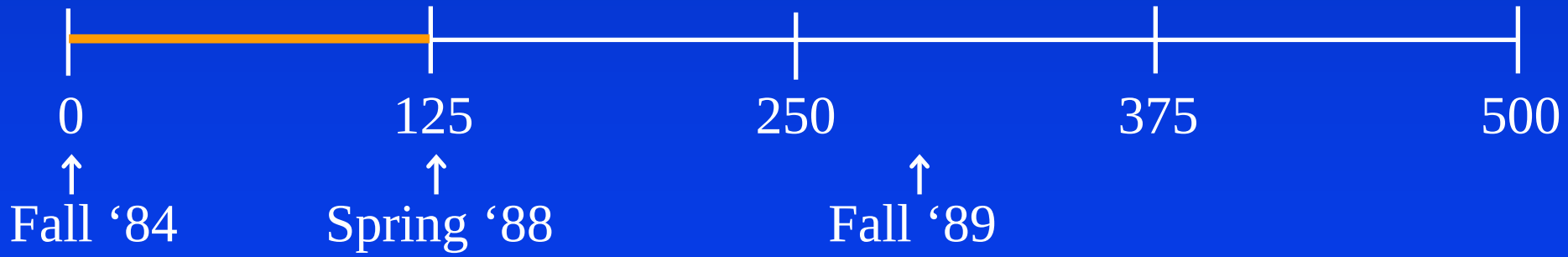
Duke's C — R

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

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

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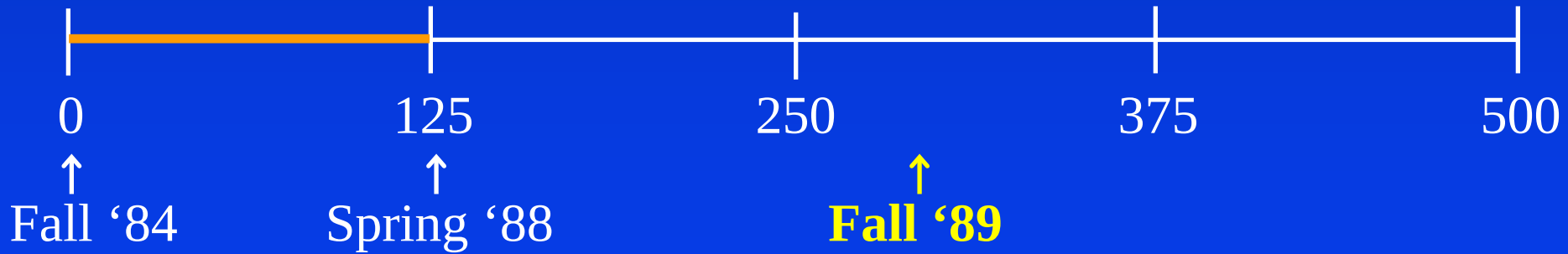
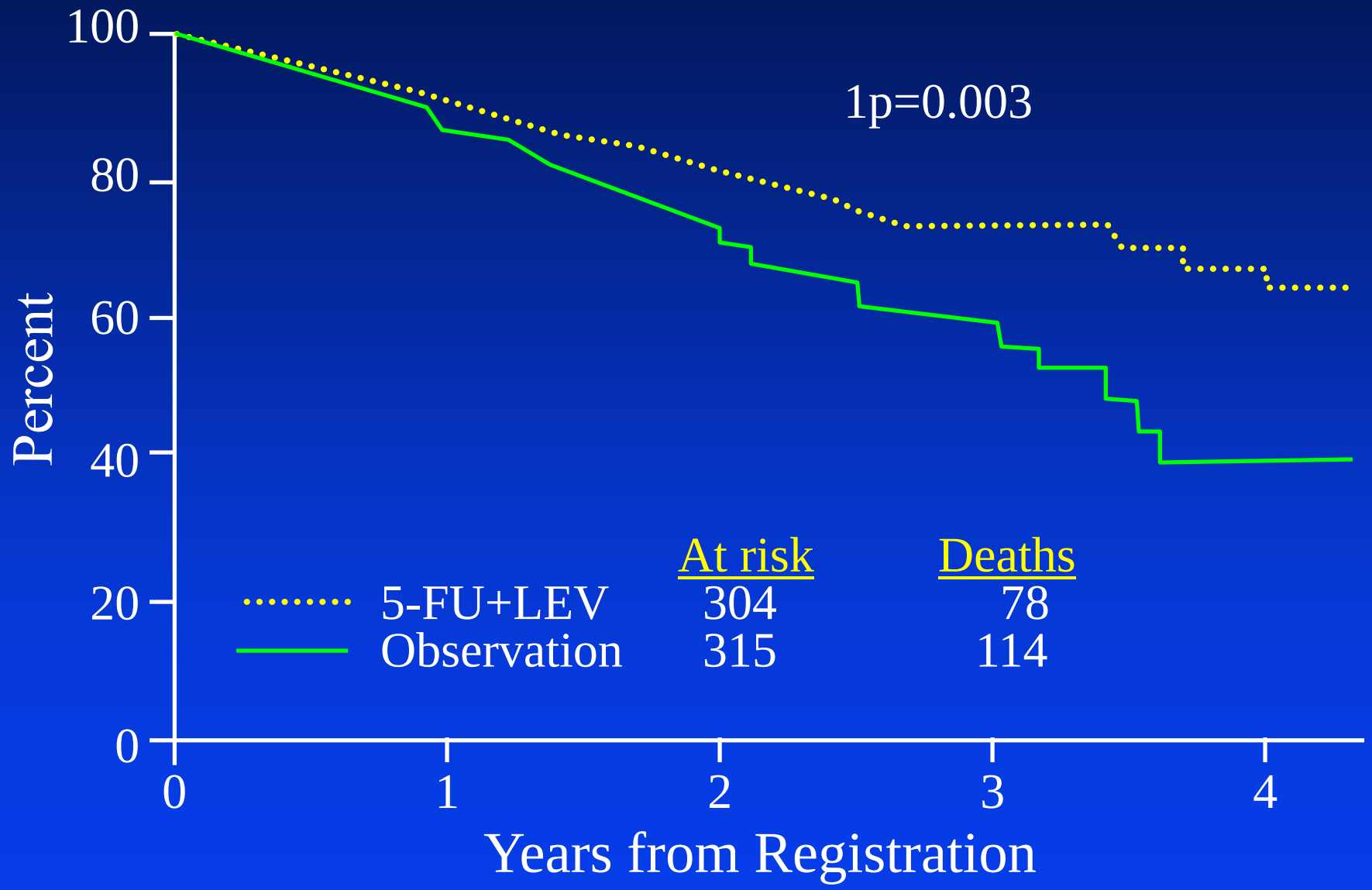


Duke's C Colon Cancer
Overall Survival



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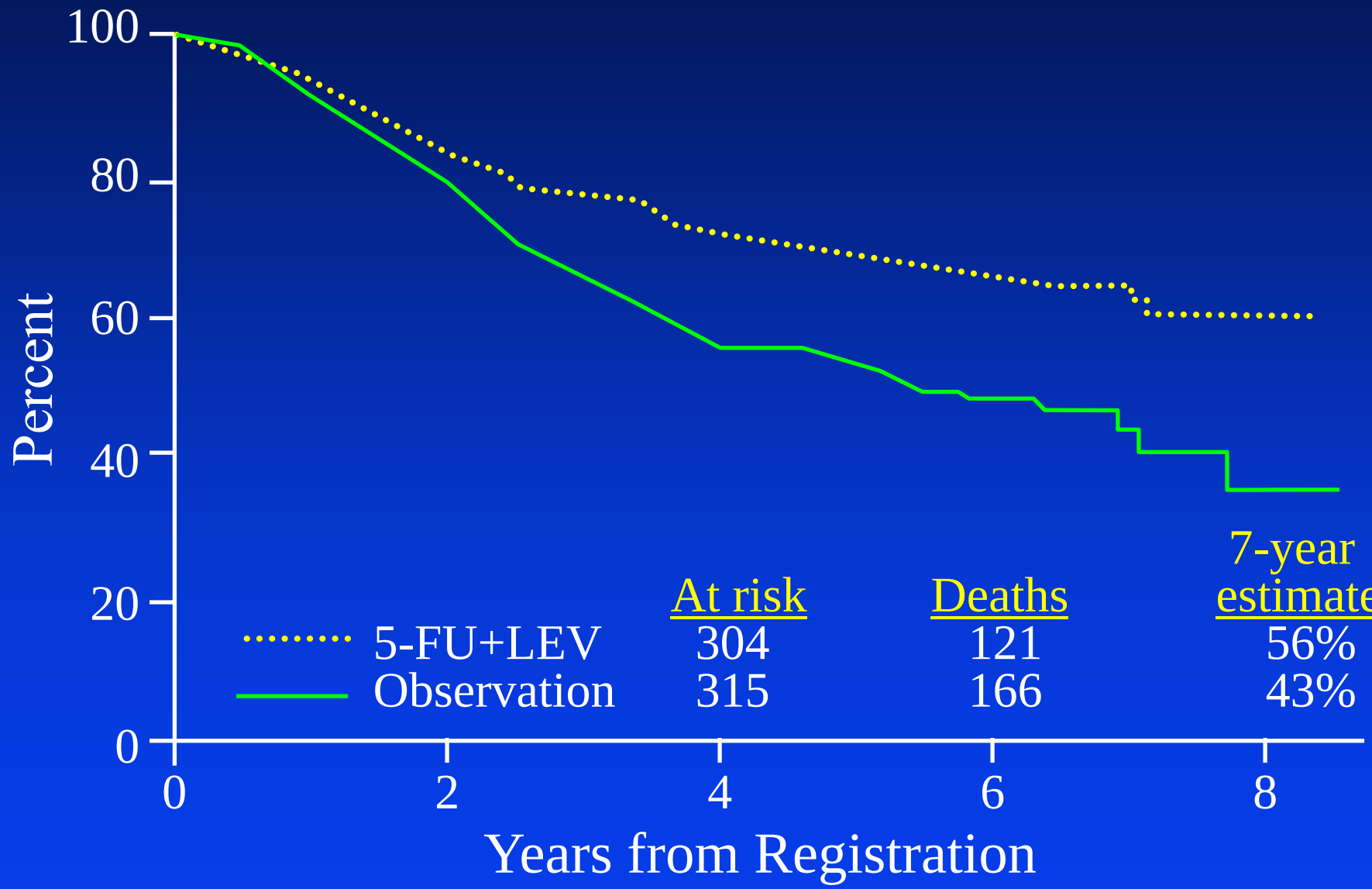

DMCs and other Oversight Bodies: Relative Responsibilities and Relationships

- **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

Workshop on Clinical Trials

Data Monitoring Committees: Promoting Best Practices

October 18, 2017

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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

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

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
- 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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  - ✓ Creating an effective DMC Charter
  - ✓ DMC recommendations through consensus, not by voting
- Defining the role of the Statistical Data Analysis Center

Indemnification of the DMC

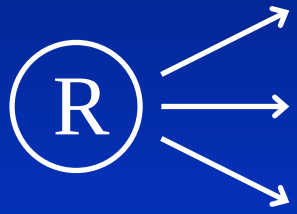
- DMC Indemnification
  - ✓ Multiple sources of possible liability from clin trial stakeholders
  - ✓ Sponsors/CROs often propose DMC members insure them
  - ✓ DMC concern about litigation could influence their performance
- DeMets et. al.; *Clinical Trials* 2004; 1: 525–531
  - ✓ Recommendations for 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

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
- Defining the role of the Statistical Data Analysis Center

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

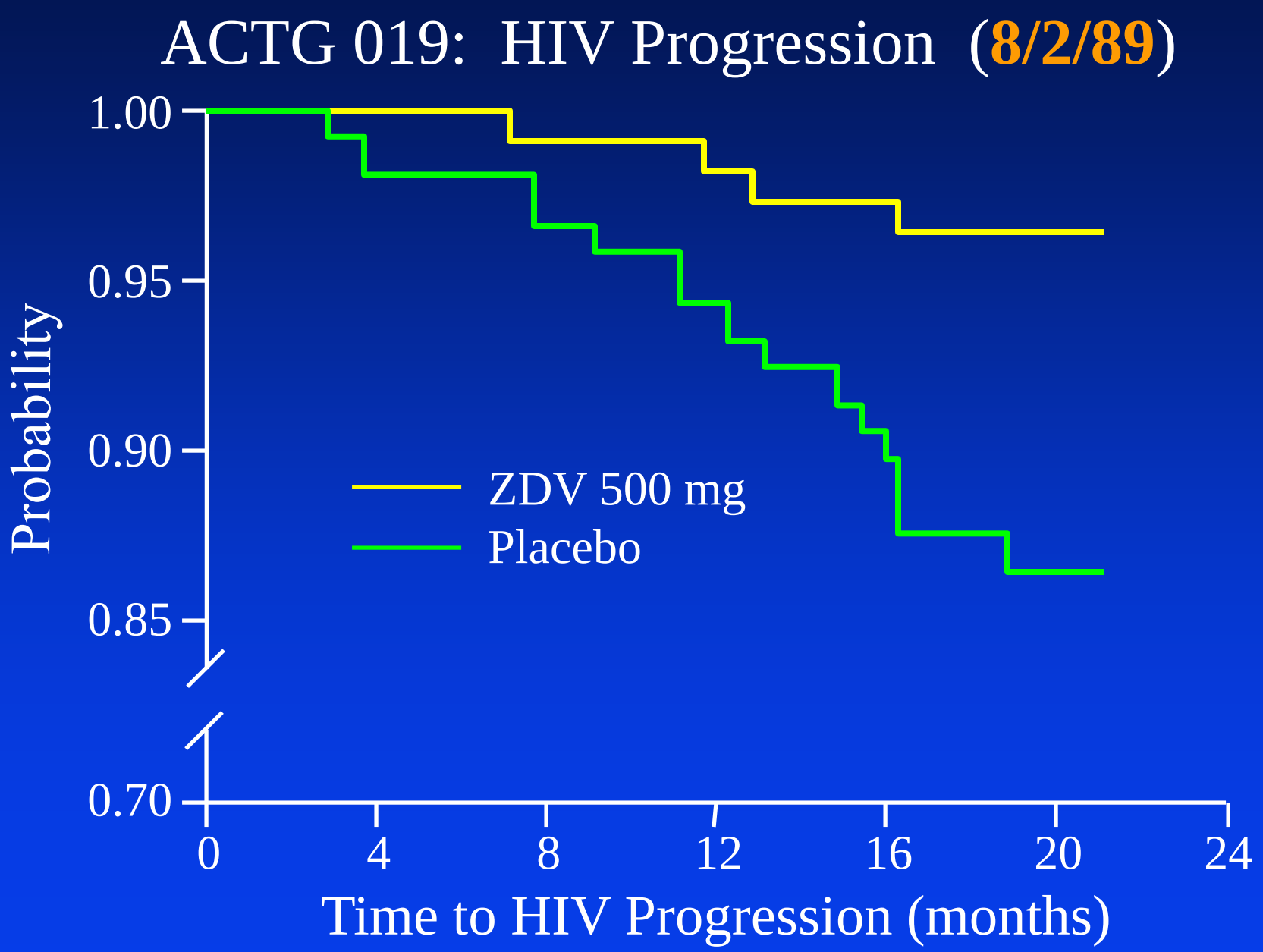
8/16/92 Updated Analysis

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

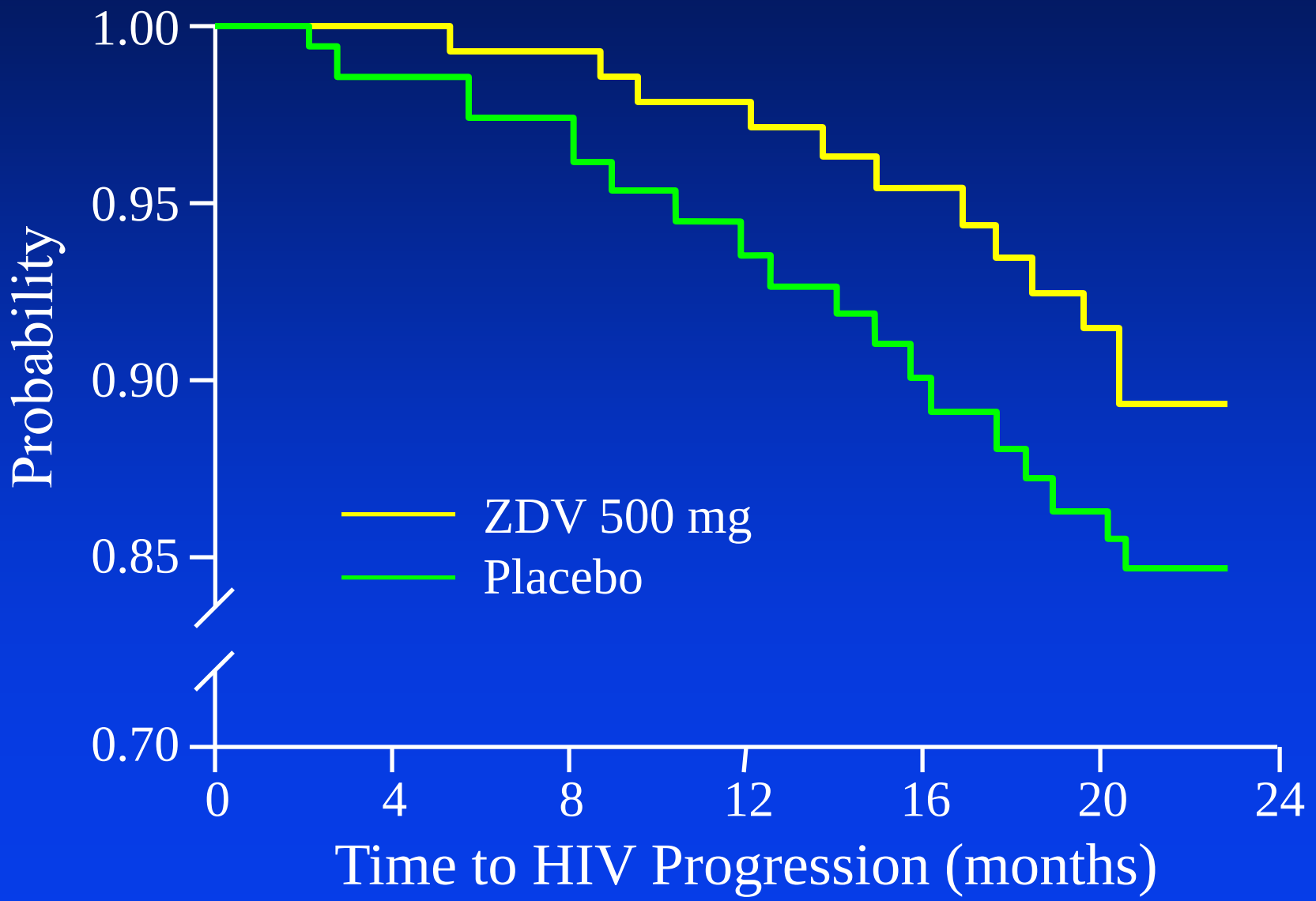
O'Brien-Fleming: .005

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*'

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
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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):

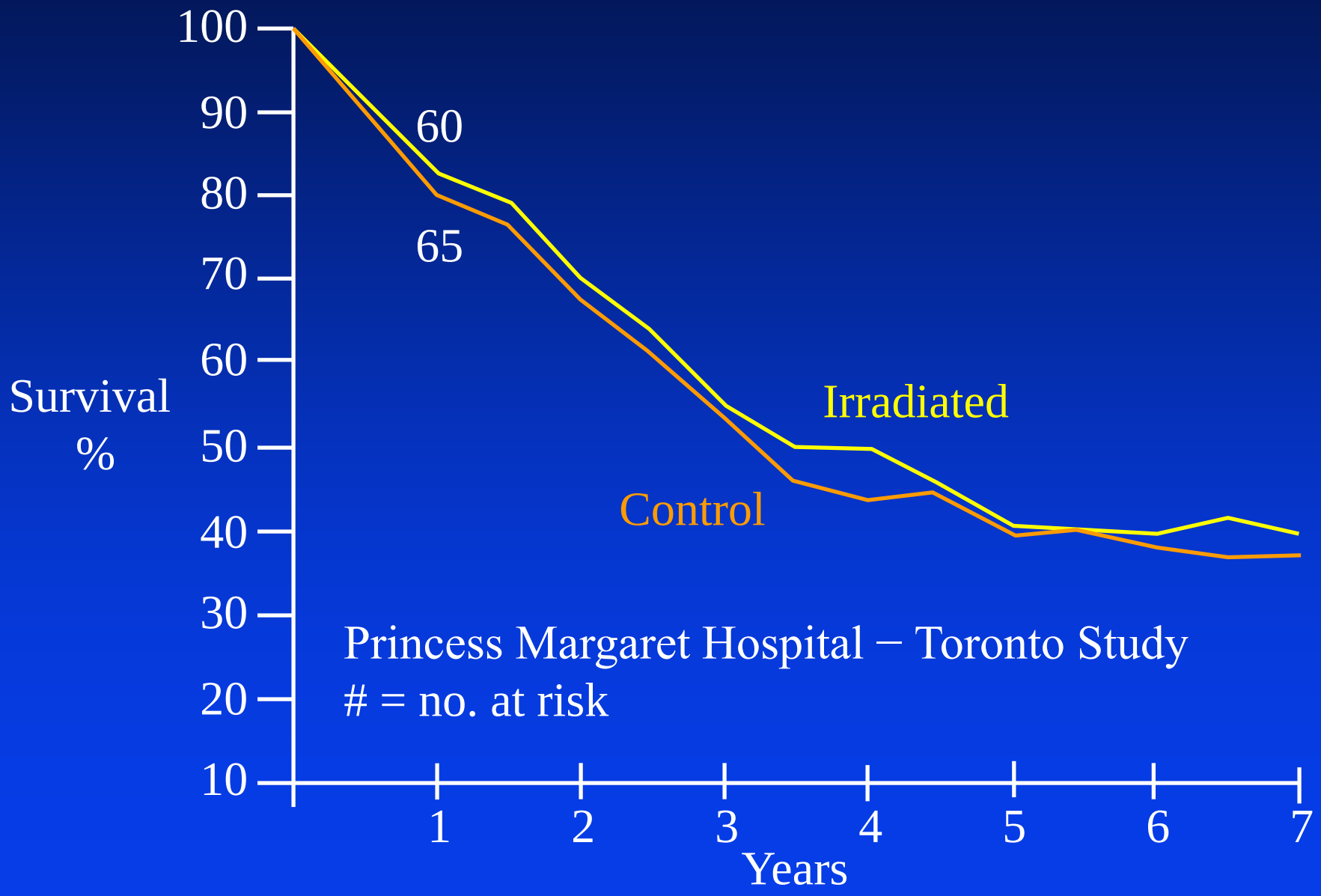
- to investigate existing processes of monitoring accumulating data
- to identify ways of improving the DMC process.

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

Evidence from NIH Cooperative Group Studies

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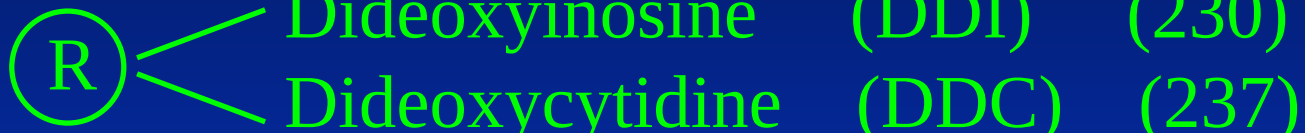
CPCRA #002 HIV Infected Patients who are AZT Intolerant/AZT Failures



Outcome:

Survival Time, Time to AIDS/Death

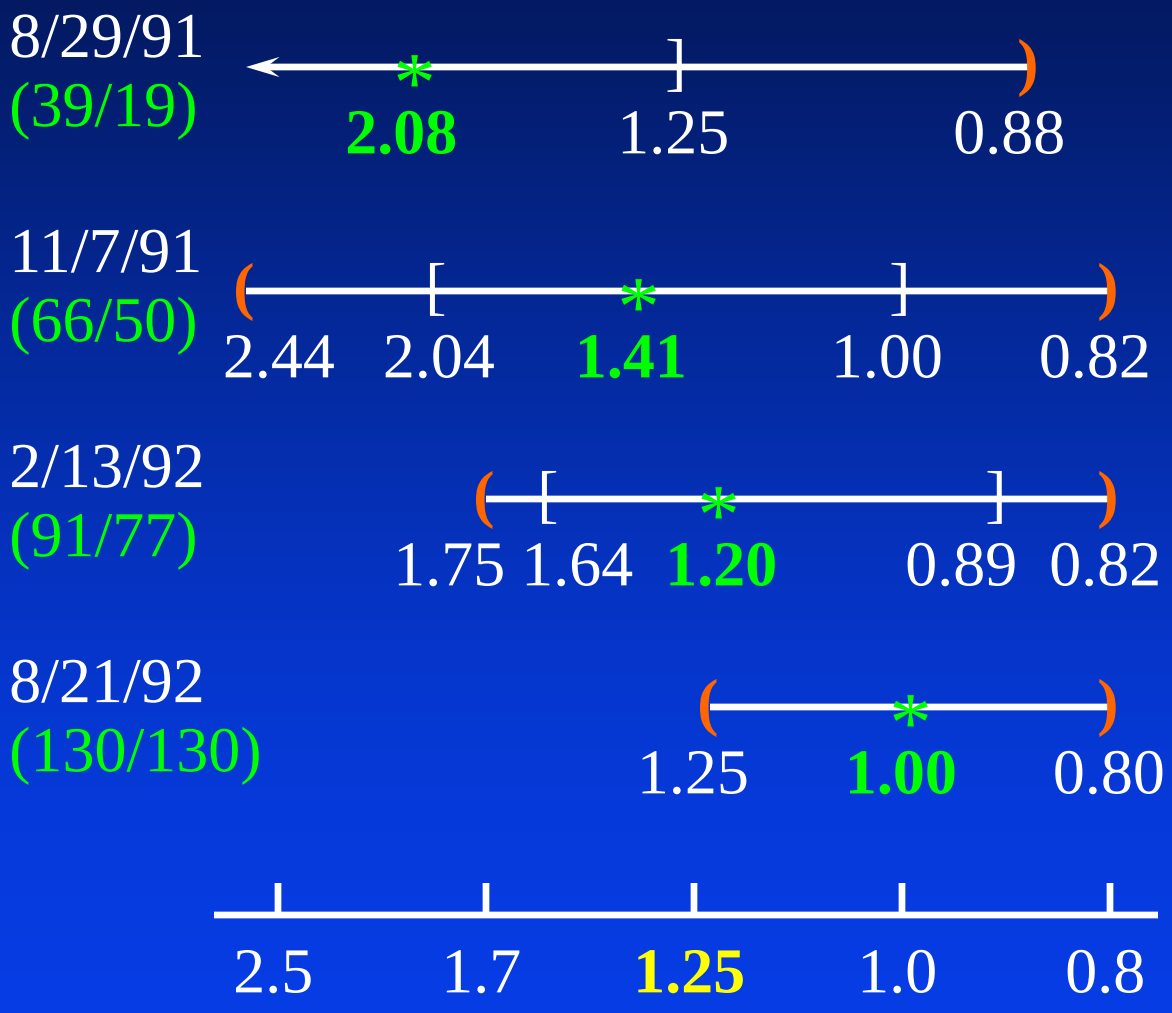
Enrollment: 12/90 - 9/91

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

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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Contrave	55	12	21	33	15	31	74
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 (RR/p)	76 (0.45 /0.0001)	72	40 (0.87 / 0.60)	23	101 (0.92 / 0.60)	55
Death (RR/p)	109 (0.71/ 0.052)	68	58 (1.27 / 0.34)	23	222 (0.83 / 0.09)	132

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
- 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

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- 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**
- Defining the role of the Statistical Data Analysis Center

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
- 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**

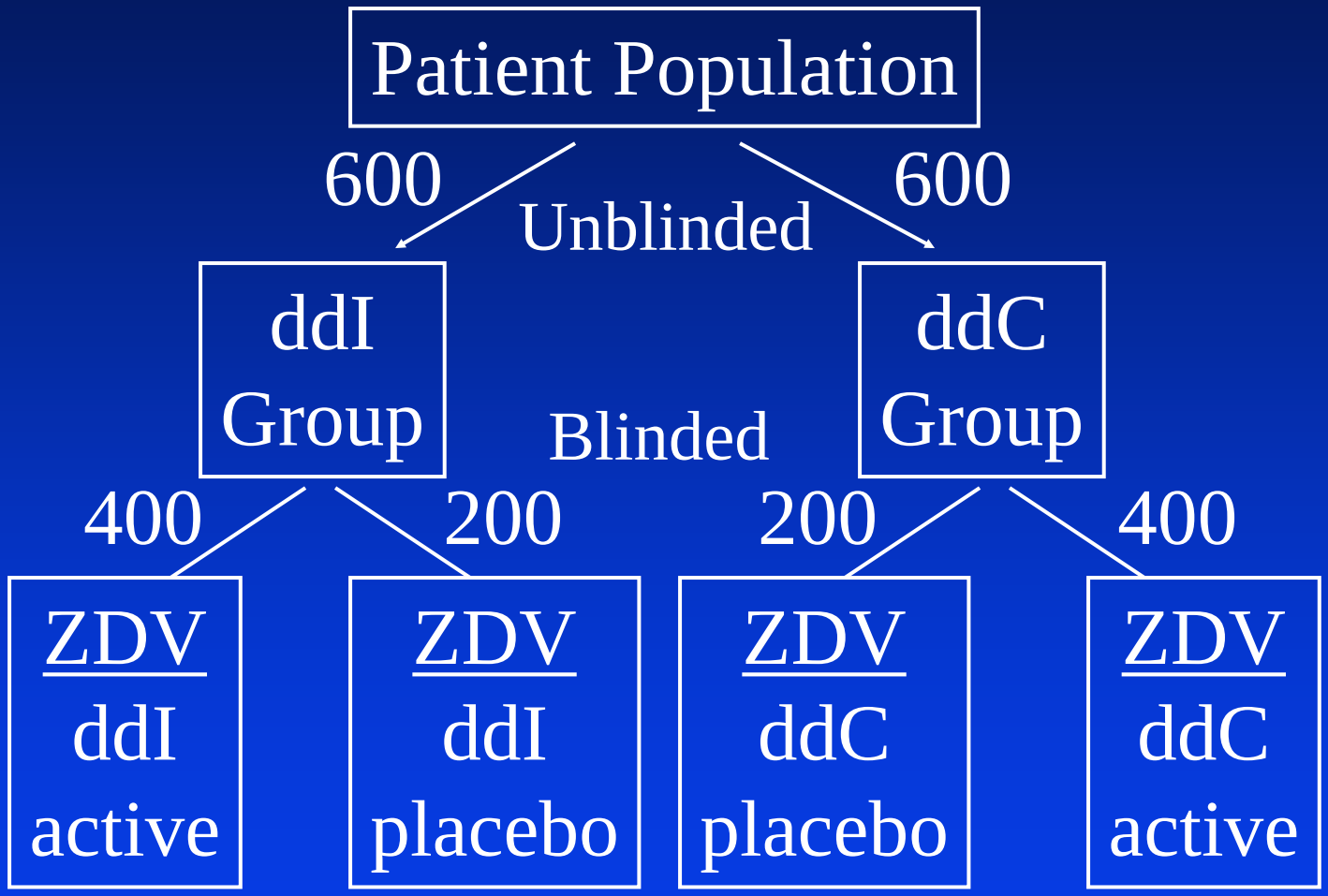
Defining the Role of the Statistical Data Analysis Center

- 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
- 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

Workshop on Clinical Trials
October 18: HPTN African Regional Meeting

- Design of Clinical Trials
  - *Biomarkers and Replacement Endpoints*
  - *Designs using Active Controls:*
    Non-inferiority (NI) Trials
  - ***Monitoring Guidelines & Adaptive Methods***
- Conduct of Clinical Trials
  - *Addressing Missing Data in Clinical Trials*
  - ***Data Monitoring Committees: Current Issues***
- Analysis/Reporting of Clinical Trials
  - *Exploratory Analyses:*
    Why do we need particular caution?

HPTN
HIV Prevention
Trials Network

ACKNOWLEDGEMENTS

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