Biostatistics Lecture

Clinical trials:
Discerning Hype from Substance

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Fleming TR "Clinical Trials: Discerning Hype from Substance"
Annals of Internal Medicine 2010; 153:400-406

Interest in "Positive" Results in Clinical Trials

- Industry Sponsors
  - ~ Company profits, ↑ value of stock options, promotion
- Government Sponsors
  - ~ Claims of success in advancing health care
  - ~ Leverage for ↑ in federal funding
- Journal Editors (Publication bias)
- Academic Investigators / Caregivers
  - ~ Increased ability to publish results
    - ↑ professional stature, earlier promotion, ↑ salary
  - ~ Desire to offer more therapeutic options to patients

….Result: *Wide Spread & Significant Conflicts of Interest*

Confirmatory vs. *Exploratory* Analyses

- Hyp. Confirmation vs. Hyp. Generation
  - ~ Post-hoc Analyses & Random High Bias
    (new endpoints, new analyses, interim analyses
    subgroup analyses, covariate adjustments)

Illustrations and Motivation:

Confirmatory vs. *Exploratory* Analyses

- Clinical Endpoints in Pulmonary Arterial Hypertension
  - ~ Overall survival
  - ~ Quality of Life: SF-36 (8 domains), Borg Dyspnea Score
- ~ NYHA Functional Class
  - ~ 6MWT: @12 wk, 16 wk, 18 wk, etc.
  - ~ Time to Clinical Worsening
    - ✓ Death, PAH Hosp, L.T., (NYHA↑ & 6MWT↓ & Rx Δ)
- Analysis Methods
  - ~ Normally distributed: T-test, ANOVA, Wilcoxon
  - ~ Time to event: Logrank, Cox Regression
  - ~ Dichotomous: Fisher's Exact Test, Pearson $\chi 2$

Confirmatory vs. *Exploratory* Analyses

- Biomarker Endpoints (Hemodynamic parameters)
  - ~ Pulmonary & Systemic BP
  - ~ Systolic & Diastolic Pulmonary Arterial Pressure
  - ~ Systolic & Diastolic Systemic Arterial Pressure
  - ~ Systemic & Pulmonary Vascular Resistance
  - ~ Heart Rate
- Analyses over Calendar Time
- ~ Normally distributed: T-test, ANOVA, Wilcoxon
- ~ Time to event: Logrank, Cox Regression
  - ~ Dichotomous: Fisher's Exact Test, Pearson $\chi 2$

Confirmatory vs. *Exploratory* Analyses

- Subgroup Analysis & Prognostic Covariate Adjustment
  - ~ WHO PAH Functional Class: I v II v III v IV
  - ~ Etiology: Idiopathic PAH, Assoc w CTD, SLE, Other
  - ~ Baseline Walking Distance: < 325 v > 325 meters
  - ~ Gender: male v female
  - ~ Age: By decade

Epoprostenol +/– Sildenafil

  - ~ Ethnicity: White v Black v Asian v Other
  - ~ mean PAP: < 50 v > 50

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Illustrations and Motivation:

Maternity Wards, Baseball & Clinical Research

20 vs 2: (.71, .99), $2p = 0.0001$

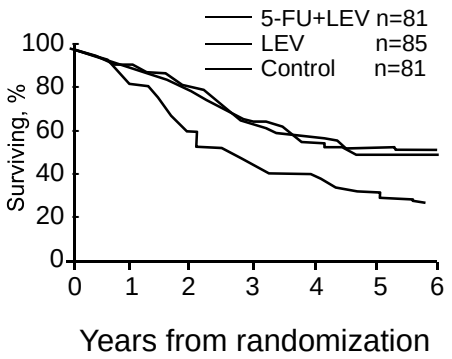
An Illustration of Exploratory Analyses: Post-hoc Subgroup Analyses

Surgical Adjuvant Therapy of Colorectal Cancer

R → 5-FU + Levamisole
R → Levamisole
R → Control

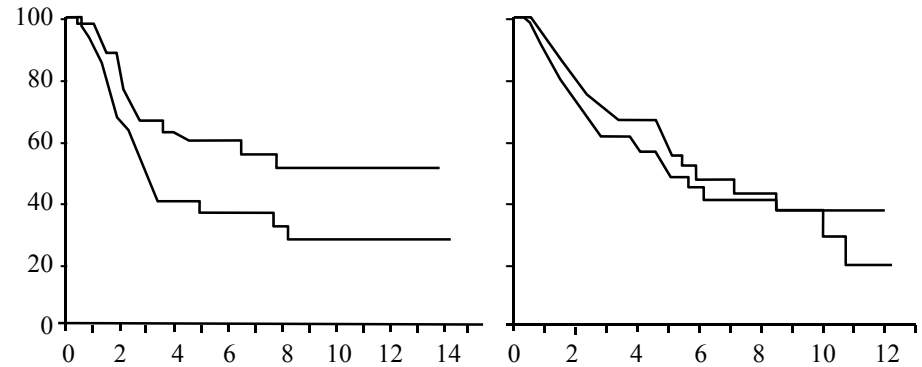
Surgical Adjuvant Therapy: Colorectal Cancer

NCCTG Trial



NORTH CENTRAL TREATMENT GROUP STUDY
Looking at Treatment Effect on Overall Survival

	Females Only			Males Only		
	At Risk	Death	5-Yr Estimate	At Risk	Death	5-Yr Estimate
5-FU+Levamisole	44	21	57%	37	25	51%
Follow-Up Only	43	29	40%	38	24	47%



Surgical Adjuvant Therapy: Colorectal Cancer

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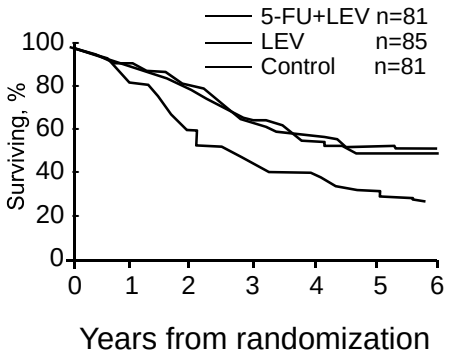

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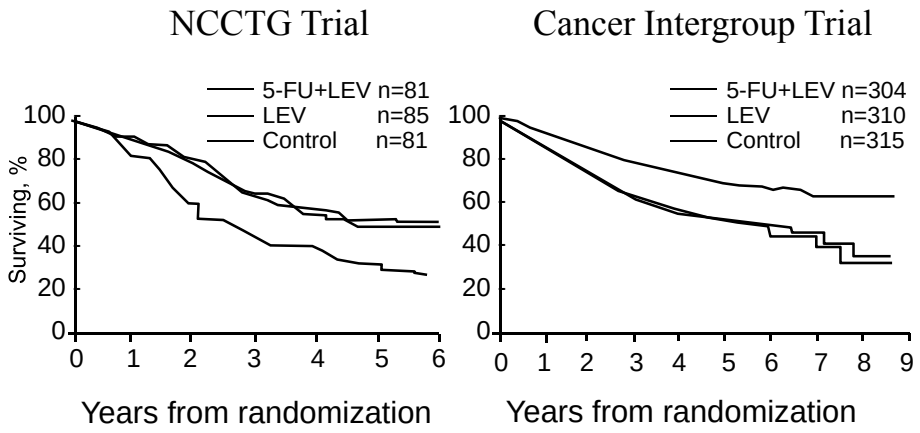
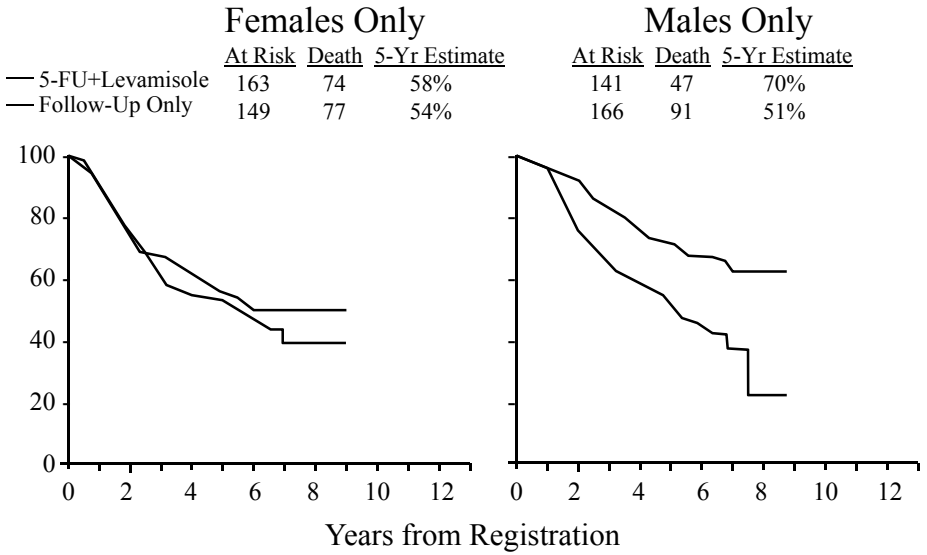


INTERGROUP STUDY 0035
Looking at Treatment Effect on Overall Survival



Duke's C Colon Cancer Adjuvant

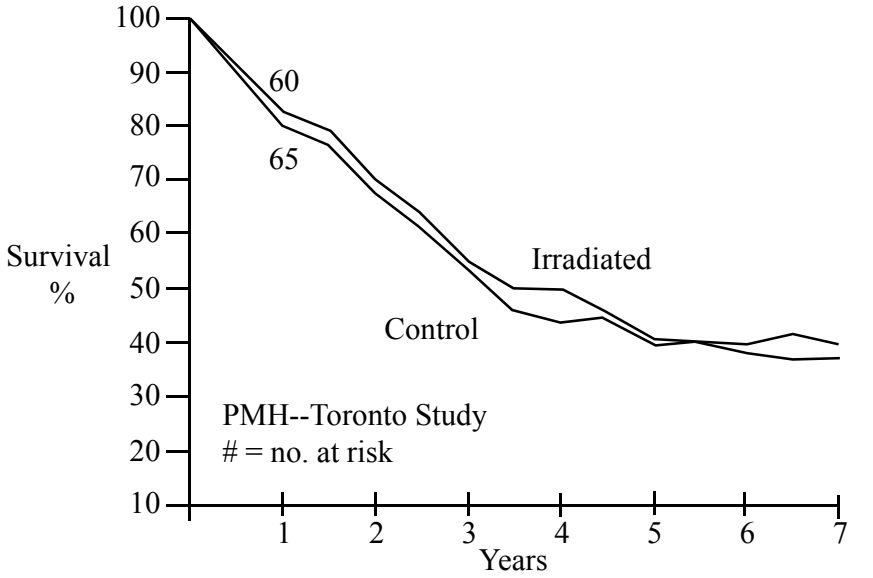
Relative Risk of Survival: $\frac{\text{5-FU + Levamisole}}{\text{Control}}$

Analysis Group	North Central Treatment Group Study (n = 162)	Intergroup Study # 0035 (n = 619)
All patients	0.72	0.67
Female	**0.57**	**0.85**
Male	**0.91**	**0.50**
Young	0.60	0.77
Old	0.87	0.59

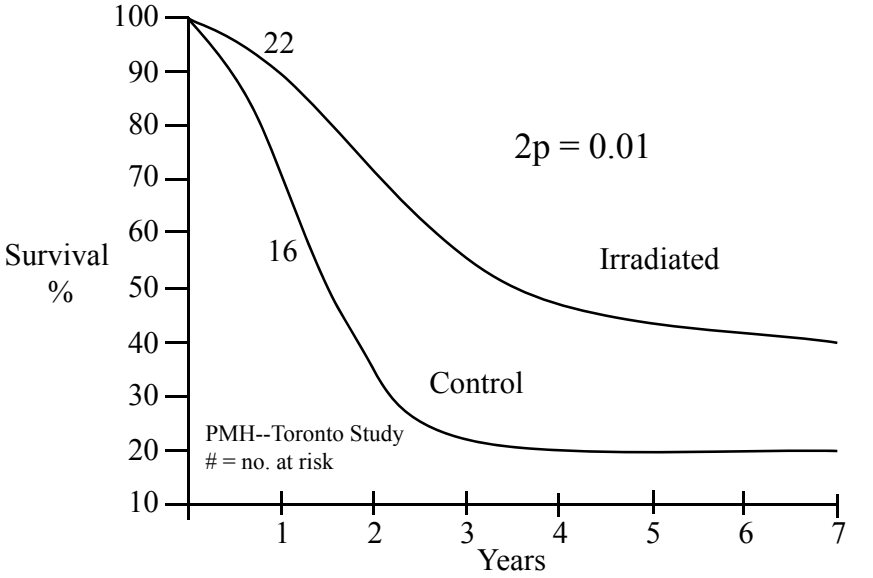
How Reliable are Exploratory Subgroup Analyses?

- Examples:
  - 5-FU + Levamisole in Adjuvant Colon Cancer NCCTG; Cancer Intergroup 0035
  - Pre-operative RT in Rectal Cancer Princess Margaret Hospital & M.R.C.

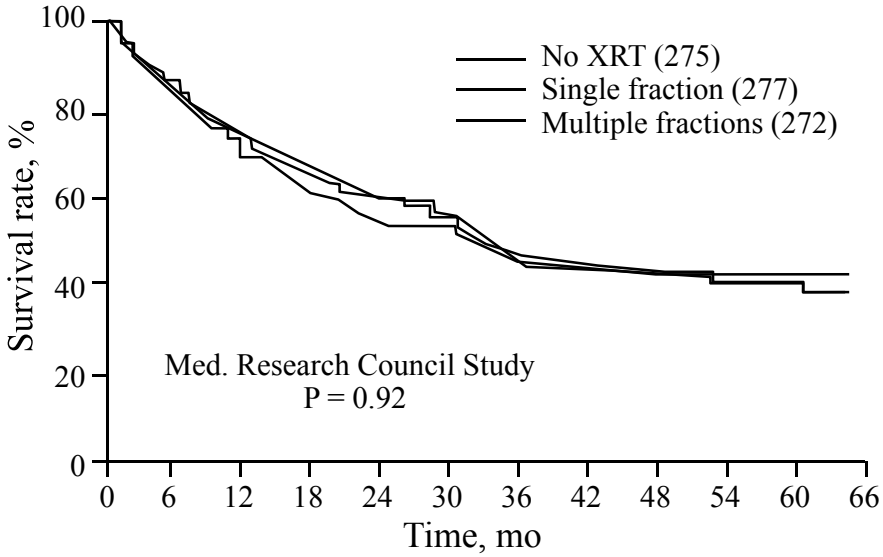
Survival of Patients with Rectal Carcinoma in Control and Irradiated Groups



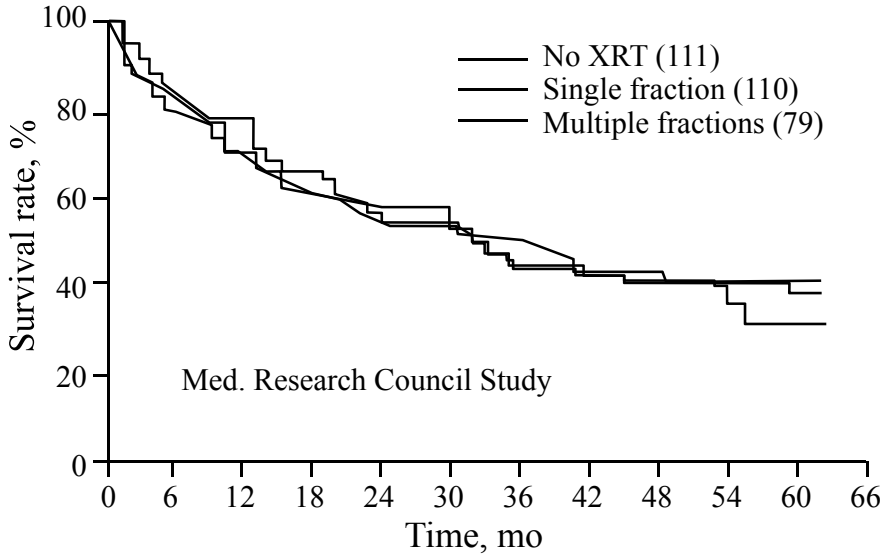
Survival of Patients with Dukes' Stage C Rectal Carcinoma in Control and Irradiated Groups



Survival by Treatment Allocated



Survival by Treatment for Dukes' C Cases



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Illustrations and Motivation:

Maternity Wards, ***Baseball*** & Clinical Research

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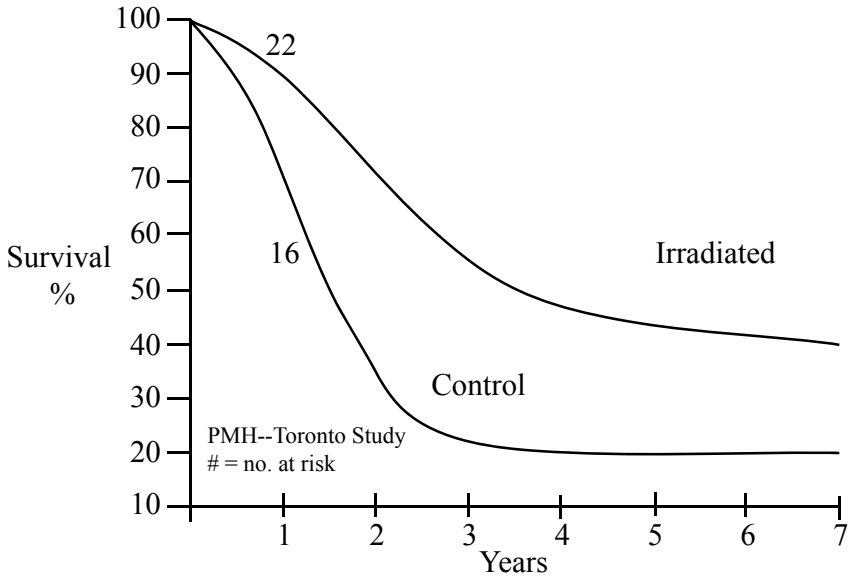

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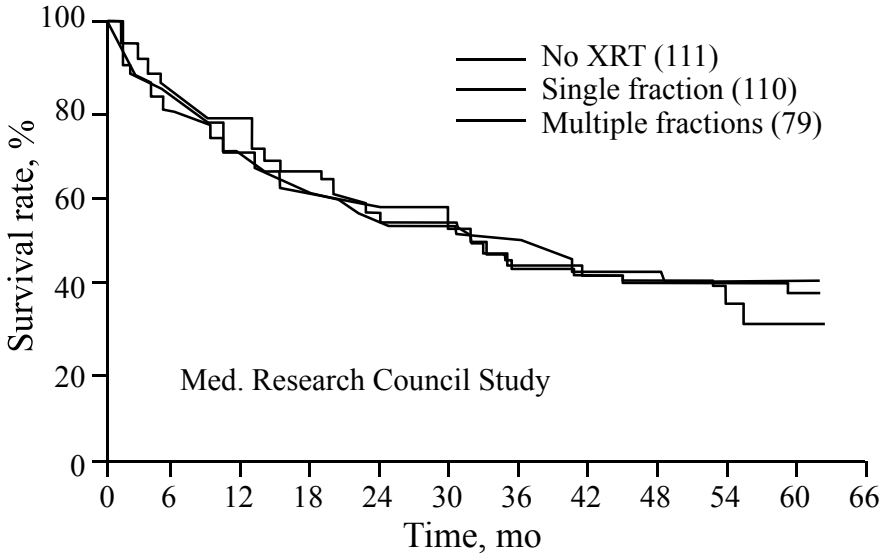

Thrombolytics in Acute Myocardial Infarction

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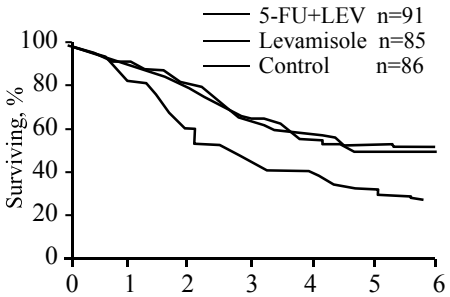
  - Subset restriction not confirmed by ISIS-2, ASSET, AIMS
  - While in ISIS-2:
    Aspirin beneficial overall…
    … yet **harmful to** patients with
    astrological signs **Libra** and **Gemini**

Can Efficacy or Safety Signals Discovered in Exploratory Analyses Be Viewed to be Reliable Results?

- Criteria to be simultaneously satisfied:
- ✓ << P-values *(e.g., Tysabri & PML)*
- ✓ Biologically plausible effect
  - ➢ *White Paper Illustration*
- ✓ Confirmed by external results

Surgical Adjuvant Therapy Of Colorectal Cancer

NCCTG Trial



Cancer Intergroup Trial

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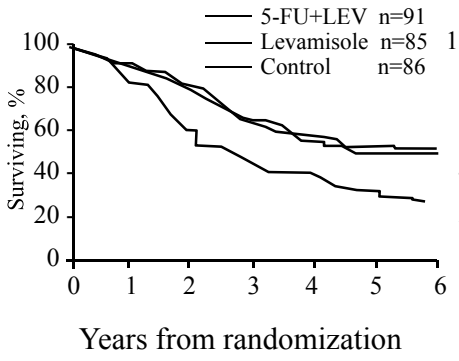

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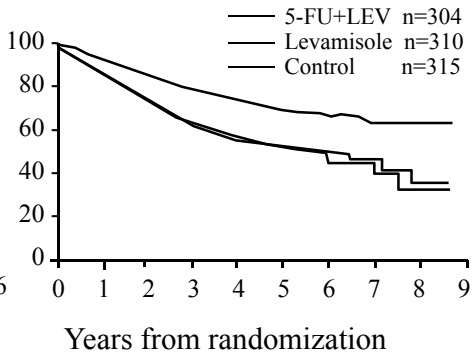


Pre-trial probability the intervention is effective is is $\pi = 0.04$

Then,

even if $\alpha = 0.025$ and $1-\beta = 0.90$,

Probability a trial positive will be a true positive is $36 / 60 = 0.60$

RESULT OF EXPERIMENT	TRUTH Positive	Negative	
Positive	36	24	60
Negative	4	936	940
	40	960	1000

Pre-trial probability the intervention is effective is
is $\pi = 0.60$ (when 1st trial is positive)

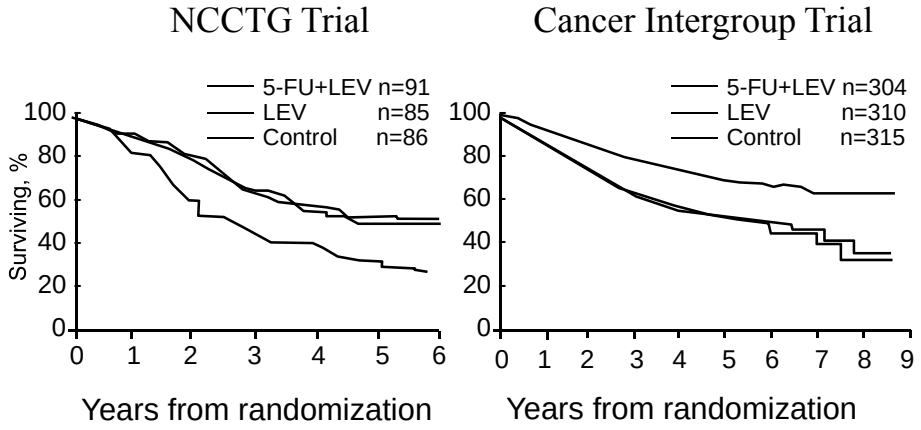
Then,

if $\alpha = 0.025$ and $1\text{-}\beta = 0.90$,

Probability a trial positive will be
a true positive is $540 / 550 = 0.98$

RESULT OF EXPERIMENT	TRUTH Positive	Negative	
Positive	540	10	550
Negative	60	390	450
	600	400	1000

Surgical Adjuvant Therapy Of Colorectal Cancer



"It isn't so much the things we *don't know* that get us in trouble.

It's the things we *know* that aren't so".

—Artemus Ward (1834-1867)

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20 vs 2: (.71, .99), $2p = 0.0001$
Meta-Analysis: 31 vs 13: (.55, .83), $2p = 0.0096$

Bias for "Positive" Results in Clinical Trials

- Protocol Specified Primary Objective of the Clinical trial:

- Very frequent wording:
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- Scientifically unbiased wording:
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~ What is the definition of a *successful* clinical trial?

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- The proper scientific response:
  "A clinical trial that *reliably answers* the questions the trial was designed to address"

Hazards of evaluating interventions Using observational databases

Mega doses of Vitamin C:

What is the effect on duration of survival in pre-terminal cancer patients?

- Linus Pauling: Loch Lomanside, Scotland

  Cameron, Pauling. *Proc Natl Acad Sci* 1976; 1978

  Median Survival: 50 vs. 210 days; 38 vs. 293 days

- Mayo Clinic sponsored randomized trial

  Moertel, Fleming, Creagan et. al. *NEJM* 1985; 312: 137-141

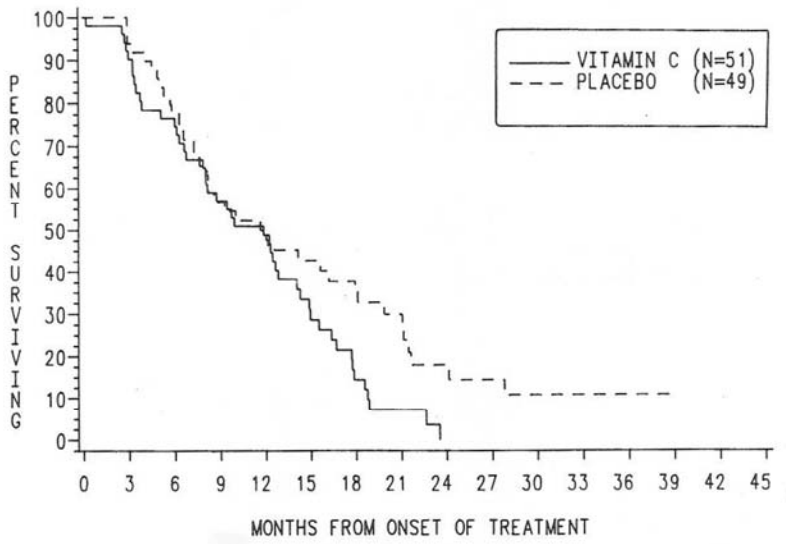

Figure 2. Survival Time from the Beginning of Therapy, According to Treatment Assignment.

Bias for "Positive" Results in Clinical Trials

…Andrew Fleming's insight from Psychology…

"Cognitive Dissonance"

…The Harvard Professor's Course…

…The Apparent Lack of Benefit in Males…

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- Abetimus Sodium: Reducing Renal Flare Rate in Lupus
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- Trial #3 conducted in high affinity subgroup
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- Trial #3 conducted in high affinity subgroup
  with prespecified truncation at 12 months follow-up:
  …early termination by DMC for futility.

Some Initial Conclusions

- *P-values* are only interpretable when you understand the sampling context from which they were derived
- Point estimates and confidence intervals are preferable to reporting *P-values* when findings about treatment effects from exploratory analyses are presented.
- Random High bias is real
- Exploratory Analyses usually should be viewed to be "Hypothesis Generating"
- Confirmatory Trials greatly enhance the reliability of conclusions

Principles & Insights

"The Goal of Clinical Research:

Principles & Insights

"The Goal of Clinical Research:
To *Determine Whether*,
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the Experimental Regimen
Is Safe and Effective"

The Mystery

Principles & Insights

The Substantial Consequences
Of Misleading Exploratory Analyses

InterMune GIPF #001
Idiopathic Pulmonary Fibrosis (IPF)

R → Actimmune (162)
R → Placebo (168)

Primary Endpoint: Progression-free Survival
- ✓ FVC ↓ by >10%
- ✓ A-a Gradient ↑ by > 5 mmHg
- ✓ Death

Enrollment: 9/00 - 9/01; Follow-up to 8/02

Secondary Endpoints:
- ✓ 10 listed, by "order of importance"
  …*Overall Survival was 7th*

Illustration: Confirmatory vs. Exploratory Analyses

Actimmune *vs* Placebo in IPF: 9/00 – 8/02
(Progression/Death: Target 20% vs 40% at 1 year)
Data Monitoring Committee Meeting: 8/19/02

GIPF-001	N	Progression	Death/Prog	Death
Actimmune	162	68 (42.0%)	75 (46.3%)	16 (18)
Placebo	168	75 (44.6%)	87 (51.8%)	28 (28)
		RR = 0.942	RR = 0.894	2p = 0.084
			2p = 0.53	(2p = 0.15)

Safety Profile	Pulmonary SAEs	Pneumonia SAEs	Vascular Disorders
Actimmune	41	20	7
Placebo	34	8	1

Actimmune in IPF

- 8/19/02: DMC Meeting, releasing data to sponsor leadership… Recommendation for follow-up of secondary endpoints to 11/02
- 8/27/02: Sponsor─FDA Meeting: FDA recognized the trial did not establish efficacy; FDA: OK to conduct confirmatory trial

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- 8/27/02: Sponsor─FDA Meeting: FDA recognized the trial did not establish efficacy; FDA: OK to conduct confirmatory trial
- 8/28/02: Sponsor released News Release:
  "*InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF…Reduces mortality by 70% in patients with mild to moderate disease, (p = 0.004). …The mortality benefit is very compelling and represents a major breakthrough in this difficult disease*."
  …interim data base with 16 vs. 28 deaths used
  …exploration of secondary endpoint, overall survival
  …exploratory subgroup of patients with "mild to mod disease"
- 9/02: Stock value rises; off label use of Actimmune in IPF soars
  …projected by sponsor to reach $400-$500 million /year .

Actimmune in IPF

- 9/5/02: DMC Chair Letter to Sponsor…
  "The claims for established survival benefit in the mild to moderate disease subgroup…are so fallacious that they would provide a humorous illustration of an absurd misrepresentation of exploratory statistical analyses if not for the serious consequences to patients, caregivers, and the investment community who might be mislead in their therapeutic and financial decision-making processes…I am calling on our colleagues at InterMune to identify corrective actions that could effectively address these serious misrepresentations..."

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- 10/17/02: DMC discovers sponsor is conducting illegal off-label advertising (through Priority Healthcare Corporation)…
  "*InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF…Reduces Mortality by 70% in Patients with Mild to Moderate Disease*"

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✓ More balanced presentation given on 11/05/02 at
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- 1/05: FBI Agents approach UW SPHCM Dean, seeking T. Fleming
  …subpoena issued to appear before attorneys for US Dept of Justice
  ...Deferred Prosecution Agreement

Actimmune in Mild-to-Moderate IPF

- GIPF #007 Trial: 2/04 to 10/07
  Primary Endpoint: Survival, Target RR = 0.50

- Data Monitoring Committee Meeting: 2/28/07

GIPF-007	N	Death
Actimmune	551	
Placebo	275	

Actimmune in Mild-to-Moderate IPF

- GIPF #007 Trial: 2/04 to 10/07
  Primary Endpoint: Survival, Target RR = 0.50
- Data Monitoring Committee Meeting: 2/28/07

GIPF-007	N	Death
Actimmune	551	80 (14.5%)
Placebo	275	35 (12.7%)

- 3/5/07: Sponsor Press Release: *"the DMC found the overall survival result crossed a predefined stopping boundary for **lack of benefit** of Actimmune® relative to placebo" and where overall mortality was "14.5% in the Actimmune group as compared to 12.7% in the placebo group."*

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Principles & Insights

"If you Torture Data Long Enough, They will Confess

***** Fleming TR "Clinical Trials: Discerning Hype from Substance" *Annals of Internal Medicine* 2010; 153:400-406

Some Additional Conclusions

- There should be a clear specification of and focus on the pre-specified primary analyses of the primary and secondary end points when submitting results for peer review and when disseminating results in press releases and journal publications.
- Protocols should have at most 3 or 4 pre-specified secondary analyses to further address multiplicity.
- Recognize strong bias for achieving "positive" results
- When refereeing journal publications, request:
  - the clinical trial protocol
  - the statistical analysis plan (i.e., the SAP)
  - the clinical study report

Some Additional Conclusions

- The criteria used by journal editors and reviewers in evaluating manuscripts should be based on the importance of the questions that the studies are designed to address and the quality of study conduct rather than on the level of positivity of study results .
- All clinical trials should be registered with ClinicalTrials.gov to reduce publication bias
- It should be recognized that bias will persist if meta-analyses include the hypothesis-generating trial.

Principles & Insights

Evaluating Safety

Illustration: Cancer Risk with Vytorin in Slowing progression of Aortic-Valve Stenosis

SEAS Trial	N	CA. Incidence	CA. Deaths
Vytorin	944	101	37
Placebo	929	65	20
Relative Risk:		1.55	1.78
95% C.I.:		(1.13, 2.12)	(1.03. 3.11)

Challenge:

Interpreting safety signals from exploratory analyses

Can Efficacy or Safety Signals Discovered in Exploratory Analyses Be Viewed to be Reliable Results?

- Criteria to be simultaneously satisfied:

✓ $<<$ *P*-values *(e.g., Tysabri & PML)*

✓ Biologically plausible effect

- *Ezetimibe blocks the absorption of phytosterols and other phytonutrients linked to protection against cancer, which provides some biologic plausibility that the drug could have an effect on the growth of cancer cells*

✓ Confirmed by external results

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• **IMPROVE-IT & SHARP Trials**	N	CA. Incidence	CA. Deaths
Vytorin	10,391	313	97
Control	10,298	326	72
Relative Risk:		**0.96**	**1.34**
95% C.I.:		(0.82, 1.12)	(0.98, 1.84)

Interpreting the SEAS, IMPROVE-IT & SHARP Trials Regarding Cancer Risk with Vytorin

✓ *Peto et. al. (NEJM, 2008)*

"The available results from these 3 trials do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer."

✓ However, safety is established by ruling out unacceptable increases in safety risks…

…i.e. by what you can say, not what you can't say…

Fleming (*NEJM*, 2008)

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Principles & Insights

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"Absence of Evidence
Is not
Evidence of Absence"

Fleming TR. Identifying and Addressing Safety Signals in Clinical Trials. 2008; *NEJM* 359(13): 1400-1402.

Characteristics Integral to being Effective as a Biostatistical Collaborator

- ✓ Statistical *Science*:
  Strong Training in Theory
- ✓ Insights into the *Art*:
  Appropriately applying Scientific Methods
  to effectively address real world problems
- ✓ *Communication* Skills, Oral and Written:
  - ➢ Ability to collaborate effectively
    with non-statistical scientists
  - ➢ Passionate and Organized

An Ideal We Should Strive to Achieve

- ✓ The Clinician's job description for a Biostatistician
- ✓ Not SSE (ref, Mary Foulkes)…
  rather, *True Collaboration*

The question initially posed by our colleagues
usually is not
what most needs to be answered

- ✓ Why aren't Biostatisticians
  more widely engaged as true collaborators?

Is it on us?

An Ideal We Should Strive to Achieve

- ✓ Rather than "*Statistical*" or "*Clinical*" Issues,
  collectively we and our collaborators face
  "*Scientific*" Issues
- ✓ Susan Ellenberg:
  …lessons from
  an ideal Data Monitoring Committee…

An Ideal We Should Strive to Achieve

- ✓ The "*Conscience of the Research Team*"
  (William Taylor, Mayo Clinic, 1977)

…Keeping in mind
the Principles & Insights...

…Bringing Objectivity,
Seeking to "Determine Whether"…

…Having the Courage
To Advocate for the Truth.