Composite Endpoints

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Outline

- Simple Phase III Trial
- Composite endpoints
- Co-equal primary endpoints
- Co-equal surrogate endpoints
- Combining 1^0 & 2^0 endpoints
- Ranking Methods
- Conclusions

Simple Phase III trial

- Choose a single relevant endpoint
  - Death
  - Ejection fraction of the left ventricle
- Size trial for 90% power to detect a clinically important effect
  - 20% reduction in mortality
  - .05 difference in EF

Sample size formula

- Treatment Effect: more is better
  - Pick a responsive endpoint
- Variability: less is better
  - Get more measurements/stable endpoint
- Events: more are better
  - Include sicker patients
  - Lengthen follow-up

Characteristics of a clinical endpoint (Neaton et al 1994)

- Should be relevant and easy to interpret.
- Should be clinically apparent and easy to diagnose.
- Should be sensitive to treatment differences.

More complicated world

- Occasionally, a single primary endpoint undesirable. Why?
  - Clinically important events are rare.
  - Effect of treatment manifested on a variety of important endpoints.

Example: ACES trial

- ACES—trial to evaluate antibiotics versus placebo in patients at risk of CHD events.
- Primary endpoint is
  - Hospitalization for unstable angina
  - CHD death
  - Nonfatal MI
  - Revascularization

Composite Concerns

- With a composite endpoint, relative importance of various constituent endpoints determined by frequency.
- CHD death or revascularization
  - CHD death 1%
  - Revascularization 10%

Composite Concerns

- Only include constituent endpoints who are reasonably influenced by treatment.
  - Treatment: 50% on death, 20% on MI

	Control rate	Treatment rate
Death	.01	.005
MI	.01	.008

- Death alone vs Death or MI: same power

Bonferroni approach.

- Use p-values for the two endpoints.
- Reject if p_1 or p_2 less than .05/2
- Inference drawn for each endpoint
- Good if treatment has entire effect on one endpoint or the other, don't know which one.

Example: PEPI

- Postmenopausal Estrogen/Progestin Interventions Trial. HRT's effect on risk factors for heart disease.
- 875 women assigned to 5 combinations.
- Primary endpoints
  - HDL-C
  - SBP
  - Serum insulin
  - fibrinogen

O'Brien (1984) Rank-Sum method

- Rank each outcome and calculate an average rank for each patient
- See if average rank differs between groups.

Sub	X_1	R_1	X_2	R_2	Avg R
Fred	3.3	2	87	1	1.5
Joe	4.1	3	105	2	2.5
Sam	1.7	1	1000	3	2.0

O'Brien OLS method

- Standardize each endpoint. Compute the average endpoint for each person and perform a t-test on the averages.

Sub	X_1	$(X_1-❍)/♦$	X_2	$(X_2-❍)/♦$	avg
Fred	3.3	.22	87	-.72	-.25
Joe	4.1	.87	105	-.42	.23
Sam	1.7	-1.10	200	1.14	.03

O'Brien GLS method

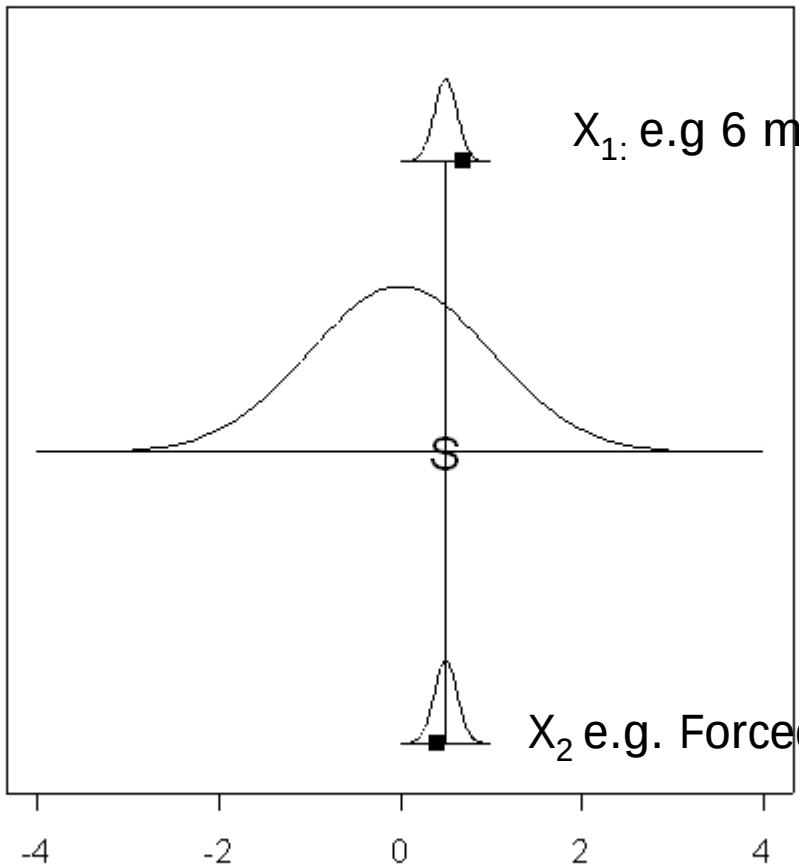
- Assume common treatment effect
  - e.g. 1 standard deviation on both endpoints.
- Calculate a statistically optimal estimate of using a weighted average. (more correlated endpoints, less weight).
- Pocock Geller Tsiatis (1987) generalize to binary/survival etc endpoints.
- Many other methods conceptually similar: specify a model with the same for many endpoints.

Latent Variable models

- Assume each person has an underlying severity, S, which influences several endpoints.
- E.g. MPS---Lysosomal enzyme deficency
  - **FVC**
  - **6 minute walk**
  - AHI
  - shoulder flexion
  - visual acuity
- Test whether the distribution of underlying severities is moved by treatment.

Conceptual framework for latent variable model

(latent) Severity dbn
in Treatment group



= Mean(S) in control - Mean(S) in treatment

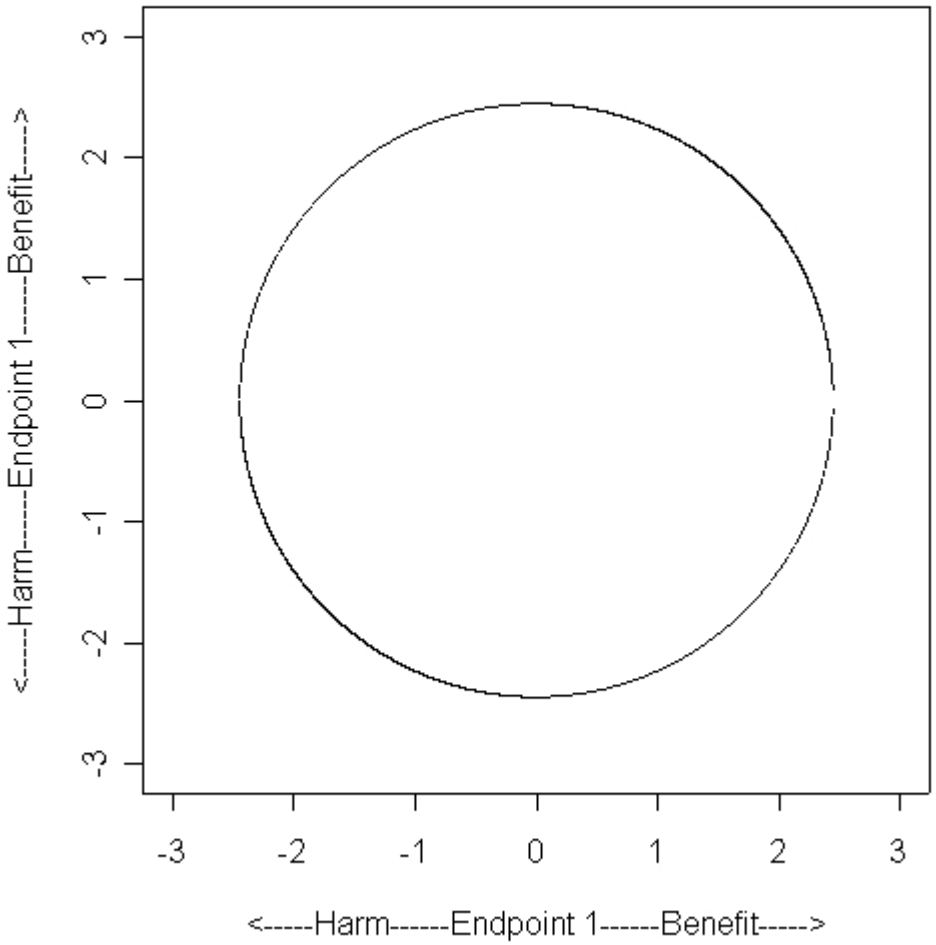
A model

- Simple Model
  - $Y_{i1} = B_{01} + D Z_i + b_i + e_{i1}$
  - $Y_{i2} = B_{02} + D Z_i + b_i + e_{i2}$
    - $e_{ij} \sim N(0, \quad Vej)$
    - $S_i \sim N(0, Vs)$

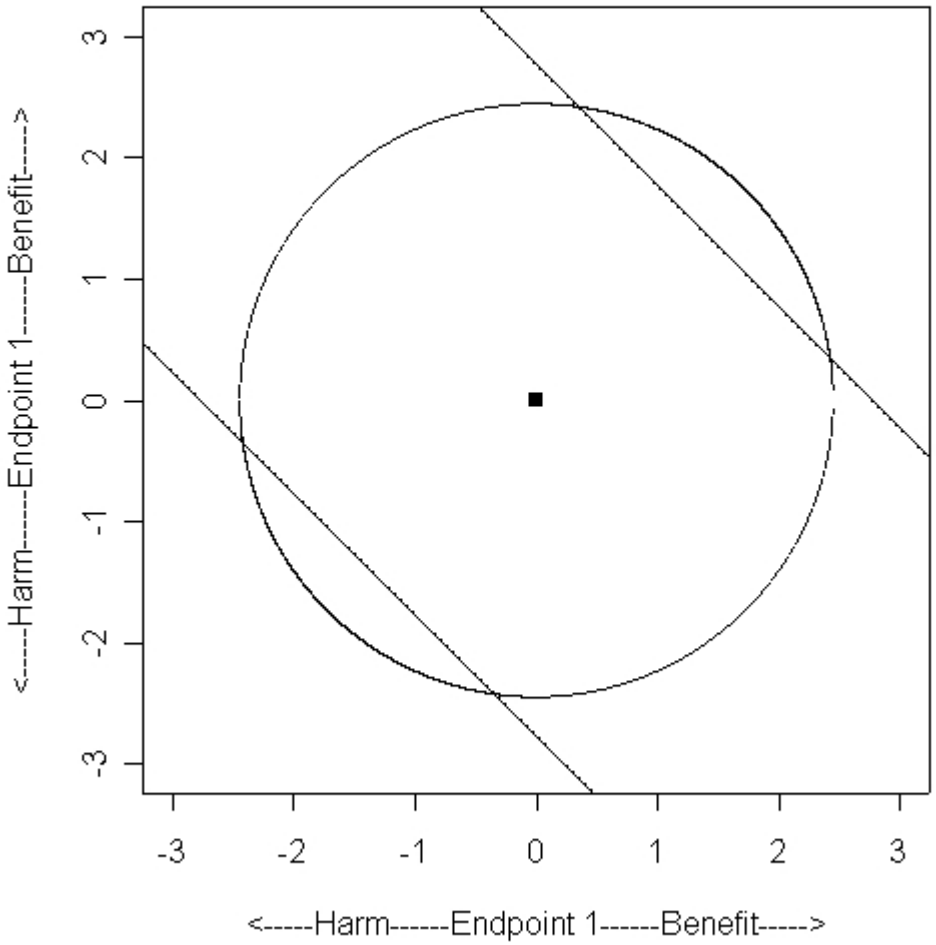
Global Tests

- Hotelling T^2---multivariate t-test
- Good for *any* treatment effect, so less good for uniformly beneficial treatment effects.

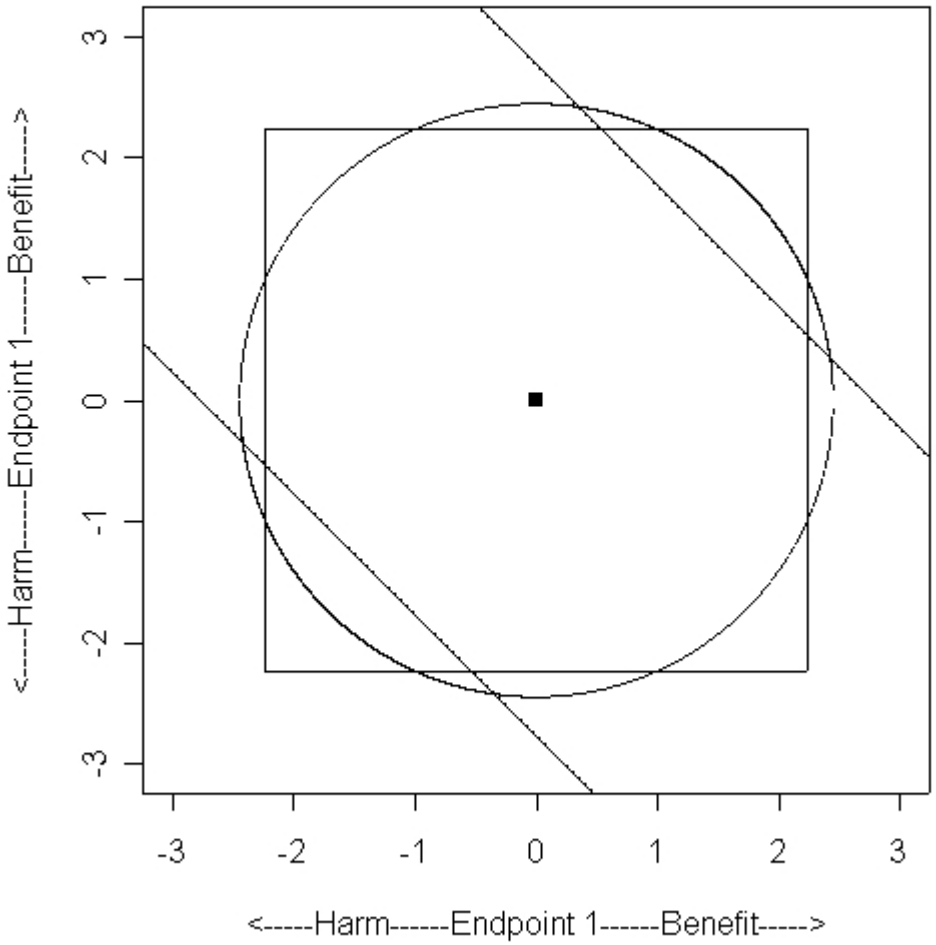
Rejection Region for Hotelling's T^2 Test



Rejection Regions for Hotelling's T^2 Test & O'Brien test



Rejection Regions for Hotelling's T^2, O'Brien, & Bonferroni Tests



Tilley et al (1996) for Stroke trial

- Trial of t-PA versus placebo in patients with acute ischemic stroke.
- Dichotomized 4 stroke scales.
- Discussed use of Bonferroni, Hotelling's Test & O'Brien's GLS test.
- Reject if
  - Mean(Z) > 1.96 * [(1+ 3 ❒
  - > 1.96 if ❒
  - 1.96/2 if ❒

Combining co-equal but surrogate endpoints

- Suppose both endpoints are surrogates.
- Ideally form a risk score.
  - $R = w_1$ DBP + w_2 SBP + w_3 serum insulin...
  - $R = w_1$ Hepatitis + w_2 sex for drugs + ...
- Do a t-test using R.

Combining 1^0 and auxiliary…

- 1^0 endpoint alone: use Wilcoxon Rank sum approach.
- Compare each pair of treatment/control patients
- Y_{ij} = 1 if "i" (in T) lives past "j" (in P)
- = 1/2 if both live
- = 0 if "i" (in T) dies before "j" (in P)
- Form mean(Y_{ij}) = Pr(live longer on T than P)
- Equivalent to ranking by death time.

Combining 1^0 and auxiliary…

- If both live, replace ½ with
  - p_{ij} = Pr(i lives longer than j | CD4s)
- May be useful if
  - CD4/death relationship in past = future
  - Treatment effects CD4 counts & they differ at end
- Similar approach taken by Faucett Schenker Taylor (2002) who imputed death times.

“Utility” Ranking Methods

- May be hard to say MI is half as bad as death. But clearly death is worse.
  - Death is worst
    - Rank by death time
  - 2 Strokes worse than 1
    - Rank by time of first stroke
  - 1 Stroke worse than nothing
    - Rank by time of stroke.
- Compare the ranks between groups

Table III. The cards ordered by consensus ranks and the mean and standard deviation of the 19 ranks

Consensus rank	Time of event (years) 0	1	2	3	4	Card number	Rank Mean	Rank Std	Time to death	Number of events
1	*					6	1·2	0·4	0·4	1
2	@					8	1·9	0·5	0·4	1
3	@					27	3·0	0·3	0·8	1
4		D				29	4·0	0·3	1·1	1
5		S	*			35	5·3	0·9	2·0	1
6			S D			16	6·9	1·5	2·1	2
7			S	S *		28	7·5	1·4	2·9	3
8	H		H	D		1	8·6	1·8	3·0	3
9			H	*		40	8·8	1·6	2·8	2
10			H	D		13	11·5	1·8	3·0	2
11			S	@		39	11·7	1·8	3·3	2
12				*		24	12·2	2·7	2·8	1
13		S			H @	21	12·2	3·1	3·7	3
14		H		@		2	12·5	1·0	3·5	2
15				H H @		38	15·2	2·3	3·4	3
16				D		10	16·7	2·1	3·5	1
17				@		36	17·6	2·2	3·6	1
18					*	34	18·5	1·6	3·7	1
19			S	S S		32	21·0	8·1		3
20	S		H			15	21·5	1·9		2
21	H	S				42	21·7	1·9		2
22	H	H				3	23·5	4·7		2
23	H H					19	23·8	4·6		2
24	S				S	4	24·2	4·0		2
25		H H	H			14	24·7	4·4		3
26		S S				20	25·2	4·6		2
27		H	S			23	27·7	3·7		2
28	S					18	28·4	5·3		1
29			S	S		17	28·6	4·4		2
30		H			H	26	30·0	4·4		2
31			H		S	30	30·9	3·5		2
32				H S		41	31·9	3·7		2
33				S H		9	32·2	3·6		2
34	H					12	32.4	4.7		1
35				S S		37	34·0	3·5		2
36		H				33	35·1	3·4		1
37				H	H	31	35·7	2·8		2
38				S		7	35·8	3·5		1
39				S		22	38·5	2·7		1
40				H		43	39·5	2·9		1
41					S	5	39·8	2·0		1
42					H	11	41·4	2·5		1
43						25	43·0	0·0		0

Time of event (years)

The mean and std (standard deviation) of the rank are based on the sample of 19 rankers.

H non-fatal heart attack
@ fatal heart attack
* fatal stroke
S non-fatal stroke
D death from neither heart attack nor stroke

HIV vaccine trials

- Want HIV vaccine to reduce acquistion and also post-infection viral load for those infected. How to combine?
  - Those who are uninfected get best rank
  - Those who are infected are ranked by viral load “setpoint” lower setpoints get higher ranks.

Weighting

- You may not be interested in weighting, but weighting is interested in you.
- Approaches we discussed.
  - Equal weight for all endpoints (e.g. OLS)
  - More weight for frequent events (e.g. composite)
  - Less correlated outcomes more weight (e.g. GLS)
- Clinically interpretable weights?

Conclusions

- Common approaches are to pick a composite endpoint or adopt a Bonferroni correction.
- Clinical relevance / interpretability paramount.
- Appropriate approach depends heavily on the application.
- Novel endpoints/analysis approaches should be thoroughly investigated.

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Mariamman: Goddess of pox

- Afflicted individuals provide offerings
- Follow them home
- Successful ring vaccination
- Smallpox eradicated

Novel Design Issues

- Would a crossover trial make sense?
  - Area under EDSS curve over time.
- Enroll patients during a remission?
- For a phase II study, could a placebo be ethically used for a short while?
- Could all patients receive drug at end of study?
- Can we cross-over at time of failure?

Aldurazyme trial in MPS

- MPS: lysosomal enzyme deficency, leads to GAG accumulation with multisystemic effects.
- Inclusion criteria:
  - Stand 6 minutes, walk > 5 meters
- weekly IV infusion for ½ year.
- N=45
- Endpoints: **FVC, 6 minute walk**, AHI, shoulder flexion, visual acuity.

Phase 3 Study: Post-Hoc Analysis Composite Endpoint

Placebo

Patient	FVC	6MWT	SHFLEX	AHI	ACUITY
	11%	54m	20 deg	10 ev/hr	2-lines
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					

Aldurazyme

Patient	FVC	6MWT	SHFLEX	AHI	ACUITY
	11%	54m	20 deg	10 ev/hr	2-lines
24					
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27					
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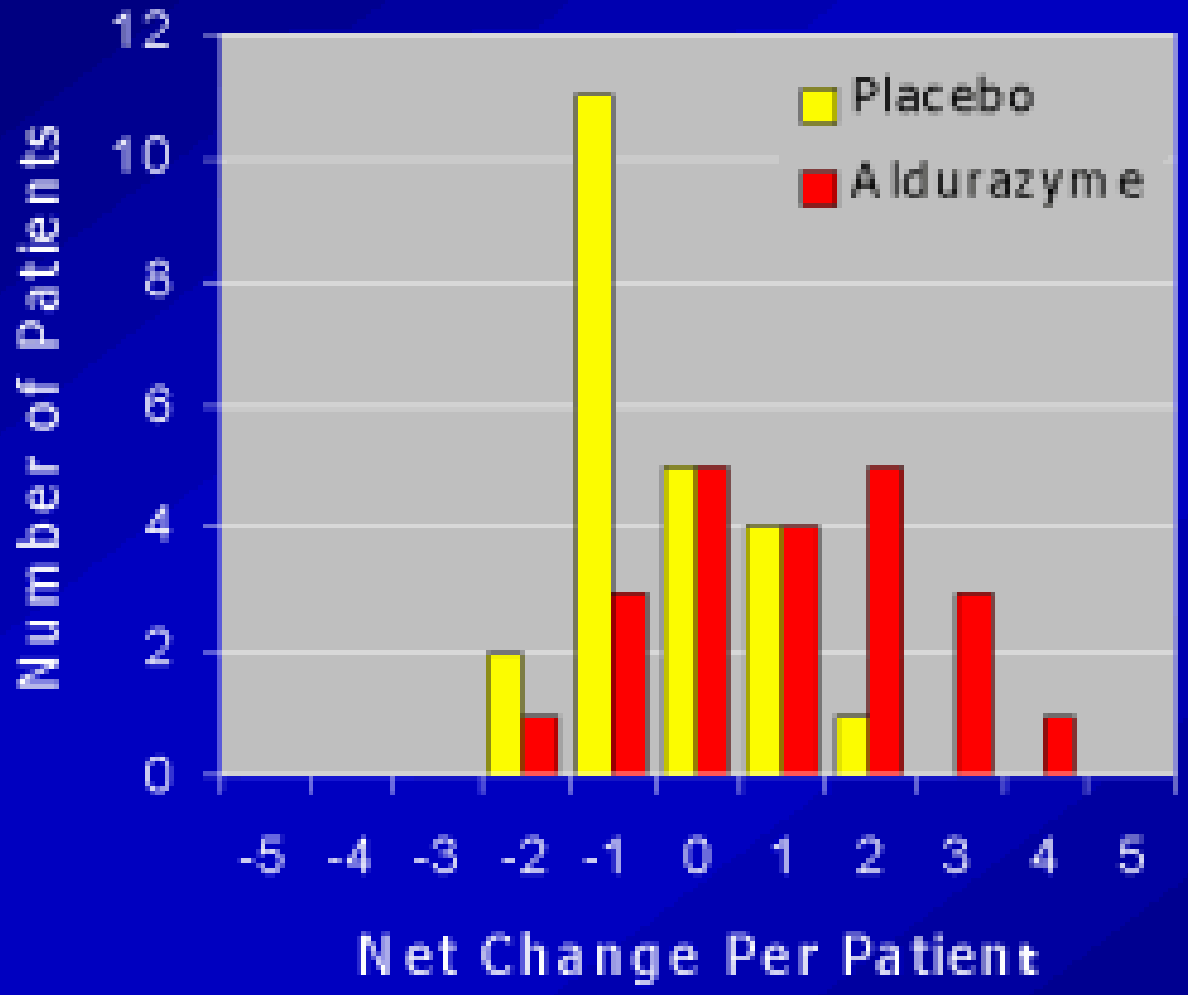
40					
41					
42					
43					
44					
45					

Clinically Significant Changes

Improvement | Decline | No Change | Not Available

Phase 3 Study: Post-Hoc Analysis Aldurazyme Leads to Net Improvement



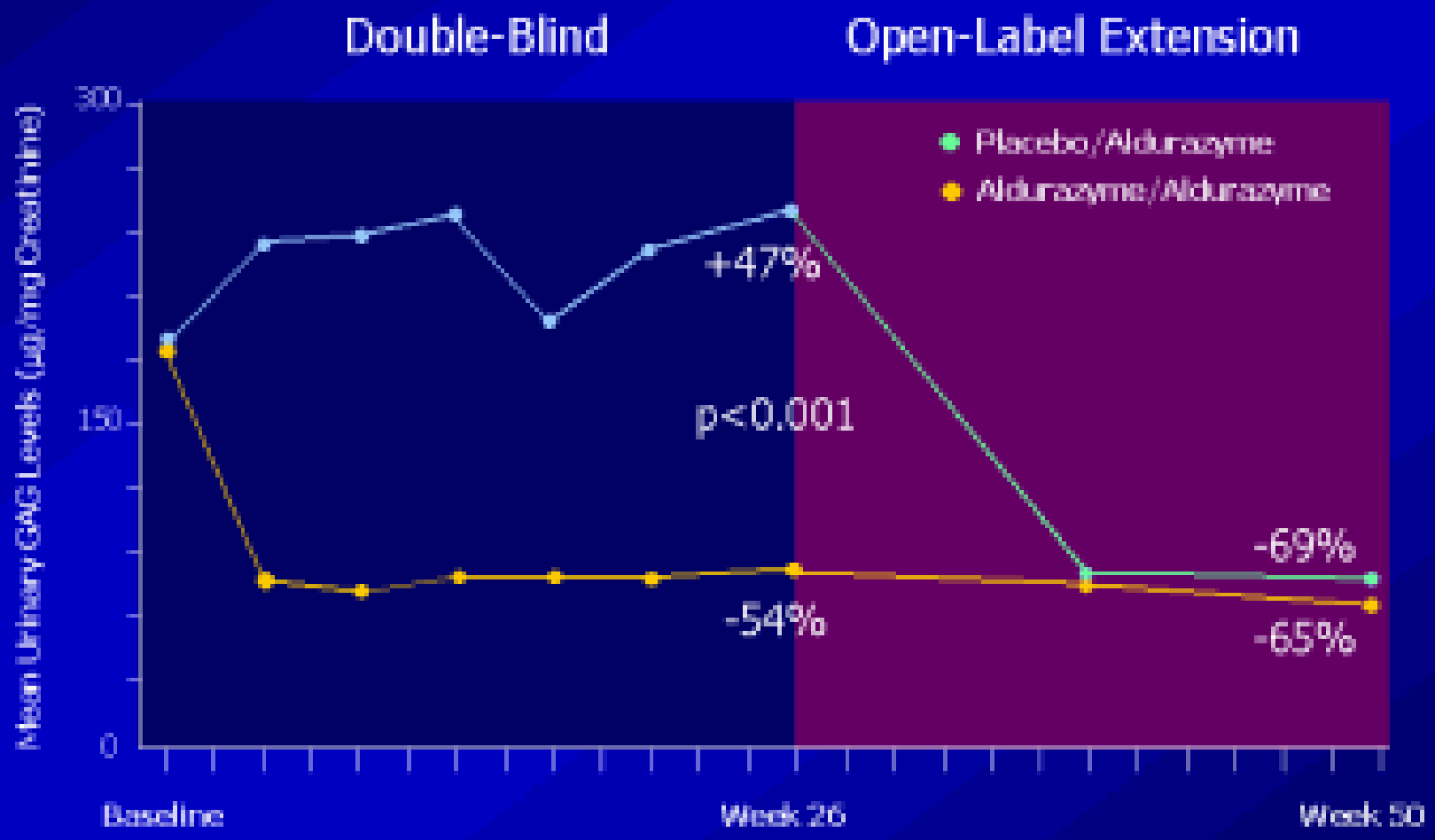
Responders

59% Aldurazyme
22% Placebo
($p=0.016$)

Mean Net Change

1.0 Aldurazyme
-0.4 Placebo

Phase 3 Study: Aldurazyme Reduces Urinary GAG Levels

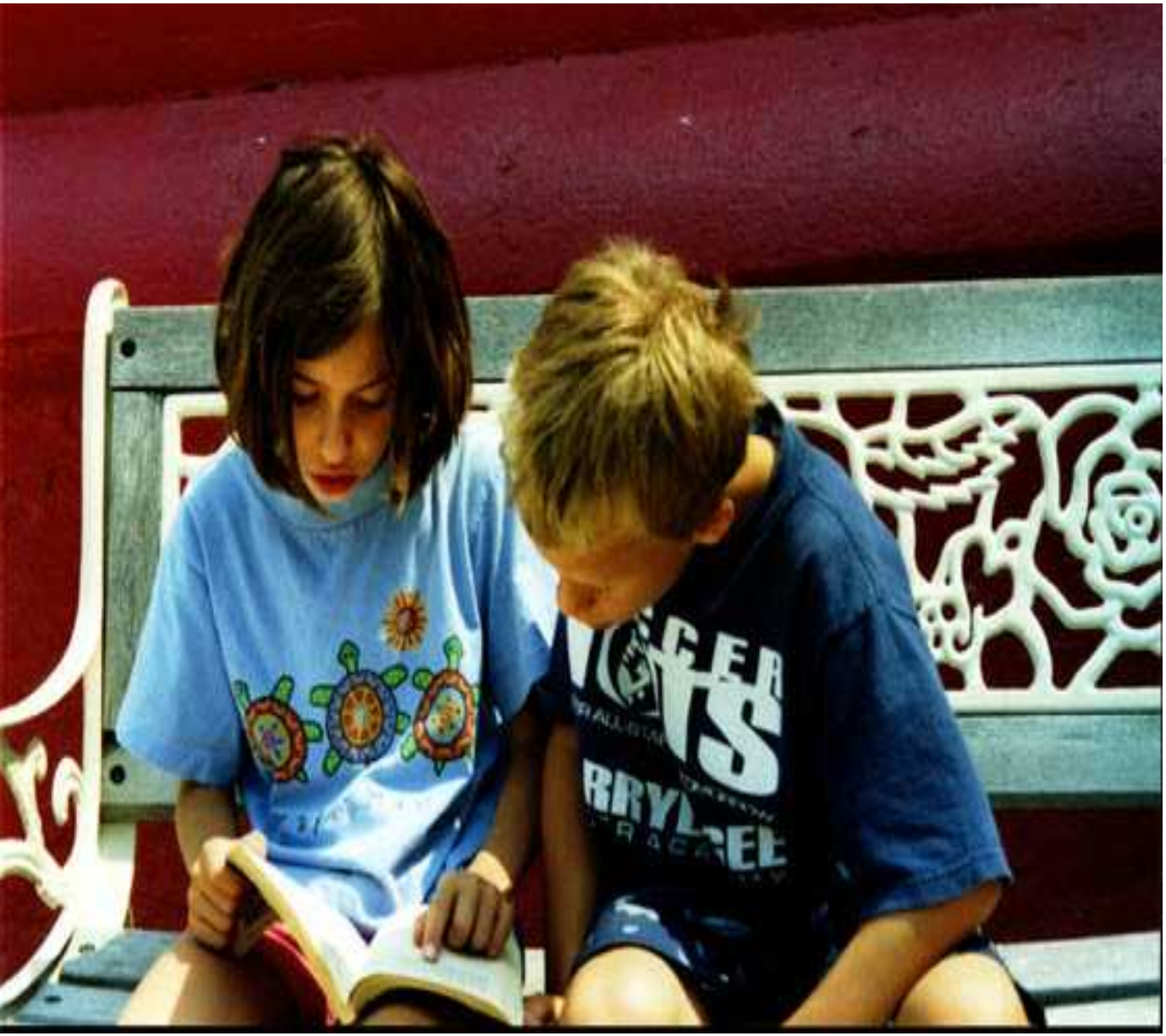


Example: asthma score

- Asthma: manifold symptoms, periodic worsening.
- Zhang, Song, Reiss (2004) proposed
  - PEF decrease >20%
  - 2+ puffs/day of beta-agnoist
  - Increase in symptom score > 50%
  - 3+ nighttime awakenings
  - PEF < 180 L/min
  - Hospital visit
- Showed good correlation with other global evaluations.

Two endpoints—setup

- Let X_1 and X_2 be two endpoints.
  - Two stroke scales, DBP & SBP, time to AIDS/Death & CD4.
- Let Z_1 and Z_2 be the associated standardized test statistics.
  - E.g. two tests of proportions, two t-tests, log-rank & t-test.
- Let p_1 and p_2 be the two p-values.
- Let's assume X_1 and X_2 are independent

Ranking generalization

- Compare each pair of treatment/control patients
- $= 1$ if "i" (in T) does better "j" (in P)
- $Y_{ij} = 1/2$ if same
- $= 0$ if "i" (in T) does worse "j" (in P)
- Can compare "i" & "j" over common followup.