Adverse Event Signal Detection

Overall Comparisons, Future Projections and False Discoveries

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Example

- Phase 3 trial:

  449 AEs observed, N_A and N_B about 500

- 50 AEs have z-values > 1.96

  Under the null, expect 11 AEs (= .025*449)

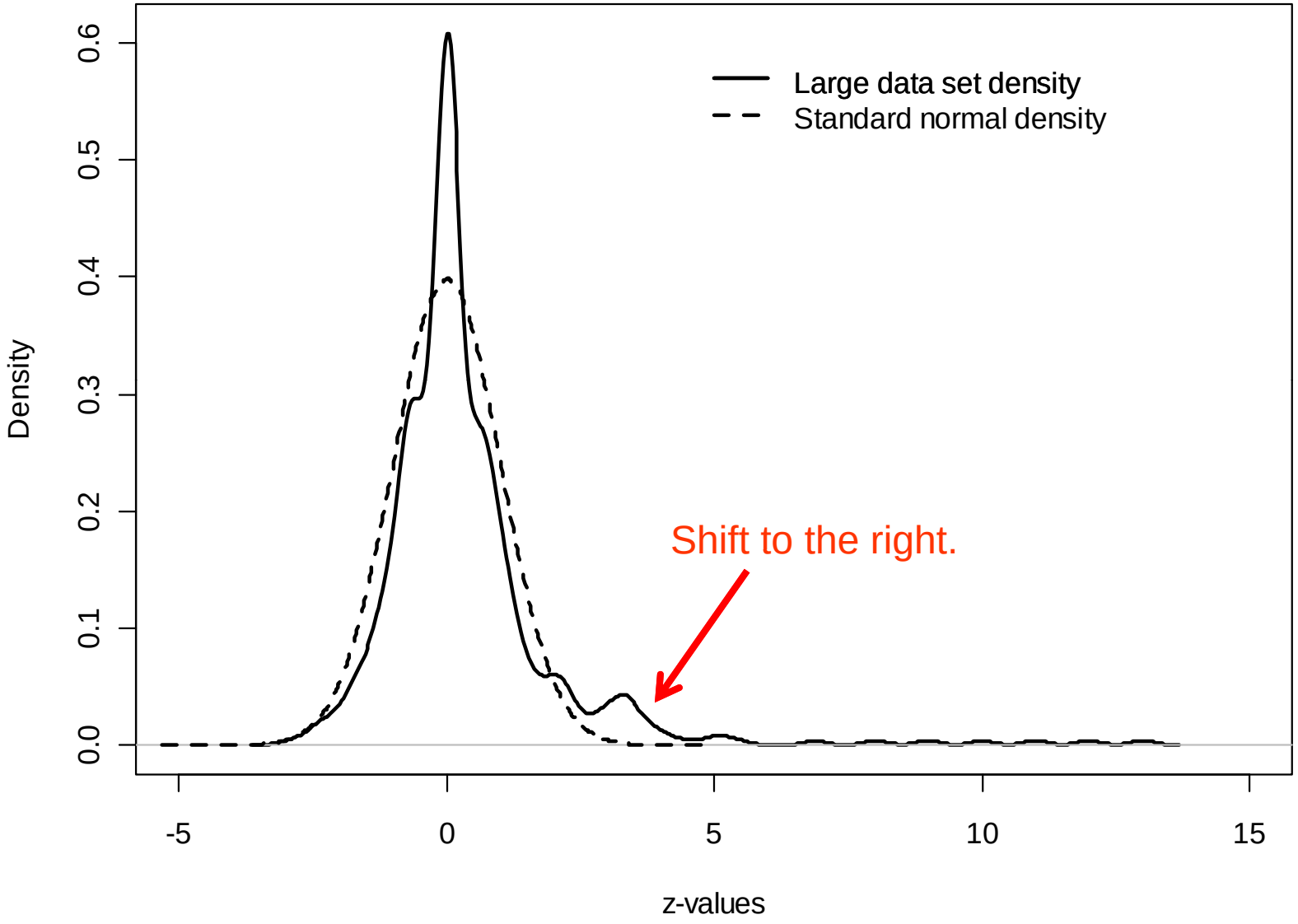
Question of Interest

- How many more subjects would experience AEs if trial period is extended?

Outline

- **Step 1**: graphically compare z scores with null distn
- **Step 2**: flag AEs by controlling FDR
- **Step 3**: for each AE, project number of subjects with a given AE into the future, using ALL AE data
- **Step 4**: Re-flag AEs by controlling FDR
- Pay attention to new AEs flagged. Informal inference.

Example: Graphical Comparison



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FDR: q-values (Storey's FDR)

- FDR: false discovery rate
- q-value is to FDR what p-value is to PCER
- Interpretation: Suppose for AE i q-value = 0.01. Then we expect 1% of AEs with p-value < 0.01to be false positives

Example data set: 29/449 AEs (6.5%) had q-values < 0.025

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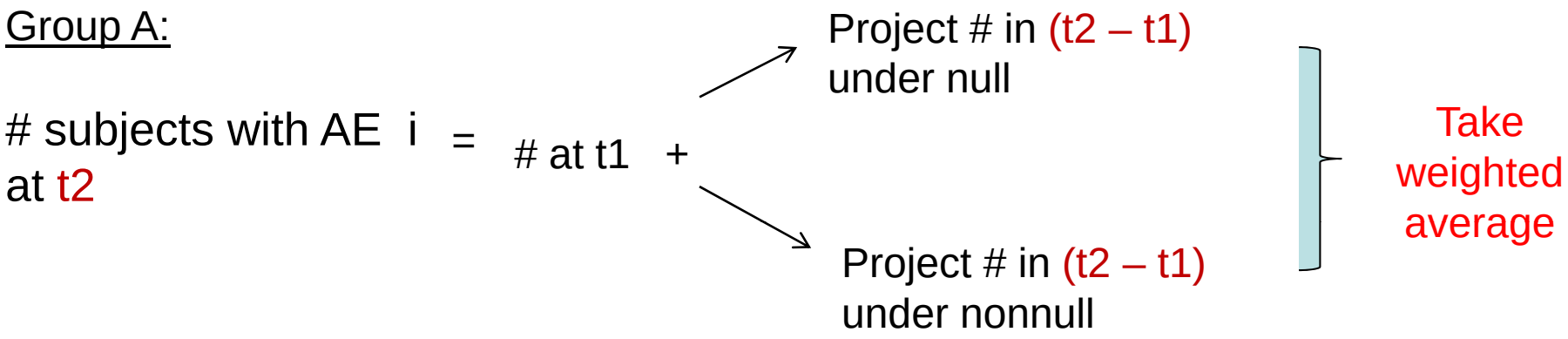
Projections: New Idea



New Approach

$$\#\text{ at t2} = \#\text{ at t1} + w * \#\text{ in (t2-t1) under null} + (1-w) * \#\text{ in (t2-t1) under nonnull}$$

$$w = P(\text{null true for AE i} \mid z_i)$$

(Efron's empirical Bayes idea, JASA 2004)

of Subj with AE *i*

Treatment	T1	T2 = T1 + delta		
		Under H_0	Under H_1	Weighted
A	20	33	36	34
B	10	23	19	22
A-B	10	10	17	12
w_i= 0.7				

No. with event under H_0 or H_1 is modeled given observed data

$w_i = P(\text{null true for AE i} \mid z_i)$

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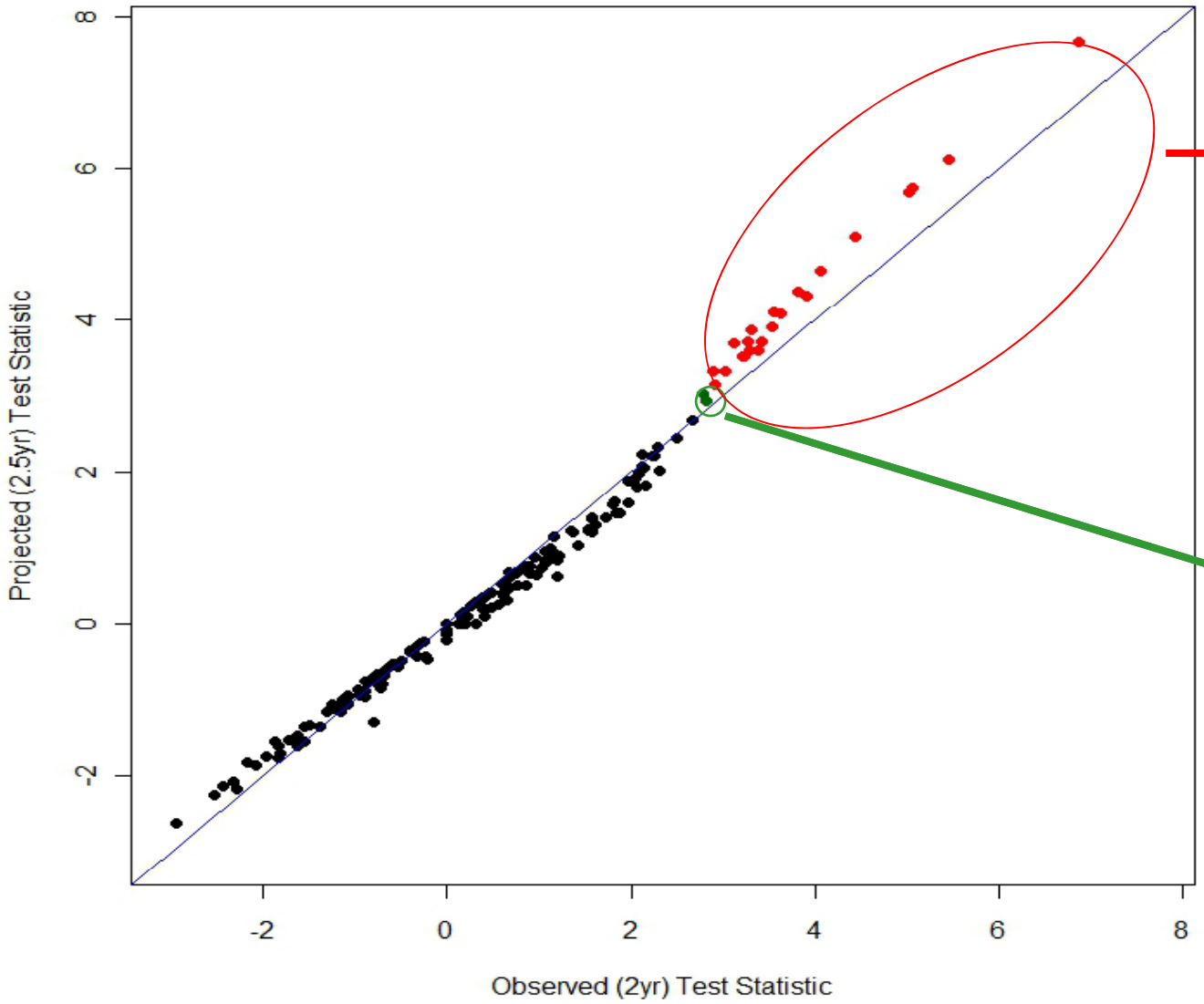
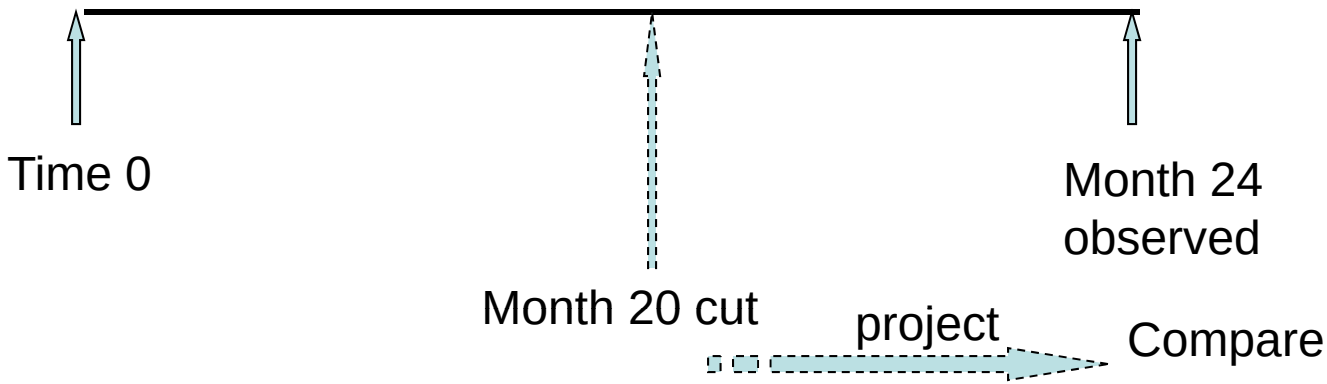
Example data set: 24 mth and 30 mth Z-values



29 significant AEs at the end of study

Additional **2** flagged by projection

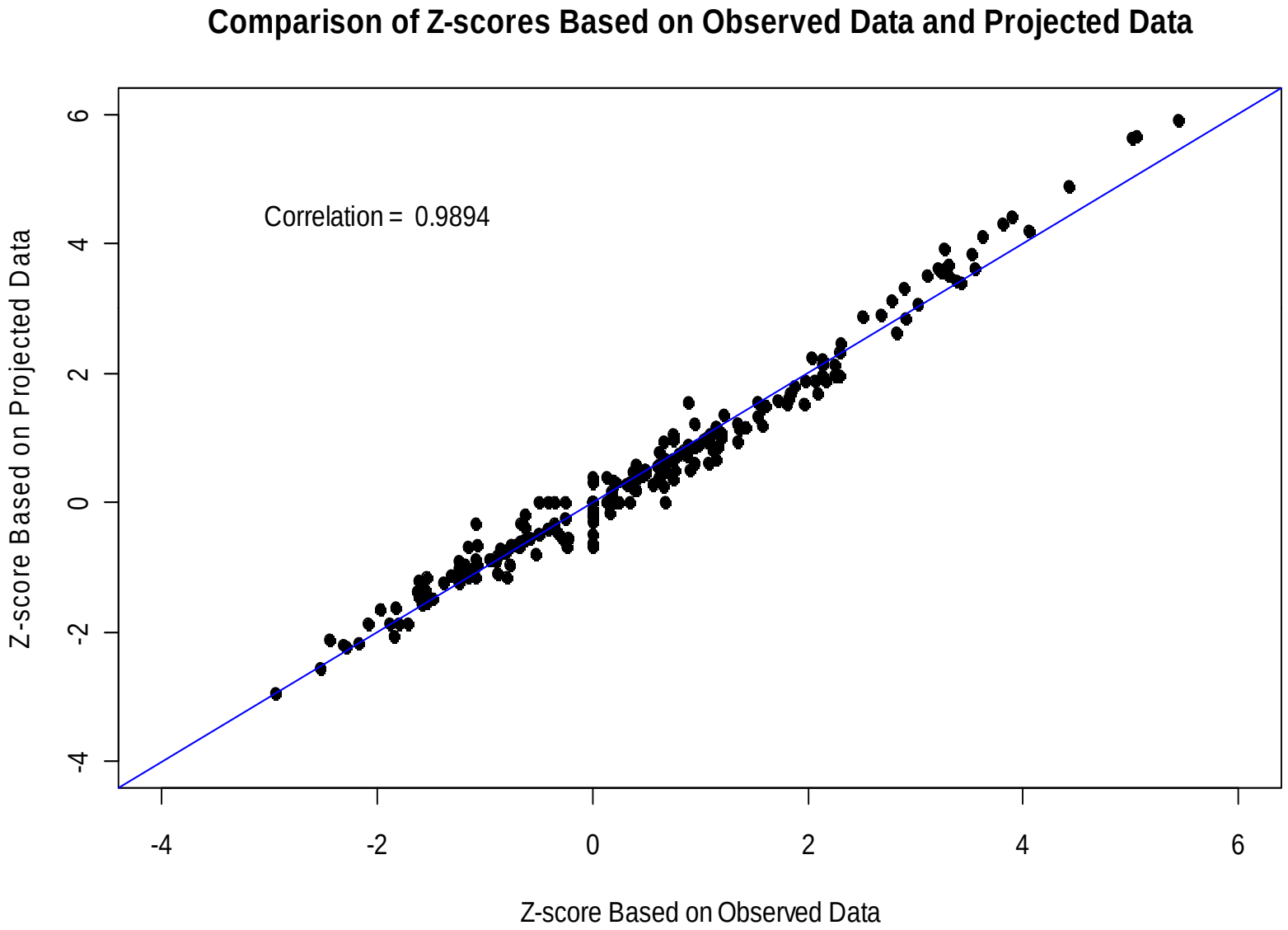
Reality Check: Projecting from 20 to 24 Months



- Assumed survival distribution is exponential.

- Did not account for subjects who were censored b/t Months 20 and 24

Reality Check: Projecting from 20 to 24 Months



Recap: Key Elements

- Compare observed data with N(0,1)
- Weight each AE to reflect the null and non-null simultaneously (empirical Bayes)
- Project # with AEs in the future: gain information
- q-values: apply to observed time and future time. Pay attention to additional AEs flagged

Pros and Cons of Method

- Pros
  - Helps with: “what would happen if trial period extended?”
  - Projection for AE i based on ALL AE data

- Cons
  - Assumes all subjects risk-free at observed time are at risk until future time
  - Doesn’t work with expected or acute events

- Additional details in “Adverse Event Signal Detection: Overall Comparisons, Future Projections and False Discoveries” (J Ma, J Ganju, J Huang). *Submitted for publication.*