Adding Value to Clinical Data

Practical issues related to the use of biomarkers in a seamless Phase II/III design

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Contents

Chapter 1
Introduction

- Definitions
- Age-related macular degeneration
- A Phase II/III concept
- A potential solution

1.1 A few definitions

Table 1 | Definitions of biomarkers and surrogate end points

Term	Definition
Biomarker	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[2]
Prognostic biomarker	Biomarker that forecasts the likely course of disease irrespective of treatment.
Predictive biomarker	Biomarker that forecasts the likely response to a specific treatment.
Clinical end point	Measurement providing systematic information on how a patient feels, functions or survives.[3]
Surrogate end point	Measurement providing early and accurate prediction of both a clinical end point, and the effects of treatment on this end point.
Validation	Confirmation by robust statistical methods that a candidate prognostic biomarker, predictive biomarkers or surrogate end point fulfills a set of conditions that are necessary and sufficient for its use in the clinic

Buyse *et al.*, *Nat Rev Clin Oncol* 2010

1.2 Age-related macular degeneration: background

- AMD is a disease associated with aging that affects the central vision.
- It is the leading cause of blindness in patients aged over 50 in the Western World.
- Two forms: dry (90% of pts.) and wet (10%).

1.3 Age-related macular degeneration: endpoints

- The FDA-approved endpoint: the loss (or gain) of at least three lines of vision *vs.* baseline at one year.

- A more efficient strategy: use longitudinal measures of the change in visual acuity *vs.* baseline (VAC, the change in the number of letters correctly read).

- The binary response is linked to the VAC: line on the vision chart = five letters.

1.4 A Phase II/III strategy

- Consider K ($k = 1, \ldots, K$) treatment groups and a control group ($k = 0$).

- Phase II/III trial:
  - ▷ Select one of the treatments in the first (Phase II) stage.
  - ▷ Compare the selected one with the control in the second (Phase III) stage.

- Issue: control of Type I error; power

- Additional: use a biomarker in Phase II, and a clinical endpoint in Phase III.
  - ▷ For instance: VAC for treatment selection, vision gain/loss for testing

1.5 A suitable design

- Stallard & Todd (*Statistics in Medicine*, 2003): a Phase II/III design with treatment selection, using the same endpoint in both stages.

- Todd & Stallard (*Drug Information Journal*, 2005): extension allowing *different* endpoints in different stages.

- We may consider using the designs in a context of a longitudinal trial in AMD.
  - ▷ The mean and variance-covariance structures of the longitudinal measurements of VAC can be described by relatively simple models that seem to fit the data for two different experimental drugs (Burzykowski & Buyse, *Pharmaceutical Statistics*, 2010).

Chapter 2
Visual-acuity-change modeling

- AMD case studies
- Mean structure
- Variance functions
- Correlation structure

2.1 AMD case studies

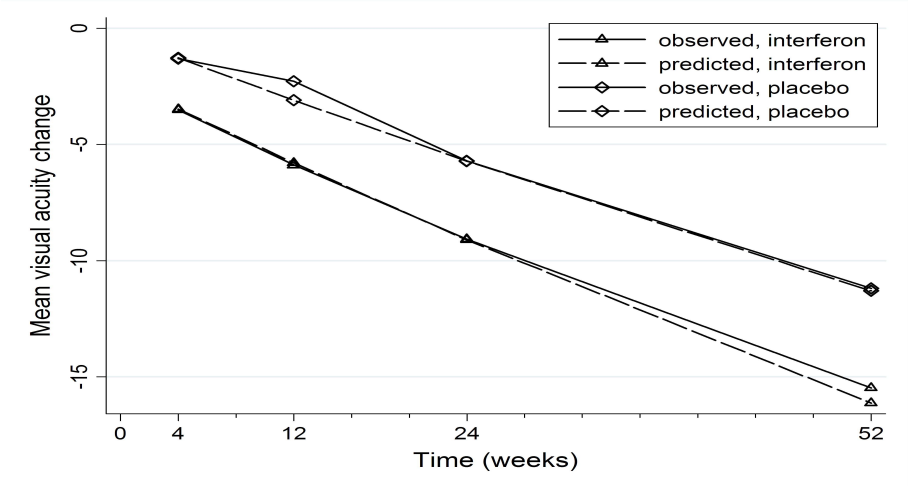
Two trials:

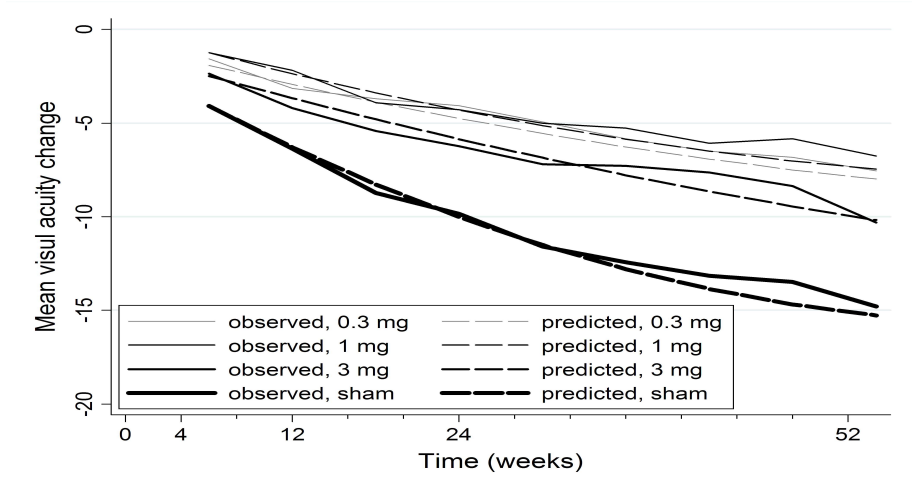
- Interferon-α ($N = 114$) vs. placebo ($N = 117$)
  - ▷ Pharmacological Therapy For Macular Degeneration Study Group (*Archives of Ophthalmology* 1997)
  - ▷ VAC measurements at 4, 12, 24, and 52 weeks
- Three doses of intravitreous pegaptanib vs. sham
  - ▷ Gragoudas *et al.* (*NEJM* 2004)
  - ▷ 0.3 mg ($N = 286$), 1 mg ($N = 292$), 3 mg ($N = 286$), and sham ($N = 291$)
  - ▷ VAC measurements every 6 weeks ($6,\ 12,\ \ldots,\ 48$) and at 52 weeks

Analyzed using a general linear model.

2.2 Mean structure

	Interferon-α trial		Pegaptanib trial			
	Interferon-α	Placebo	0.3 mg	1 mg	3 mg	Sham
Intercept	-2.28	-0.33	-1.22	-0.82	-0.03	-1.66
	(-4.14,-0.42)	(-2.17,1.50)	(-2.63,0.18)	(-2.22,0.59)	(-1.43,1.37)	(-3.06,-0.26)
time	-0.30	-0.23	-0.21	-0.19	-0.21	-0.42
	(-0.50,-0.10)	(-0.43,-0.04)	(-0.33,-0.10)	(-0.31,-0.07)	(-0.33,-0.09)	(-0.54, -0.31)
time^2	0.0006	0.0005	0.0009	0.001	0.001	0.003
	(-0.002,0.004)	(-0.002,0.004)	(-0.001,0.003)	(-0.001,0.003)	(-0.0004,0.003)	(0.001,0.005)

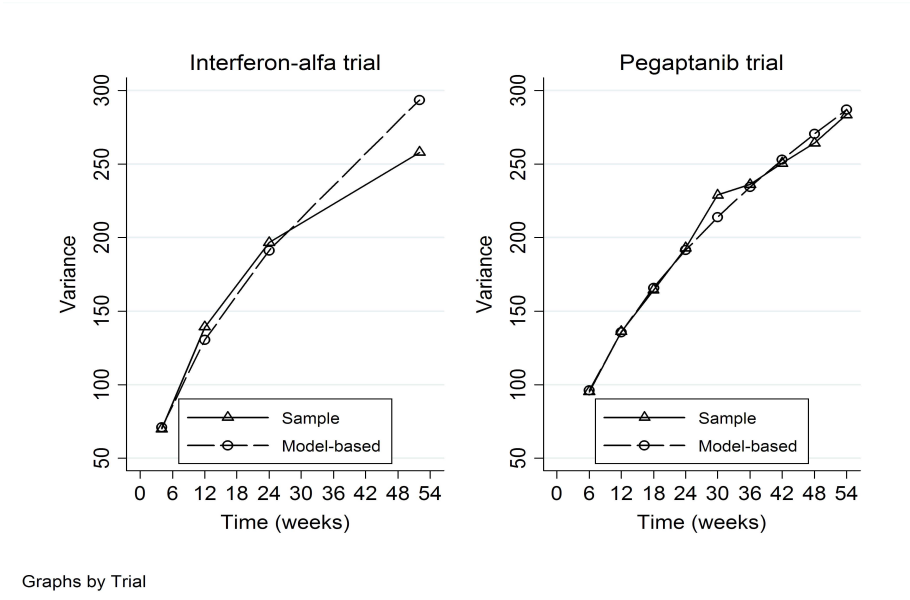




2.3 Variance-covariance structure: variance function

Variance functions:

- Interferon-α trial: $\text{Var}(VAC_m) = (5.7)^2\sqrt{t_m} = 32.5\sqrt{t_m}$
- Pegaptanib trial: $\text{Var}(VAC_m) = (6.3)^2\sqrt{t_m} = 39.7\sqrt{t_m}$

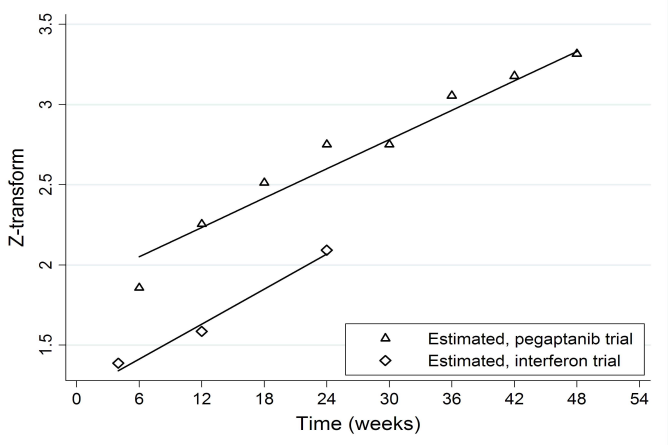


2.4 Variance-covariance structure: correlation

Antedependence correlation structure ($1 \leq m < m' \leq M$):

$$\begin{aligned} \text{Corr}(VAC_m, VAC_{m+1}) &= \rho_{m,m+1} \equiv \rho_m = \{e^{z(t_m)} - 1\}/\{e^{z(t_m)} + 1\} \\ \text{Corr}(VAC_m, VAC_{m'}) &= \rho_m \cdot \rho_{m+1} \cdot \ldots \cdot \rho_{m'-1} \end{aligned}$$

- Interferon-α trial: $z(t_m) = 1.195 + 0.036 \cdot t_m$
- Pegaptanib trial: $z(t_m) = 1.869 + 0.030 \cdot t_m$



Chapter 3
The Phase II/III design

- Setting/notation
- Hypotheses
- The design
- Power

3.1 Setting/notation

- N pts. with repeated measures at M occasions, at times t_m $(m = 1, \ldots, M)$

- $X_{k,i,m}$ - the mth measurement for patient i in treatment group k
  - ▷ $X_{k,i,m} \sim N(\mu_{k,m}, \sigma_m^2)$
  - ▷ Corr$(X_{k,i,m}, X_{k,i,m'}) = \rho_{m,m'}$

- n_k - the total # of pts. in treatment group k
  - ▷ Assume $n_1 = \ldots = n_K \equiv n_T$

- $n_{k,m}(t)$ - # of pts. with mth measurement for treatment k at calendar time t
  - ▷ Assume $n_{1,m}(t) = \ldots = n_{K,m}(t) \equiv n_{T,m}(t)$

3.2 Hypotheses

- Define the effect of treatment k for VAC_M as $\Delta_{k,M} \equiv \mu_{k,M} - \mu_{0,M}$.

- We want to select treatment and then test

$$H_0 : \ \Delta_{S,M} \leq 0 \quad \text{vs.} \quad H_A : \ \Delta_{S,M} > 0.$$

- To select the treatment, we use VAC_m (an earlier measurement).

- Related effect of treatment k for VAC_m is $\Delta_{k,m} \equiv \mu_{k,m} - \mu_{0,m}$.

3.3 Design

- Test statistics for an analysis at calendar time t using the mth measurement:

$$Z_{k,m}(t) = \{\bar{X}_{k,m}(t) - \bar{X}_{0,m}(t)\} / \left[\sigma_m^2 \{1/n_{T,m}(t) + 1/n_{0,m}(t)\}\right],$$

  where $\bar{X}_{k,m}(t)$ is the mean of the mth VAC measurement in the kth treatment group obtained by using data available at (calendar) time t.

- At the first stage, at time t, we select the treatment with the largest test statistic:

$$Z_{S,m}(t) = \max_{k=1,\ldots,K}\{Z_{k,m}(t)\}$$

- The final analysis of the last, Mth measurement, based on the test statistic

$$Z_{S,M} = \{\bar{X}_{S,M} - \bar{X}_{0,M}\} / \left\{\sigma_M^2 (1/n_T + 1/n_0)\right\},$$

  where $\bar{X}_{S,M}$ is the mean of the Mth VAC measurement in (selected) treatment group S, computed by using data available for all patients in that group.

3.4 Power

The power of the design depends on

- sample sizes $n_{k,m}(t)$ and $n_{k,M}$, for $k = 0, \ldots, K$
- effects of *all* treatments on VAC_m ($\Delta_{k,m}$) and VAC_M ($\Delta_{k,M}$)
  - ▷ "least favorable configuration":

$$\delta_m^{(2)} = \Delta_{1,m} > \Delta_{(2),m} = \ldots = \Delta_{K,m} = \delta_m^{(1)} \geq 0$$
$$\delta_M^{(2)} = \Delta_{1,M} > \Delta_{(2),M} = \ldots = \Delta_{K,M} = \delta_M^{(1)} \geq 0$$

- variances of VAC_m and VAC_M
- correlation between the mth and Mth VAC measurements ($\rho_{m,M}$)

Chapter 4
Issues

- Specifying treatment effect for a new trial
- Specifying variance-covariance structure effect for a new trial
- Continuous endpoint for Phase II, binary for Phase III

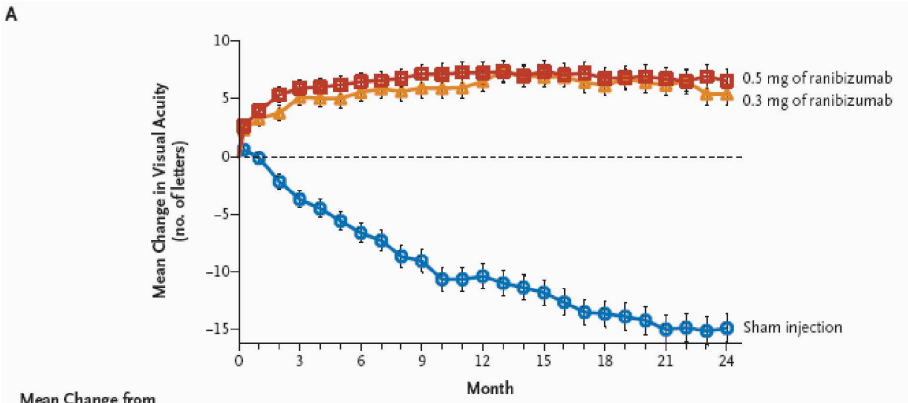
4.1 Designing a new trial: treatment effects

- Comparison of two doses *vs.* a control ($K = 2$)
- Measurements at 8, 16, 24, 32, 40, 48, and 52 weeks ($M = 7$).
- Use the 2nd measurement ($t_2 = 16$) in Phase II, the last ($t_7 = 52$) in Phase III.
- Need to specify $\Delta_{k,7}$ and *corresponding* $\Delta_{k,2}$.
  - ▷ The mean structure for the interferon-α trial?
  - ▷ The mean structure for the pegaptanib trial?
  - ▷ Or a completely different one?

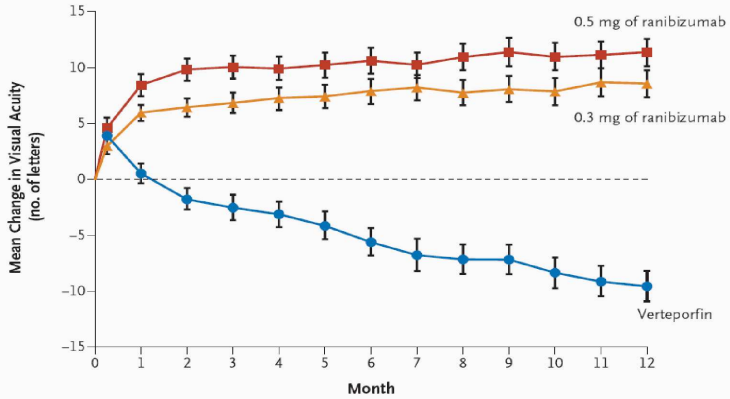
4.2 Mean structure

Ranibizumab trials:

- Brown *et al.* (*NEJM* 2006)
- Rosenfeld *et al.* (*NEJM* 2006)



Mean Change from Baseline	(day 7)								
0.5 mg of ranibizumab	+2.6	+5.9	+6.5	+7.2	+7.2	+7.4	+6.8	+6.7	+6.6
0.3 mg of ranibizumab	+2.3	+5.1	+5.6	+5.9	+6.5	+6.9	+6.1	+6.2	+5.4
Sham injection	+0.6	−3.7	−6.6	−9.1	−10.4	−11.8	−13.6	−15.0	−14.9



Mean Change from Baseline	(day 7)												
0.5 mg of ranibizumab	+4.6	+8.4	+9.8	+10.0	+9.9	+10.2	+10.6	+10.2	+10.9	+11.4	+10.9	+11.1	+11.3
0.3 mg of ranibizumab	+2.9	+5.9	+6.4	+6.8	+7.2	+7.4	+7.9	+8.2	+7.7	+8.1	+7.8	+8.6	+8.5
Verteporfin	+3.9	+0.5	−1.8	−2.5	−3.1	−4.1	−5.6	−6.8	−7.1	−7.1	−8.3	−9.1	−9.5

4.3 Association between treatment effects

- A meta-analytic validation of association between treatment effects might help
  - ▷ Burzykowski, Molenberghs, Buyse (2005, Springer)
  - ▷ How to reflect the uncertainty about the association in the hypotheses?
- For a completely new treatment mechanism, it may still be problematic.

4.4 Designing a new trial: variance-covariance structure

- Variance functions $\approx 6^2\sqrt{t}$
- Measurements every 6 weeks: use $z(t)$ similar to the pegaptanib trial
  - ▷ Influence of the choice on the sample size by simulations
- Straightforward for VAC; not so for *different* endpoints at two stages

4.5 Continuous endpoint for Phase II, binary for Phase III

- Assume we want to use the mth VAC measurement for treatment selection, but to conduct the final analysis using the FDA-approved binary endpoint.
- Use $Z_{k,m}(t)$ to select the treatment.
- Final analysis based on the test statistic

$$Z_{S,M} = \{\widehat{\pi}_{S,M} - \widehat{\pi}_{0,M}\}/(1/n_T + 1/n_0),$$

  where $\widehat{\pi}_{S,M}$ is the proportion of responses at t_M in (selected) treatment group S, computed by using data available for all patients in that group.
- What is covariance Cov$\{Z_{S,m}(t), Z_{S,M}\}$?

4.6 Covariance between the endpoints/test statistics

- It appears that

$$\text{Cov}\{Z_{S,m}(t), Z_{S,M}\} = \frac{1}{c(t)}\left[\frac{\pi_{S,M}\{\mu^*_{S,m} - \mu_{S,M}\}}{n_{T,m}(t)} + \frac{\pi_{0,M}\{\mu^*_{0,m} - \mu_{0,M}\}}{n_{0,m}(t)}\right]$$

  where

$$c(t) = \sigma^2_m\{1/n_{T,m}(t) + 1/n_{0,m}\}\{1/n_T + 1/n_0\}$$

  and $\mu^*_{S,m}$ is the mean value of the mth VAC measurement for subjects in (selected) treatment group S with a binary response at the Mth measurement.

- Issue: $\mu^*_{S,m}$ will not be known in general.

- For the gain of at least three lines of vision, however, we could write

$$\mu^*_{S,m} = \text{E}(VAC_{S,m} \mid VAC_{S,M} \geq 15).$$

Chapter 5
Conclusions

To use a biomarker in a Phase II/III design

- Knowledge of the association between the biomarker and the clinical endpoint is needed
  - ▷ Can be obtained by modeling of previous data
- Knowledge of the association between the treatment effects is needed
  - ▷ Can be obtained from a surrogate endpoint validation study...
  - ▷ ... but care is needed with the extrapolation of the results.