'Recent' History of Survival Analysis in Clinical Trials

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Some Context

Smith (1998)

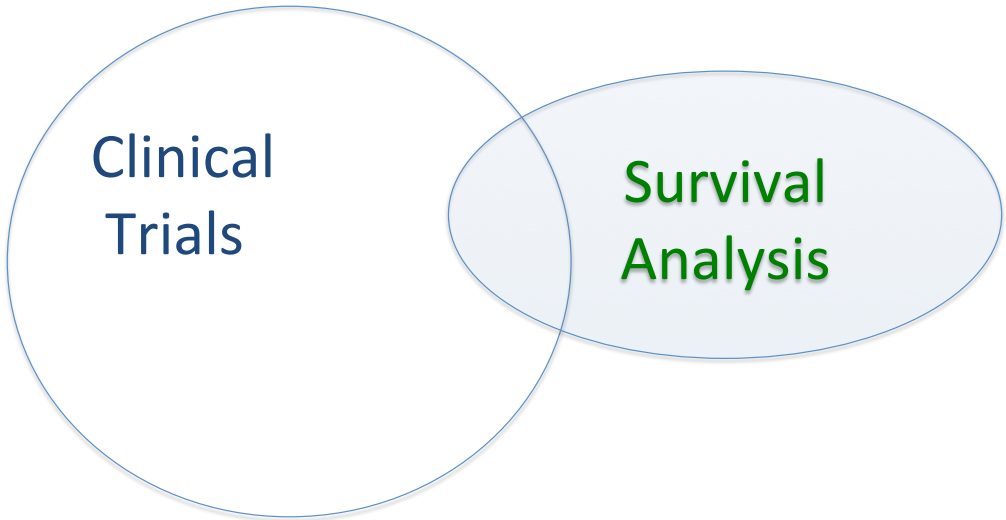
> *Was the randomised controlled trial the most important development in medicine this [20th] century?*

In T. Jefferson's 1807 letter to Caspar Washington [Peterson (1985)]

> *The patient, treated on the fashionable theory, sometimes gets well in spite of the medicine. The medicine therefore restored him, and the young doctor receives new courage to proceed in his bold experiments on the lives of his fellow creatures.*

All references at the end. First edition dates used for texts.

Why link clinical trials and survival analysis?



First ‘modern’ randomized clinical trial in 1948 [Marshall et al. (1948)]

Earliest work in estimating survival distributions seems to be Graunt’s 1661 life tables [Graunt (2008), Kindle (!) Edition].

Some important features of survival analysis responded to problems in clinical trials.

Clinical trials and the shift to non-parametric methods.

The study of reliability produced parametric methods for estimating life distributions. From Mann et al. (1974):

> *"the probability of a device (or item or organism) performing its (or his or her) defined purpose adequately for a specified period of time, under the operating conditions encountered"*

Early skepticism of modeling in JW Boag's discussion of Armitage (1959).

Difficult to determine when the use of non-parametric survival methods became routine for clinical trials.

Non-parametric approaches build momentum

Early non-parametric approaches:

- Berkson and Gage (1952) (estimation)
- Gehan (1965) (testing)

Non-parametrics 'flourished' with

- Kaplan and Meier (1958) (11^{th} most highly cited paper in Web of Science) and
- Mantel (1966), Peto and Peto (1972)

Elveback (1958) (118 citations) vs KM (approx 46,000 citations) shows power of marketplace: parametric vs. non-parametric.

More refined analysis of clinical trials

The early nonparametric approach did not support modeling, adjusting for confounders, etc.

- The proportional hazards model and its partial likelihood provided a modeling tool [Cox (1972), approx. 40,000 citations, 24^{th} most highly cited].
  - $\lambda(t|z) = \lambda_0(t)\exp(\beta' z)$
  - Contribution to the partial likelihood for β at failure time t_i

$$\frac{\exp(\beta' Z_{(i)})}{\sum_{l \in R_i} \exp(\beta' Z_l)}$$

- Early hints of the PH model in exponential regression [Feigl and Zelen (1965)].
- Accelerated failure time model provided an alternative.

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Moving on from 1972

Many wonderful side trips . . .

- Buckley and James (1979) proposed using linear regression
- Competing risks, sample size calculations, model checking, interval censored data, examining efficiency, adjusting for tied failure times.

Kalbfleisch and Prentice (1980), Miller (1981), and Cox and Oakes (1984) provided important contributions and consolidations.

Some vexing problems in trials:

- Theory lacked the elegance of linear models
- Interim monitoring
- Causal inference in randomized trials with some non-adherence

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First, the mathematics

Heroic efforts to pin down asymptotics using 'traditional methods'

- Kaplan-Meier product limit estimator: Breslow and Crowley (1974), others
- Proportional hazards model: Tsiatis (1981b), others
- Partial likelihood: Efron (1977), Wong (1986)

Structure came from surprising source: French school of probability [Meyer (1966)], via Aalen (1978). Partial likelihood score for β:

$$U(\beta, t) = \sum_i \int_0^t [Z_i(u) - E(\beta, u)] dM_i(u)$$

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The mathematics . . .

Important contributions using the martingale approach:

- The Kaplan-Meier estimate and the two sample problem: Gill (1980).
- The proportional hazards model: Andersen and Gill (1982)
- A general summary, with many applications Andersen et al. (1993). Affectionately, *ABGK*

Surprisingly useful in exploratory data analysis; Therneau and Grambsch (2000)

Made many difficult problems more accessible, e.g., sequential monitoring

Sequential Designs

Sequential monitoring was a 'not so immediate' response to the natural question: can we have a look at the data?

Some of the early work was not survival specific:

- Armitage (1960) important, early work (not survival focused).
- Haybittle (1971), early group sequential approach.
- Pocock (1977), the group sequential approach.
- O'Brien and Fleming (1979), for the boundaries most often used today.
- Lan and DeMets (1983), flexible computation of boundaries.

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Causal Inference

Methods for causal inference in observational studies well developed.

What do clinical trials add here? Immediacy, aversion to models . . .

- A clinical trial disrupted by non-adherence is distressing and expensive.
- Trialists studying chronic diseases are allergic to fully specified models.

Standard approach: Intent-to-Treat (ITT) in superiority RCTs, Per Protocol (PP) and ITT in non-inferiority RCTs.

Neither approach is very satisfying, despite FDA and EMA endorsement.

Causal inference . . .

Imbens and Rubin (2015) summarizes theory and applications of the *Rubin Causal Model*.

- Useful for binary or normally distributed 'immediate outcomes', not easy to adapt to censored event time data without a parametric model.

Robins and Tsiatis (1991) use Rank Preserving Structural Failure time models, or the structural version of the accelerated failure time model.

- Inference not based on assumptions about shape of baseline event rate function.
- Inspired by the prevalence of self-medication in the early days HIV clinical research.

Neither approach has substantially penetrated practice.

Causal inference . . .

Some side trips that show promise, but still used more often in observational studies

- Principal Stratification: Frangakis and Rubin (2002)
- Instrumental variables: Angrist et al. (1996)
- Propensity scores: Rosenbaum and Rubin (1983)

Emerging areas

- Adaptive designs. Tsiatis and Mehta (2003) and Gallo et al. (2006) give different views on this.
- Bayes. Slightly perverse to cite this as something that is coming. Spiegelhalter et al. (1994) very compelling argument for Bayesian designs and analysis. Ibrahim et al. (2005) consolidates what was known in 2005.
- Design and analyses for 'targeted' therapies biomarker adaptive designs [Jiang et al. (2007), Barker et al. (2009): I-SPY 2 trial].
- Patient-level prediction [Graf et al. (1999), Gerds et al. (2008)].

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