Slide 1

The Effects of Informative Dropouts on the Design and Evaluation of Clinical Trials

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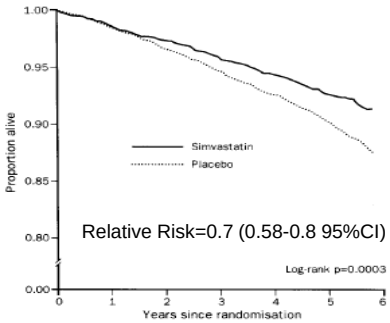
Slide 2

Outline

- Definitions
  - » Largely missing!
- The Pharmacokinetics of Dropout
  - » Why PK scientists know more than statisticians
- The Hazard: Biological Basis For Survival
  - » Dropout is just a special case of survival
- What Are Dropout Models Good For?
  - » Learning about clinical trials
- Examples

Slide 3

How Not to Understand About the Causes of Dropout (Death)



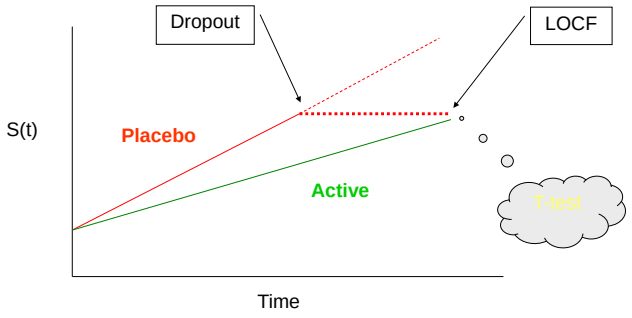
Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-89.

This landmark study led to the introduction of statins with a major impact on cardiovascular morbidity and mortality worldwide.
However, this Kaplan-Meier plot shows that statins don't seem to have any effect on survival until at least a year after starting treatment.
As far as I know there has never been any good explanation of why the benefits of statins are so delayed but when properly analysed this kind of survival data can describe the time course of hazard and give a clearer picture of how long it takes for statins to be effective.

Slide 4

How Not to Deal With Missing Data

Statistical Madness



The traditional statistician faced with analysing a clinical trial typically expects to compare two groups at the end of the trial e.g. using a t-test to compare the average disease status in a placebo group compared with an active treatment group. When, surprise, surprise, there are dropouts during the trial then in order to use a t-test the statistician imputes (i.e. fabricates) some missing data as if it has been actually observed. The simplest form of imputation is last observation carried forward (LOCF). When there is disease progression this is a quite unreasonable imputation method. In the example shown here where dropout is related to worsening disease status the LOCF method combined with a t-test would conclude the active drug was indistinguishable from placebo. This is clearly wrong when the time course of disease status is considered.

Slide 5

Missing Data Mechanisms

- Missing Completely at Random (MCAR)
  P(M|Y) = P(M) for all Y
- Missing at Random (MAR)
  P(M|Y) = P(M|Yobs) for all Ymiss
- Missing Not at Random (MNAR)
  P(M|Y) depends on Ymiss

Statistical Analysis with Missing Data, 2nd edition, Roderick J. A. Little and Donald B. Rubin (New York: John Wiley & Sons, 2002).

When data are missing there are 3 commonly recognized categories. The categories are based on a mechanism (M) for causing data to be missing. The probability of data being missing may be

- independent of any observed value (missing completely at random)
- Predictable from an observed value (missing at random)
- Predictable from an unobserved (and unpredictable) value i.e. the missing data (not missing at random)

Slide 6

Translation

- Missing Completely at Random
  - » There is no reason for the dropout
- Missing at Random
  - » There is a reason for the dropout
- Missing Not At Random
  - » There is a reason for the dropout but we have no idea what it is!

If no reason is suspected as a cause of dropout then the dropout is considered to be completely at random. Because dropouts are then equally likely irrespective of treatment then the dropouts are ignorable.
If there is a reason for the dropout that has been observed or can be predicted from some observation e.g. due to treatment toxicity, then in principle one can adjust the observed outcome to account for this explanatory covariate.
If there is a reason for the dropout e.g. due to treatment toxicity, but the adverse event was not observed and was not predictable from any observation then this is “missing not at random”. There is not much that can be done to recover from this problem and a biased conclusion about treatment effects could occur if the analysis assumed that dropout was missing completely at random or was missing at random using an observation that did not in fact predict the adverse event that caused the dropout.

Slide 7

Missing at Random Informative Missingess

- The understandable case of informative missingness
- The missing value is predictable from something that we observed (or we can predict from an observation)
- Hu & Sale opened the door for PKPD

Hu C, Sale ME. A joint model for nonlinear longitudinal data with informative dropout. J Pharmacokinet Pharmacodyn. 2003;30(1):83-103.

The term informative missingness has various interpretations. One useful interpretation is to consider it as a synonym for "missing at random". Hu & Sale showed how to use NONMEM to describe the hazard of dropout based on a prediction of disease status. They gave examples of HIV viral load and blood glucose as disease status markers which were predictors of the hazard of dropout.
http://pkpdrx.com/holford/docs/dropout-models.pdf
Since that time there have been enhancements to NONMEM that make it quite simple to apply this approach to many kinds of time to event problem.
http://pkpdrx.com/holford/docs/time-to-event-analysis.pdf

Slide 8

Not Missing At Random

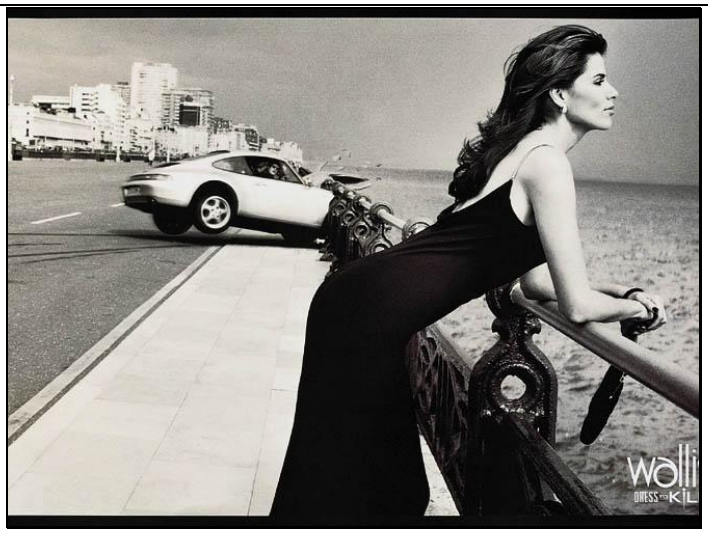
- A television set is not missing at random
- Negative statements are not definitions
  - » (this statement is not a definition!)
- NMAR is an example of a missing definition for a mechanism of missing data

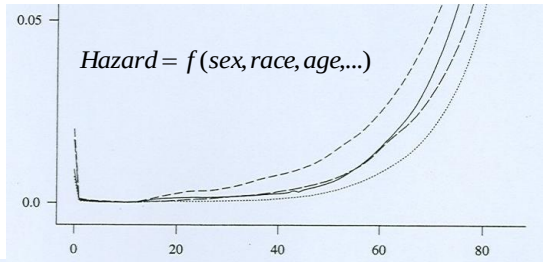
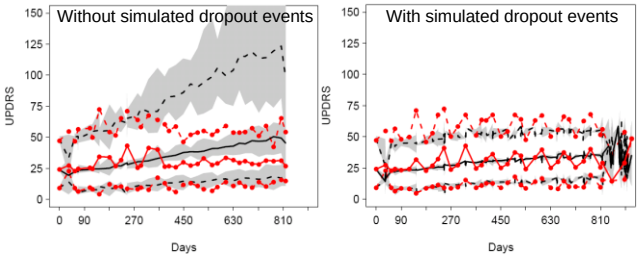
Slide 9

A PK Approach to Dropout

	Drug	Events
Rate of loss N=people alive A=molecules remaining	$\frac{dA}{dt} = -k_{el} \cdot A$	$\frac{dN}{dt} = -\lambda \cdot N$
Hazard	k_{el}	λ
Integral	AUC	Cumulative Hazard
Non-parametric	Non-compartmental	Kaplan-Meier
Time Course	$C(t) = \exp(-k_{el} \cdot t)$	$S(t) = \exp(-\lambda \cdot t)$

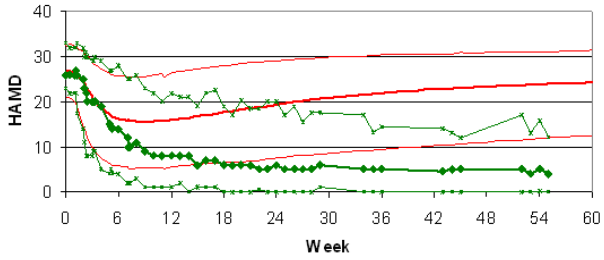
The elimination of a drug molecule can be described in term of a rate constant. This expresses the rate of removal of the drug molecule from the body. The time course of survival is exactly analogous to the time course of drug amount in the body. In the simplest case the elimination rate constant of a drug is assumed to be a constant and the analogous value determining survival, the hazard, can also be assumed to be constant. PK can be made more complex e.g. mixed order elimination and hazard can also be made more complex e.g. varying with age or drug exposure. But the maths remains the same for solving the PK or the survival function equation.
Few statisticians are familiar with how to deal with hazards that are not constant or just simple functions of time. Many pharmacokinetic scientists are able to write models for time varying elimination rate constants involving drug interactions or changing disease state. Thus PK scientists are usually better equipped to describe complex time to event models.

		The event rate is frequently scaled to a standard number of persons e.g. death rates per 100,000 people. Hazard models are more typically scaled to a single person. Pharmacokinetic models are scaled to the dose. In this example a unit dose is assumed for the time course of concentration.
Slide 10	Why do women live longer than men? 	
Slide 11		http://www.allowe.com/Humor/whymendieyounger.htm

Slide 12	**Survival in a Bathtub**  **Figure 2.6** *Hazard functions for all cause mortality for the US population in 1989. White males (————); white females (·····); black males (- - - - -); black females (—— ——).* "… a bathtub-shaped hazard is appropriate in populations followed from birth." Klein, J.P., and Moeschberger, M.L. 2003. *Survival analysis: techniques for censored and truncated data*. New York: Springer-Verlag. http://en.wikipedia.org/wiki/Bathtub_curve "The bathtub curve" 	The hazard describes the death rate at each instant of time. The shape of the hazard function over the human life span has the shape of a bathtub. US mortality data shows the hazard at birth falls quickly and eventually returns to around the same level by the age of 60. The hazard is approximately constant through childhood and early adolescence. The onset of puberty and subsequent life style changes (cars, drugs,…) adopted by men increases the hazard to a new plateau which lasts for 10 to 20 years. It would require a time varying model to describe how development (children) and ageing (adults) are associated with changes in death rate.
Slide 13	**Hazard and Survival** $$hazard = h(t)$$ $$CumulativeHazard(t) = \int_0^t h(t)$$ $$Survivor(t) = \Pr(T > t) = e^{-CumulativeHazard(t)}$$ 	The probability of a having an event at a particular time can be predicted by describing the hazard for the event. Hazard is the instantaneous rate of the event. As time passes the cumulative hazard predicts the risk of having the event over the interval 0-t. The hazard model can be of any form but the hazard cannot be negative. The risk is the cumulative hazard. It is obtained by integrating hazard with respect to time. The probability of survival (not having the event) can be predicted from the cumulative hazard. This is called the survivor function. The probability of having an event at a particular time is predicted by the probability density function (pdf(t)). The pdf can be calculated from the survivor function and hazard at that time. The cumulative density is the integral of the pdf.
Slide 14	**Parkinsons Disease DATATOP Trial**  h(t)=Base*exp(UPDRS*Beta) Constant hazard plus increase due to disease status Ma SC, Holford NHG. Quantifying disease progress with inactive treatments in multiple Parkinson's disease trials. http://wwwpaganzorg/defaultasp?abstract=1143. 2011. 	Dropout from the DATATOP trial was mainly due to worsening of the disease and need to start dopaminergic therapy. The dropout endpoint was well recorded because this was a primary endpoint of the trial. If the dropouts had been missing completely at random the hazard would have been constant. But because the Unified Parkinsons Disease Response scale, a measure of disease severity, was associated with an increased hazard as the disease got worse the dropout process could be describe by a missing at random process.

Slide 15

Something Missing?



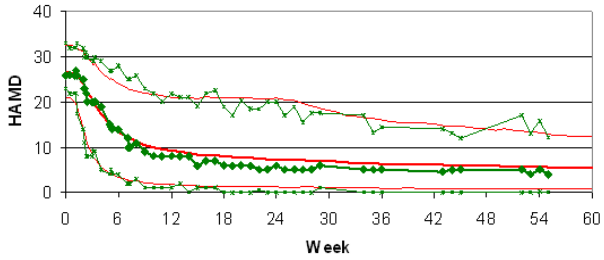
Total Dropouts	Unknown	Drug Toxicity	Disease got worse	Disease got better
23.4%	14%	2.0%	6.8%	0.6%

A model for the time course of response of the Hamilton D rating scale for depression (HAMD) was developed from a large collection of clinical trials involving both active and placebo treatments. The initial visual predictive check has predictions that show patients getting worse when the observed values seem to indicate HAMD continues to improve.

In these kinds of trials the clinical investigators wisely paid attention to the dropouts and tried to determine the most likely reason.

Slide 16

Mixed Effect Model Describes The Data without Bias



$$h(t)_k = \beta_{0,k} \cdot e^{\beta_{LNT,k} \cdot \ln(time) + \beta_{CE,k} \cdot Ce + \beta_{HAMD,k} \cdot HAMD(time)}$$

K= 1 Disease got better, 2 Disease got worse 3 Drug toxicity 4 None of the other reasons

Holford NHG. The Time Course of Drug Action… When PK is Not Needed. Lewis B Sheiner Memorial Symposium December 2006

A competing hazards model was developed based on the recorded reasons for dropout. Simulation of dropout events based on these different reasons markedly improves the match between observed and predicted distributions of HAMD over time. The hazard of dropout was predictable by reason specific hazards related to time, drug exposure (Ce) and the HAMD score.

Slide 17

What Every Trial Should Have in the Protocol – But Very Few Do

- When did the dropout occur?
  - » When was the patient last seen?
  - » When was the patient found to be missing?
- What was the reason for the dropout?
  - » Disease got better
  - » Disease got worse
  - » Drug toxicity
  - » None of the above

Dropout events are often interval censored i.e. the exact time of the event is not known. For example if patients are followed up in a clinical trial every 3 months and at a scheduled visit the patient does not turn up then the dropout event is only known to have occurred in the 3 month interval since they were last seen. This is not a problem for data analysis because the likelihood of an interval censored event is easily computed from the hazard.
Note that the list of reasons is applicable to almost any drug and clinical trial that is observing disease outcome. If the reasons are known then a competing hazard model can be developed to predict the cause of the dropout event in an individual.

Slide 18	## If Dropout is Informative Can It Change the Results of A Trial?
	
	- If the analysis is too simple e.g. uses LOCF to make up missing data
	  » YES – The wrong conclusion may be drawn
	- If the analysis uses a mixed effects model to account for individuals
	  » NO – The drug effect will be estimated without bias due to dropouts
	
		The statements here are a reflection of practical experiences of analysing clinical trials using mixed effect PKPD models. There may be trials that cannot be analysed using this kind of method and they may then be open to bias due to not using information about dropouts or using unrealistic imputation methods.

Slide 19	## Conclusion - Knowing the cause of dropout will not change the results of a properly analysed trial - The dropout model can be used to evaluate trial results - Designing a trial can be helped by simulating dropouts - Understanding a trial can be helped by recording dropout details 	