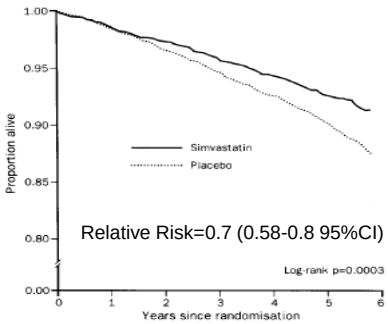
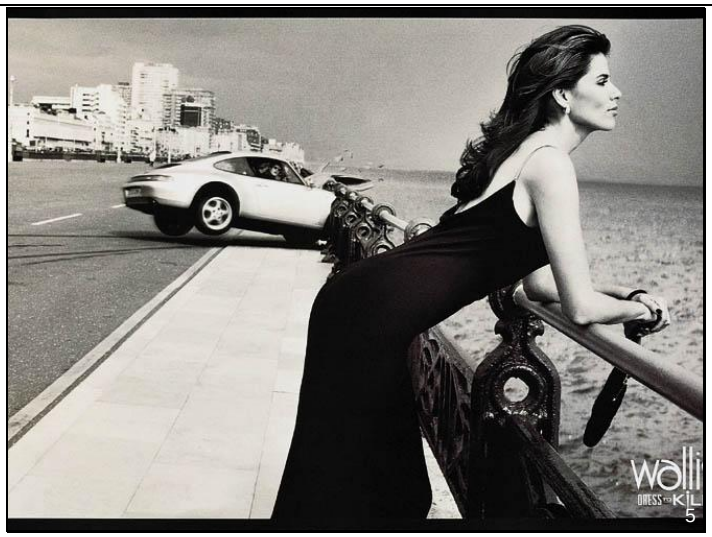
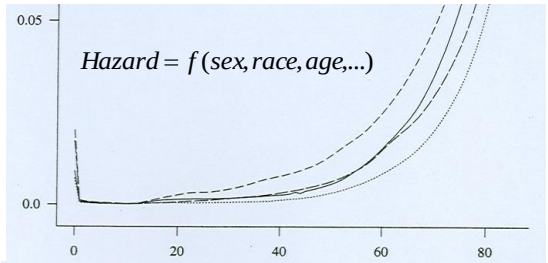
Slide 1	# Time to Event Analysis for Pharmacokineticists Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	
Slide 2	## Outline • The Hazard: Biological basis for survival • Types of Event and their Likelihood » Exact time » Right censored » Interval censored • Joint Modelling of Continuous and Event Data 2	
Slide 3	## How Not to Understand Time to Event  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. 3	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	Why do women live longer than men? 4	
Slide 5	 5	http://www.allowe.com/Humor/whymendieyounger.htm
Slide 6	Life is hazardous  **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" 6	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 7

Why Pharmacokineticists are Time to Event Experts

- What is an elimination rate constant?
  - » Proportionality factor relating elimination to amount of drug

$$RateOut = k \cdot Amount$$

- What is a hazard?
  - » Proportionality factor relating death rate to number of people still alive

$$RateOut = h \cdot N_{ALIVE}$$

- Everything you know about elimination rate constants applies to hazards!

7

The elimination rate constant is the hazard of a molecule 'dying'.
Elimination rate constants and hazards always have units of 1/time
Unlike most drugs the hazard is not usually constant ('first-order elimination') but may change with time ('time dependent clearance') or with the number of people ('concentration dependent clearance')

Slide 8

PK and Survival

	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	$C(t) = \exp(-k_{el} \cdot t)$	$S(t) = \exp(-\lambda \cdot t)$

8

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 9

Pharmacokinetic Survival

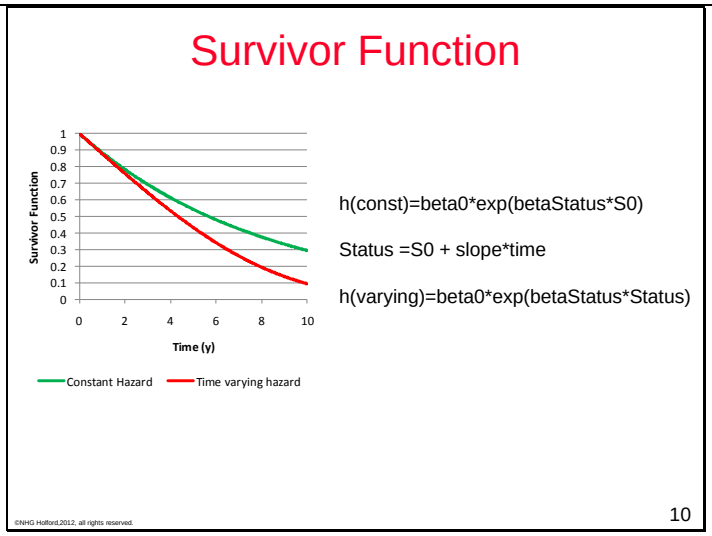
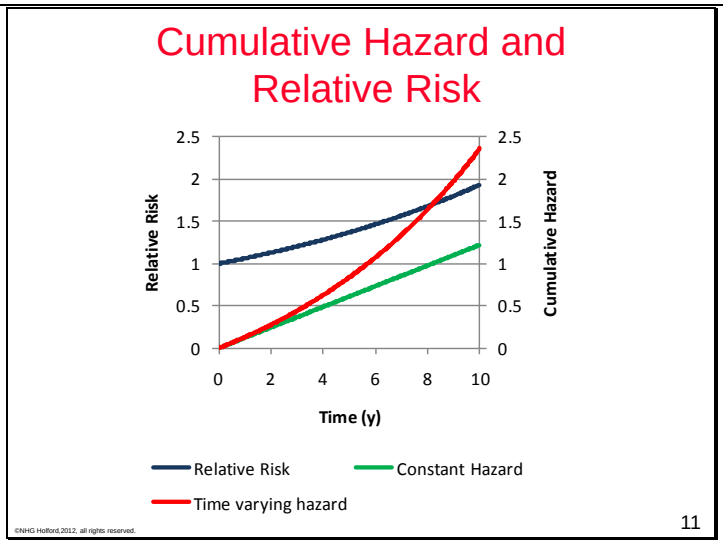
$$\text{hazard}(t) = \text{Rateconstant}(t) = CL/V$$

$$\text{Risk}(t) = \text{Cumhazard}(t) = \int_0^t \text{hazard}(t)$$

$$\text{Survival}(t) = C(t) = e^{-\text{Cumhazard}(t)}$$

9

If the hazard varies with time (or a function of time, such as concentration) then exactly the same relationships between hazard, risk and survival exist as for the constant hazard case. It is possible to make non-linear pharmacokinetic model predictions of the amount eliminated and the time course of concentration using survival analysis functions.

Slide 10		METHOD RK4 STARTTIME = 0 STOPTIME=10 DT = 0.02 beta0=0.1 betaStatus=0.01 S0=20 status=S0+12*time hazpla=beta0*exp(betaStatus*S0) haztrt=beta0*exp(betaStatus*status) init(cumpla)=0 d/dt(cumpla)=hazpla survpla=exp(-cumpla) init(cumtrt)=0 d/dt(cumtrt)=haztrt survtrt=exp(-cumtrt) pdfpla=survpla*hazpla pdftrt=survtrt*haztrt
Slide 11		

Slide 12

Explanatory Variable Functions

$$h(t) = \beta_0 \cdot e^{\beta_1 \cdot x_1 + \beta_2 \cdot x_2 \ldots + \beta n \cdot x_n}$$

Includes exponential, Weibull, Gompertz as special cases

$$h(t) = \beta_0 \cdot e^{f(B, X)}$$

Linear and non-linear functions of explanatory variables

12

The explanatory variable function is quite empirical. This form is used because there are some simple solutions for integrating the hazard and the exponential form ensures that the hazard is always non-negative.

Slide 13

Exponential Coefficients and the Hazard Ratio

$$h(t) = \beta_0 \cdot e^{\beta_1 \cdot x_1 + \beta_{SEX} \cdot SEX \ldots + \beta n \cdot x_n}$$

If the explanatory variable is 0 for females and 1 for males and the value of β_{SEX} is 0.693 then the hazard ratio for men is 2 (compared to women).

13

The coefficients of the exponential function are convenient for describing how the hazard varies with the explanatory variable. Exponentiation of the coefficient gives the hazard ratio for the effect of the explanatory variable.

Slide 14

Pharmacokinetic Survival Non-Linear

$$\text{hazard}(t) = \text{Rateconstant}(t) = (\text{Vmax}/V)/(\text{Km} + C(t))$$

$$\text{Risk}(t) = \text{CumConstant}(t) = \int_0^t \text{Rateconstant}(t)$$

$$\text{Survival}(t) = C(t) = e^{-\text{CumConstant}(t)}$$

14

If the hazard varies with time (or a function of time, such as concentration) then exactly the same relationships between hazard, risk and survival exist as for the constant hazard case. It is possible to make non-linear pharmacokinetic model predictions of the amount eliminated and the time course of concentration using survival analysis functions.

Slide 15

Non-linear PK and Survival

```
dose=100
v=1
vmax=100
km=50

rateconstant=(vmax/v)/(km+conc)
init(conc)=dose/v
d/dt(conc)= -rateconstant*conc

init(cumconstant)=0
d/dt(cumconstant)=rateconstant
survival=dose*exp(-cumconstant)
```

Time	Conc	Survival
0	100	100
1	42.6303	42.6303
2	10.8858	10.8858
3	1.76793	1.76793
4	0.246655	0.246655
5	0.033524	0.033524
6	0.00454	0.00454
7	6.14E-04	6.14E-04
8	8.32E-05	8.32E-05
9	1.13E-05	1.13E-05
10	1.52E-06	1.52E-06

Slide 16

Baseline Hazard Functions

$h(t) = \lambda$ Exponential

$h(t) = \lambda \cdot \gamma \cdot t^{\gamma-1}$ $h(t) = \lambda \cdot \gamma \cdot e^{(\gamma-1)\cdot\ln(t)}$ $h(t) = \beta_0 \cdot e^{\beta_1 \cdot \ln(t)}$ Weibull

$h(t) = \lambda \cdot e^{\beta_1 \cdot t}$ Gompertz

Parametric: Can be used for simulation and time varying hazards

h(t) = Similar for everyone but undefined Cox Proportional

Non-Parametric: No good for simulation. Tricky with time varying hazards.

The hazard function is associated with a distribution of event times. Some common distributions have names e.g. Gompertz (one of the first mathematicians to explore survival analysis). Standard baseline hazard functions used by statisticians are chosen for their mathematical simplicity rather than any biological reason.
The biology of event time distributions is largely based on descriptive and empirical approaches. However, the hazard is the way to introduce biological mechanism and understanding the variability of time to event distributions.

Slide 17

Likelihoods for Survival

For an uncensored datum, with T_i equal to the age at death, we have

$\Pr(T = T_i|\theta) = f(T_i|\theta)$ = $S(T_i|\theta) * h(T_i)$

For a left censored datum, such that the age at death is known to be less than T_i, we have

$\Pr(T < T_i|\theta) = F(T_i|\theta) = 1 - S(T_i|\theta)$

For a right censored datum, such that the age at death is known to be greater than T_i, we have

$\Pr(T > T_i|\theta) = 1 - F(T_i|\theta) = S(T_i|\theta)$

For an interval censored datum, such that the age at death is known to be greater than $T_{i,r}$ and less than $T_{i,l}$, we have

$\Pr(T_{i,l} < T < T_{i,r}|\theta) = S(T_{i,l}|\theta) - S(T_{i,r}|\theta)$

http://en.wikipedia.org/wiki/Survival_analysis

An alternative way of describing the likelihoods in terms of the survivor function and hazard function alone.

Slide 18

Practical Implementation

Slide 19

Encoding Single Events

ID	TIME	DV	MDV (NONMEM)	Comment
1	0	.	1	Start observing
1	50	1	0	Exact Time Event
2	0	.	1	Start observing
2	100	0	0	Censored Event
3	0	.	1	Start observing
3	55	0	0	Start Event Interval
3	70	2	0	End Event Interval

A record at time=0 is needed to define when the hazard integration starts.
Remark: the MDV data item is required by NONMEM: it is a reminder that that the interval censored event computes the likelihood from two observation events (MDV=0).

Slide 20

Single Event Time Varying Hazard (CP) NONMEM

```
$ESTIM MAXEVAL=9990 METHOD=COND
NSIG=3 SIGL=9
LAPLACE LIKE

$THETA
10  FIX    ; CL
100 FIX    ; V
(0,0.01)   ; BASE
0.1        ; BETACP

$OMEGA
0 FIX ; PPV_CL
0 FIX ; PPV_V

$SUBR ADVAN=6 TOL=9
$MODEL
   COMP=(CENTRAL)
   COMP=(CUMHAZ)

$PK
   IF (NEWIND.LE.1) CHLAST=0
   CL=THETA(1) *EXP(ETA(1))
   V=THETA(2) *EXP(ETA(3))
   BASHAZ=THETA(3)
   BETACP=THETA(4)
```

```
$DES
   DCP=A(1)/V
   DADT(1)=-CL*DCP
   DADT(2)=BASHAZ*EXP(BETACP*DCP)

$ERROR
  CP=A(1)/V
  CUMHAZ=A(2)        ; cumulative hazard

  IF (DV.EQ.0) THEN ; right censored
     Y=EXP(-CUMHAZ)
     CHLAST=CUMHAZ ; start of interval
  ELSE
     CHLAST=CHLAST ; keep NM-TRAN happy
  ENDIF
  IF (DV.EQ.1) THEN ; exact time
     HAZNOW=BASHAZ*EXP(BETACP*CP)
     Y=EXP(-CUMHAZ)*HAZNOW
  ENDIF
  IF (DV.EQ.2) THEN ; interval censored
     Y=1 - EXP(-(CUMHAZ - CHLAST))
  ENDIF
```


Estimation of the parameters of any hazard model can be done using this kind of code. It uses ADVAN6 to integrate the hazard and obtain the cumulative hazard. This can be used with the hazard at the time of the event to calculate the likelihood of right censored, exact time and interval censored events. Note that the likelihood for an individual is the product of each of the contributions. This is important for interval censored events which are described by the likelihood of the right censoring event at the start of the interval (DV.EQ.0) and the interval censored event at the end of the interval (DV.EQ.2).
Random effects on hazard model parameters (e.g. BASHAZ and BETACP) are not estimable with single events.

Slide 21

Extension to Joint Models

- Basic concept
  Compute LIKELIHOOD for ANY kind of response
  - » Predict likelihood of an observation for a continuous variable (e.g. disease status)
  - » Predict likelihood of time of event for time to event data
- All types of response can be combined
  - » Continuous, categorical, count, time to event

Any kind of response, continuous or non-continuous, can be used for estimation by using the joint likelihood computed for each observation.

Slide 22

Applications

- Continuous Response
  - » Standard PKPD
- Non-continuous Response
  - » Binary Response
    - – Awake or Asleep
  - » Ordered Categorical Response
    - – Neutropenic adverse event type
  - » Count Response
    - – Frequency of epileptic seizures
  - » Time to Event
    - – Death
    - – Dropout
- Joint Response
  - » Continuous plus non-continuous

NONMEM (and many other parameter estimation procedures) uses the likelihood to guide the parameter search. The likelihood is the fundamental way to describe the probability of any observation given a model for predicting the observation. NONMEM shields us from the details for common PKPD models that use continuous response scales for the observation (e.g. drug concentration, effect on blood pressure).

A variety of non-continuous responses are widely used to describe drug effects – especially clinical outcomes. By computing the likelihood directly for each of these kinds of response we can ask NONMEM to estimate parameters for any mixture of response types.

Slide 23

Joint Model Data

ID	TIME	TRT	DVID	DV	MDV	Comment
1	0	0	.	.	1	Start observing
1	20	0	1	67.4	0	Biomarker
1	30	0	1	43.2	0	Biomarker
1	50	0	2	1	0	Exact Time Event
2	0	1	.	.	1	Start observing
2	25	1	1	50.2	0	Biomarker
2	40	1	1	43.7	0	Biomarker
2	60	1	1	13.5	0	Biomarker
2	100	1	2	0	0	Censored Event

The TRT data item indicates if the subject is receiving active treatment (TRT=1) or not (TRT=0).
DVID is used to distinguish between continuous value biomarker observations (e.g. DVID=1 for drug concentration) and event observations (e.g. DVID=2).

Slide 24

Example of Joint Model: Disease Progress and Time Varying Hazard

1) Continuous biomarker

$$f(t) = a + bt$$
$$y(t) = f(t) + \varepsilon(t)$$

2) Time to event

$$\lambda(t) = h e^{\beta f(t)}$$

24

Slide 25

Disease Progress and Time Varying Hazard NONMEM

```
$INPUT ID TRT DVID TIME DV MDV
$ESTIM MAX=9990 NSIG=3 SIGL=9
METHOD=CONDITIONAL
LAPLACE

$SUBR ADVAN=6 TOL=9

$MODEL
COMP=(CUMHAZ)

$PK
IF (NEWIND.LE.1) CHLAST=0 ; Initialize
;-------------------------------
; Hazard
BASHAZ   = THETA(1) ; Baseline hazard
BETADP   = THETA(2) ; Disease progress effect
;-------------------------------
; Symptomatic treatment effect
EFFECT   = TRT*THETA(3)
;-------------------------------
;Disease Progress
INTRI    = (THETA(4)+ EFFECT)*EXP(ETA(1)
SLOPI    =  THETA(5)* EXP(ETA(2)

$DES
DPRG     = INTRI + SLOPI*T
DADT(1) = BASHAZ*EXP(BETADP*DPRG) ; h(t)
```

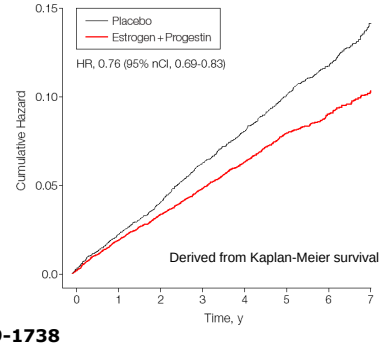
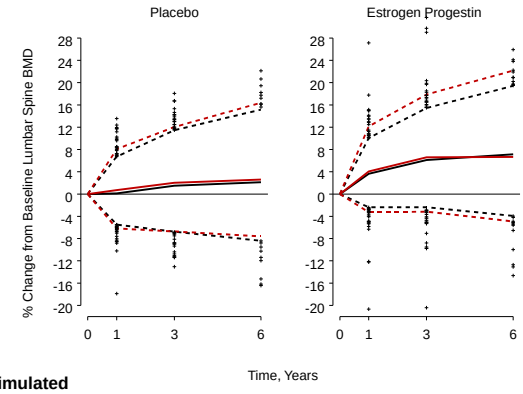
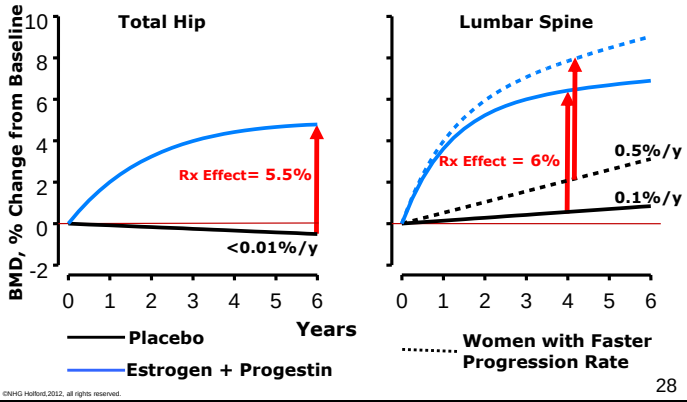
```
$ERROR
CUMHAZ=A(1) ; Cumulative hazard
DISPRG=INTRI + SLOPI*TIME
;-------------------------------
IF (DVID.EQ.1) THEN ; disease progress
   F_FLAG = 0 ; Continuous
   Y = DISPRG + ERR(1); Disease Progress
ENDIF
;-------------------------------
IF (DVID.EQ.2.AND.DV.EQ.0) THEN ; right censored
   F_FLAG = 1 ; Likelihood
   Y = EXP(-CUMHAZ)
   CHLAST=CUMHAZ ; start of interval
ELSE
   CHLAST=CHLAST ; keep NM-TRAN happy
ENDIF
;-------------------------------
IF (DVID.EQ.2.AND.DV.EQ.1) THEN ; exact time
   F_FLAG = 1 ; Likelihood
   HAZARD = BASHAZ*EXP(BETADP*DISPRG)
   Y = EXP(-CUMHAZ)*HAZARD
ENDIF
;-------------------------------
IF (DVID.EQ.2.AND.DV.EQ.2) THEN ; interval censored
   F_FLAG = 1 ; Likelihood
   Y = 1 - EXP(-(CHLAST-CUMHAZ))
ENDIF
```

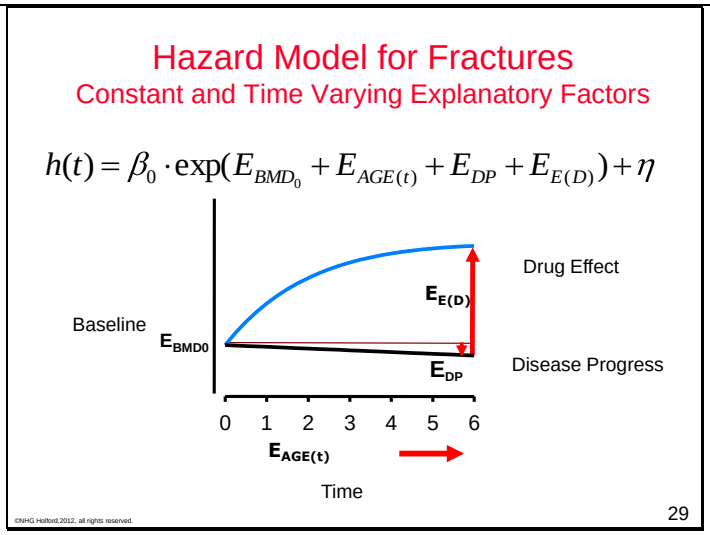
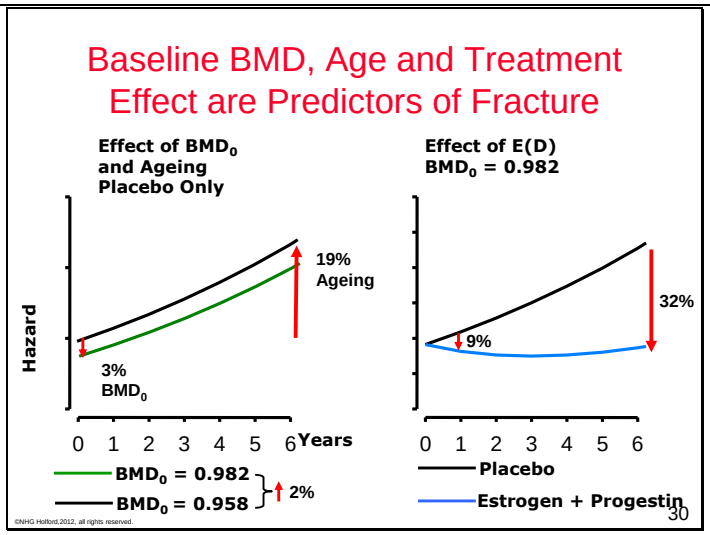
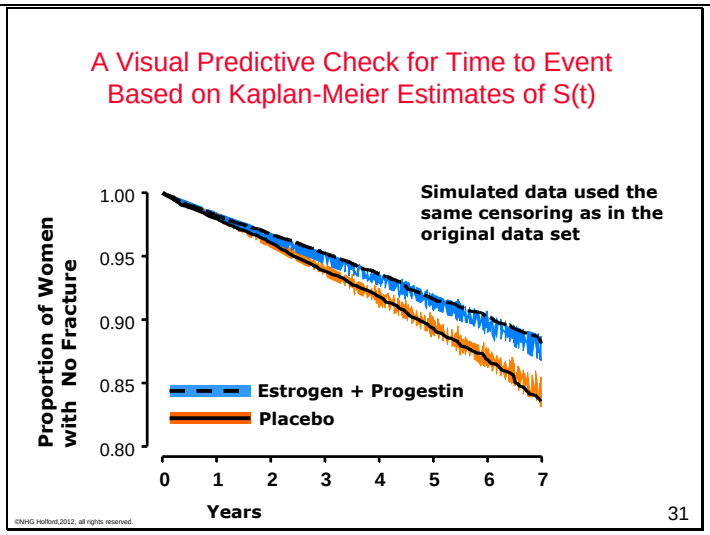

25

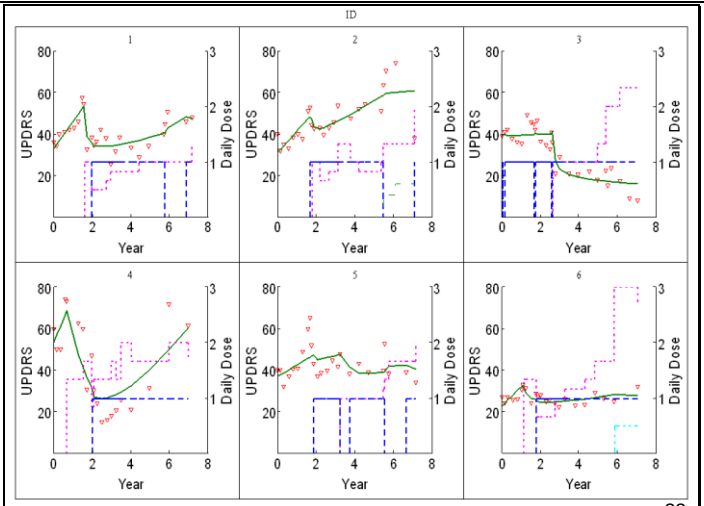
This illustrates joint modelling for disease progress and an event. The event hazard depends on disease progress.
A differential equation is used to integrate the hazard.
An effect of treatment (TRT) is assumed to affect the intercept of the disease progress model which in turn influences the hazard of the event.

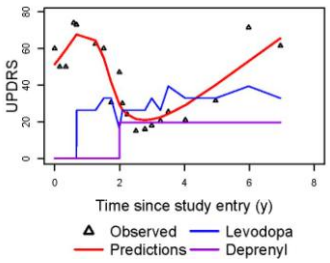
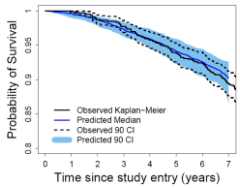
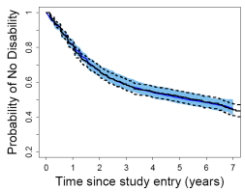
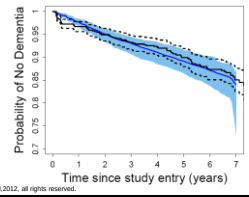
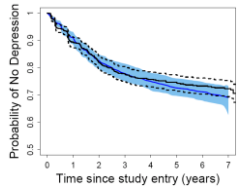
It is useful to be able to save the value of the cumulative hazard in order to calculate the likelihood of an interval censored event. In this example DV=0 is used to indicate the start of the interval censored event period and the cumulative hazard at this time is saved in the CHLAST variable.

The F_FLAG variable is used to tell NONMEM how to use the predicted Y value. F_FLAG of 0 is the default i.e. Y is the prediction of a continuous variable. F_FLAG of 1 means the prediction is a likelihood. F_FLAG of 2 means the prediction is -2*ln(Likelihood).

Slide 26	**Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density** The Women's Health Initiative Randomized Trial Jane A. Cauley, DrPH John Robbins, MD Zhao Chen, PhD Steven R. Cummings, MD Rebecca D. Jackson, MD Andrea Z. LaCroix, PhD, MPH Meryl LeBoff, MD Cora E. Lewis, MD, MSPH Joan McGowan, PhD Joan Neuner, MD, MPH Mary Pettinger, MS Marcia L. Stefanick, PhD Jean Wactawski-Wende, PhD Nelson B. Watts, MD for the Women's Health Initiative Investigators  **JAMA, 2003;290:1729-1738** ©NHG Holford,2012, all rights reserved. 26	NOTE: Ca/vitamin D at doses administered show increases in BMD without added reduction in fracture (hip and total fracture) Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus Vitamin D Supplementation and the Risk of Fractures. N Engl J Med. 2006 February 16, 2006;354(7):669-83.
Slide 27	**Bone Mineral Density – Slow Biomarker** **Women's Health Initiative Randomized Trial**  Simulated Observed Analysis with Christine Garnett (CDDS/FDA) ©NHG Holford,2012, all rights reserved. 27	The Women's Health Initiative trial observed the time course of changes in bone mineral density in 1000 women who were treated with placebo or with hormone replacement therapy. Both groups were treated with vitamin D and calcium. Half of the placebo patients were given placebo vitamin D and calcium. This plot is a visual predictive check showing the median and 90% interval for the observed (black) and predicted (red) BMD changes. The increase in BMD in the placebo group (and some of the change in the HRT group) is attributable to treatment with vitamin D and calcium.
Slide 28	**BMD Time Course** 70 kg woman 13 years post menopause  ©NHG Holford,2012, all rights reserved. 28	These figures shows some key results for the Hip and Spine models which represent the two different types of bone. **Teq for lumbar spine 0.81 y. Teq for hip 1.53 y.** For the hip bone, there was a trend for bone loss with a progression rate of less than 0.01% per year. Maximum treatment effect was estimated to be 6% of baseline. But by year 6, 94% of treatment effect was observed. For spine, women gained bone mass during the trial. Approximately 52% of the women's progression rate was 0.1% per year and the remaining women gained bone with a rate of 0.5% per year. Maximum treatment effect from hormones was approximately 6% of baseline. Due to the shorter equilibration T1/2, maximum treatment effect was observed by year 4.

Slide 29		Key to our modeling approach was to specify the hazard model for fractures as a function of Bone Mineral Density. Instead of using the predicted BMD as a single time-varying covariate in the hazard, we chose to parameterize the hazard function by including each component of the disease status model as a covariate. This allowed us to assess the relative contributions of each component to the risk of fracture. Some women had more than one fracture which allowed the between subject difference in hazard to be estimated (η). This kind of random effects model is called a 'frailty model' in the statistical survival analysis literature.
Slide 30		This is a deterministic simulation of the final fracture model using total body BMD NOTE: Ca/vitamin D at doses administered show increases in BMD without added reduction in fracture (hip and total fracture. JAMA 2006)
Slide 31		The slide shows a predictive check using the Kaplan-Meier method to generate the predicted uncertainty in the survivor function (based on 500 replications of the WHI data set). The 90% predictive interval for placebo is shaded in orange and the blue represents the predictive interval for E+P. The black lines represent the observed probability of no fracture. Overall, we concluded that the model describes the observed data well.

Slide 32	# Disease Progression  BJCP British Journal of Clinical Pharmacology DOI:10.1111/j.1365-2125.2012.04192.x Progression of motor and nonmotor features of Parkinson's disease and their response to treatment Thuy C. Vu,[1] John G. Nutt[2] & Nicholas H. G. Holford[3] [1]Department of Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA, USA, [2]Department of Neurology, Oregon Health and Science University, Portland, OR, USA and [3]Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT Correspondence Professor Nick Holford, Department of Pharmacology & Clinical Pharmacology, University of Auckland, 85 Park Road, Private Bag 92019, Auckland, New Zealand. Tel.: +64 9 923 6730 Fax: +64 9 373 7090 E-mail: n.holford@auckland.ac.nz Keywords disease progression, levodopa, motor subscales, Parkinson's disease, pharmacodynamics, selegiline Received 21 January 2011 Accepted 15 January 2012 Accepted Article Published Online 29 January 2012 Vu TC, Nutt JG, Holford NHG. Progression of motor and nonmotor features of Parkinson's disease and their response to treatment. Br J Clin Pharmacol 2012; 74: 267-83. ©NHG Holford,2012, all rights reserved. 32	
Slide 33	 ©NHG Holford,2012, all rights reserved. 33	Disease status was followed with the Unified Parkinson's Disease Response Scale (UPDRS). The UPDRS patterns were quite variable from patient to patient. A major source of variability was the response to individual drug treatments.
Slide 34	# Joint Time to Event Model  BJCP British Journal of Clinical Pharmacology DOI:10.1111/j.1365-2125.2012.04208.x Disease progress and response to treatment as predictors of survival, disability, cognitive impairment and depression in Parkinson's disease Thuy C. Vu,[1] John G. Nutt[2] & Nicholas H. G. Holford[3] [1]Department of Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA, [2]Department of Neurology, Oregon Health and Science University, Portland, OR, USA and [3]Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT Correspondence Professor Nick Holford MBChB FRACP, Department Pharmacology & Clinical Pharmacology, University of Auckland, 85 Park Rd, Private Bag 92019, Auckland, New Zealand. Tel.: +64 (9) 923 6730 Fax: +64 (9) 373 7090 E-mail: n.holford@auckland.ac.nz Keywords disease progress, levodopa, Parkinson's disease, selegiline, time-dependent covariate, time to event Received 21 January 2011 Accepted 25 January 2012 Accepted Article Published Online 2 February 2012 Vu TC, Nutt JG, Holford NHG. Disease progress and response to treatment as predictors of survival, disability, cognitive impairment and depression in Parkinson's disease. Br J Clin Pharmacol 2012; 74: 284-95. ©NHG Holford,2012, all rights reserved. 34	

Slide 35	**Outcome Event Hazard in Parkinson's Disease** **Hazard Model with Explanatory Variables** $h(t) = h_0(t) \cdot exp(\beta_{deprenyl} \cdot deprenyl(t) + \beta_{status} \cdot status(t) + \ldots + \beta_n X_n)$  *deprenyl(t)* = 1 for on periods, 0 for off periods *status(t)* = predicted disease status as measured by UPDRS or its subscales at time *t* Other Explanatory Factors: (X_n) • *Levodopa(t)*, baseline motor subtypes status • Age, sex, smoking status at study entry 35	The severity of Parkinson's disease is usually assessed by the Unified Parkinson's disease response scale (UPDRS). The UPDRS score increases with time as the disease progresses. The disease status can be described by a model for disease progression (natural history) and the effects of treatment e.g. the use of levodopa (the mainstay of treatment) with or without deprenyl (a mono-amine oxidase inhibitor commonly used as an adjunctive treatment) The hazard of a clinical outcome event e.g. death, can be described by a baseline hazard, h0(t), and explanatory factors such as drug treatment and the time course of disease status. Other factors (age, sex, smoking, etc) are easily included in this kind of model.
Slide 36	**Evaluation of Hazard Models** **visual predictive check** Death  Disability  Cognitive Impairment  Depression  36	The change of disease status, reflected by the time course of UPDRS, is the most important factor determining the hazard of clinical outcome events in Parkinson's disease. The different shapes of the survival function for death, disability, cognitive impairment and depression reflect different contributions of disease status to the probability of not having had the event as time passes.
Slide 37	**Putting Time Back into The Picture** "*Science is either stamp collecting or physics*" Ernest Rutherford Stamp Collecting → Models → Physics Biomarker + Time → Hazard + Time → Outcome 37	

Slide 38

Acknowledgements

- Christine Garnett
  - Jay Nutt
  - Thuy Vu
- Marc Lavielle