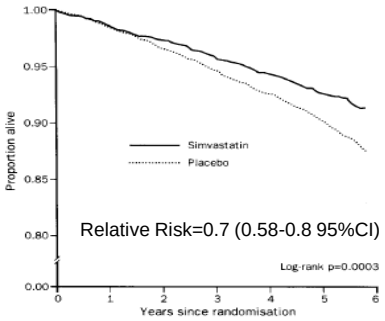
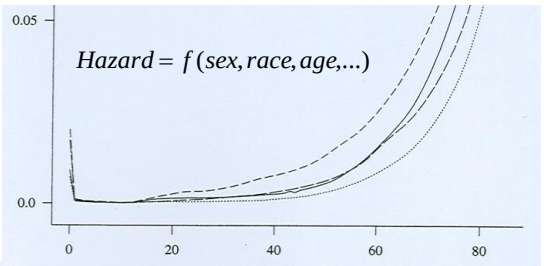
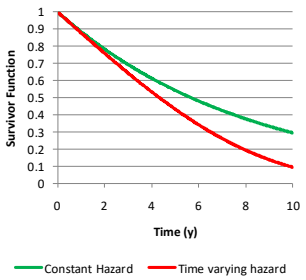
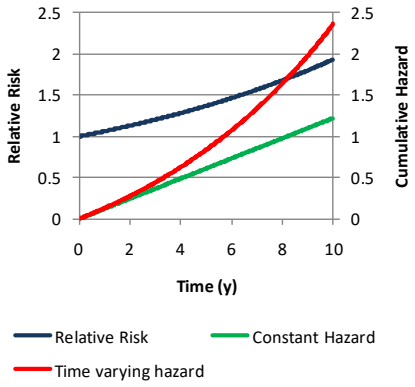
Slide 1	# Repeated Time to Event Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	Holford N. A Time to Event Tutorial for Pharmacometricians. CPT: pharmacomet syst pharmacol. 2013;2:e43 doi:10.1038/psp.2013.18.
Slide 2	# Outline • The Hazard: Biological basis for survival • Types of Event and their Likelihood » Exact time » Interval censored » Right censored • Joint Modelling of Continuous and Event Data 	
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. 	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? 	
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" 	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	# Survivor Function  h(const)=beta0*exp(betaStatus*S0) Status =S0 + slope*time h(varying)=beta0*exp(betaStatus*Status) 	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 8

Cumulative Hazard and Relative Risk



Relative Risk Constant Hazard

Time varying hazard

Slide 9

Explanatory Variable Functions

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

Includes exponential, Weibull, Gompertz as special cases

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

Linear and non-linear functions of explanatory variables

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 10

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 11	# Likelihoods for Survival For an uncensored datum, with T_i equal to the age at death, we have $\Pr(T = T_i \mid \theta) = f(T_i \mid \theta)$ = $S(T_i\|\theta) * h(T_i)$ For a left censored datum, such that the age at death is known to be less than T_i, we have $\Pr(T < T_i \mid \theta) = F(T_i \mid \theta) = 1 - S(T_i \mid \theta)$ For a right censored datum, such that the age at death is known to be greater than T_i, we have $\Pr(T > T_i \mid \theta) = 1 - F(T_i \mid \theta) = S(T_i \mid \theta)$ 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 $\Pr(T_{i,l} < T < T_{i,r} \mid \theta) = S(T_{i,l} \mid \theta) - S(T_{i,r} \mid \theta)$ 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 12	# Immediate Probability of Event - Hazard function predictions of events are based on the cumulative history of the hazard e.g. death due to atherosclerotic blood vessels - Some events are not dependent on history but just the immediate probability e.g. bleeding due to bolus injection of heparin 	
Slide 13	# Logistic Regression or Hazard for Time to Event? - Logistic regression is used to predict a probability at an instant of time - Can be used with similar covariates used for hazard based time to event - Choice of hazard or logistic approach should be determined by biology 	

Slide 14

Practical Implementation

Slide 15

Encoding Single Events
Interval Starts with DV=3

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	3	1	Start Event Interval
3	70	2	0	End Event Interval

A record at time=0 is needed to define when the hazard integration starts.
Exact event has DV=1, Interval Censored event has DV=2
A DV value of 3 is used to signal the start of an interval containing an event.

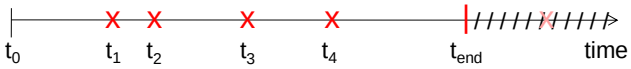
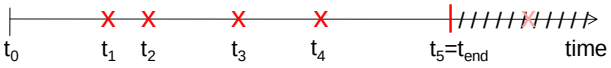
Slide 16

Single Event Time Varying Hazard (CP)
Interval starts with DV=3

```
$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
0.1 FIX ; PPV_CL
0.1 FIX ; PPV_V

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

$PK
   IF (NEWIND.LE.1) THEN
      ; for interval censoring
      SURLAST=1
   ENDIF
   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
HAZ= BASHAZ*EXP(BETACP*CP)
CUMHAZ=A(2)
SUR=EXP(-CUMHAZ)

; Estimation Code
IF (DV.EQ.0) THEN ; Censored event
   Y=SUR ; Likelihood is the survivor function
ENDIF

IF (DV.EQ.1) THEN ; Exact Time event
   Y=SUR*HAZ ; likelihood of event in interval
ENDIF

IF (DV.EQ.2) THEN ; Interval Censored event
   Y=SURLAST-SUR ; likelihood of event in interval
ENDIF

IF (DV.EQ.3) THEN ; start of new event interval
   SURLAST=SUR ; survivor function at start of new
interval
ELSE ; save recursive random variable
   SURLAST=SURLAST ; survivor function at end of
previous interval
ENDIF
```

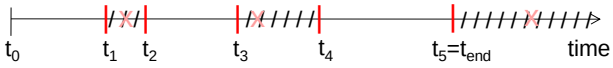

Estimation of the parameters of any hazard model can be done using this kind of code. It uses ADVAN6 to integrate the hazard and obtain the cumulative hazard. This can be used with the hazard at the time of the event to calculate the likelihood of right censored, exact time and interval censored events.
Random effects on hazard model parameters (e.g. BASHAZ and BETACP) are not estimable with single events.

Slide 17	**Extension to repeated events** 1) Exact times of events  	Repeated event observations (e.g. seizures) have several observation events.
Slide 18	**Extension to repeated events** The likelihood of the observations is the joint probability: $$\begin{aligned} L(\boldsymbol{t}) &= \mathbb{P}(T_1 \in [a_1,b_1], T_2 \in [a_2,b_2], \ldots, T_K \in [a_K,b_K], T_{K+1} > t_{end}) \\ &= \int_{a_1}^{b_1}\int_{a_2}^{b_2}\cdots\int_{a_K}^{b_K}\int_{t_{end}}^{+\infty} p(t_1,t_2,\ldots,t_K,t_{K+1})\,dt_1\,dt_2,\ldots,dt_K,dt_{K+1} \\ &= \left(\prod_{k=1}^{K}\int_{a_k}^{b_k} p(t_k|t_{k-1})\right)\int_{t_{end}}^{+\infty} p(t_{K+1}|t_K)\,dt_1\,dt_2,\ldots,dt_K,dt_{K+1} \\ &= \left(\prod_{k=1}^{K}\int_{a_k}^{b_k} \lambda(t_k)e^{-\Lambda(t_{k-1},t_k)}\right)\int_{t_{end}}^{+\infty} \lambda(t_{K+1})e^{-\Lambda(t_K,t_{K+1})}\,dt_1\,dt_2,\ldots,dt_K,dt_{K+1} \\ &= \left(\prod_{k=1}^{K}\int_{a_k}^{b_k} \lambda(t_k)dt_k\right)\int_{t_{end}}^{+\infty} \lambda(t_{K+1})e^{-\Lambda(t_0,t_{K+1})}\,dt_{K+1} \\ &= \left(\prod_{k=1}^{K}\int_{a_k}^{b_k} \lambda(t_k)\right)e^{-\Lambda(t_0,t_{end})} \\ &= \left(\prod_{k=1}^{K-1}\Lambda(a_k,b_k)e^{-\Lambda(t_{k-1},t_k)}\right)e^{-\Lambda(t_K,t_{end})} \end{aligned}$$ 	A careful calculation of the likelihood of repeated events is not straightforward… but is possible!
Slide 19	**Extension to repeated events** 1) Exact times of events  | ID	TIME	DV	MDV	Comment	Likelihood
---	---	---	---	---	---
1	t_0	.	1	Start observing	-
1	t_1	1	0	Exact Time Event	$\lambda(t_1)\,e^{-\Lambda(t_0,\,t_1)}$
1	t_2	1	0	Exact Time Event	$\lambda(t_2)\,e^{-\Lambda(t_1,\,t_2)}$
1	t_3	1	0	Exact Time Event	$\lambda(t_3)\,e^{-\Lambda(t_2,\,t_3)}$
1	t_4	1	0	Exact Time Event	$\lambda(t_4)\,e^{-\Lambda(t_3,\,t_4)}$
1	t_5	0	0	Right Censored Event	$e^{-\Lambda(t_4,\,t_5)}$ | 	The same formulas used for exact times of event and right censored events can be used for repeated events.

Slide 20

Extension to repeated events

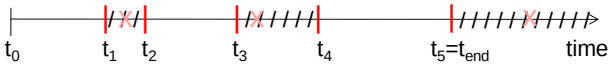
2) Interval censored events



Slide 21

Extension to repeated events

2) Interval censored events



ID	TIME	DV	MDV	Comment	Likelihood
1	t_0	.	1	Start observing	-
1	t_1	0	0	Start Event Interval	$e^{-\Lambda(t_0, t_1)}$
1	t_2	2	0	End Event Interval	$\Lambda(t_1, t_2)e^{-\Lambda(t_1, t_2)}$
1	t_3	0	0	Start Event Interval	$e^{-\Lambda(t_2, t_3)}$
1	t_4	2	0	End Event Interval	$\Lambda(t_3, t_4)e^{-\Lambda(t_3, t_4)}$
1	t_5	0	0	Right Censored Event	$e^{-\Lambda(t_4, t_5)}$

For each interval, we have to compute 2 likelihoods: the likelihood when the interval starts and the likelihood when the interval ends.

Slide 22

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 23

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 24

Joint Model Data
Interval start uses DV=3

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	20	1	1	50.2	0	Biomarker
2	30	1	2	3	1	Start event interval
2	30	1	1	13.5	0	Biomarker
2	50	1	2	2	0	Interval 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). Start of an event interval is marked by DV=3 and DVID=2.

Slide 25

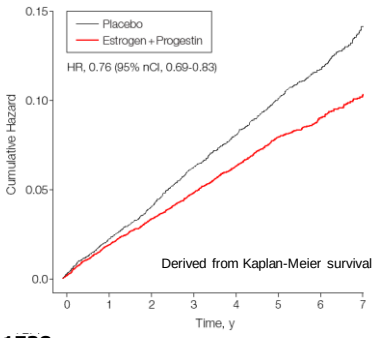
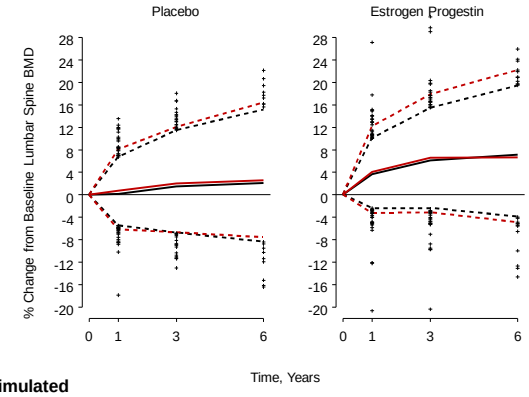
RTTE Disease Progress and Time Varying Hazard
Interval start uses DV=3

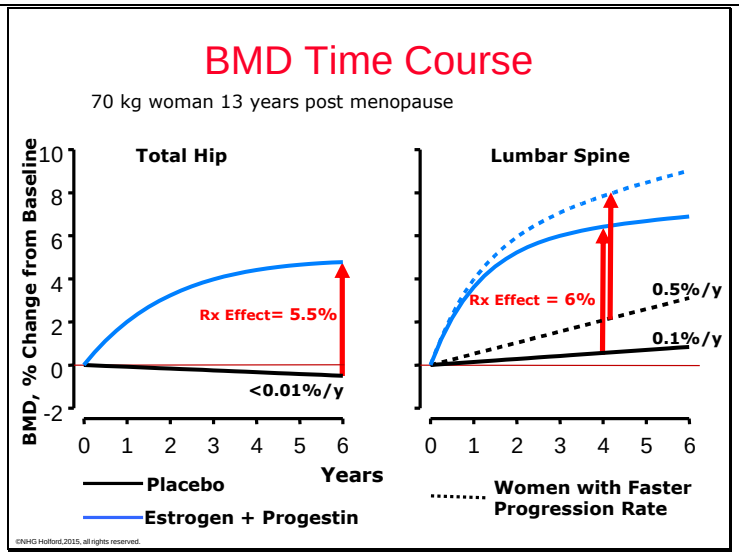
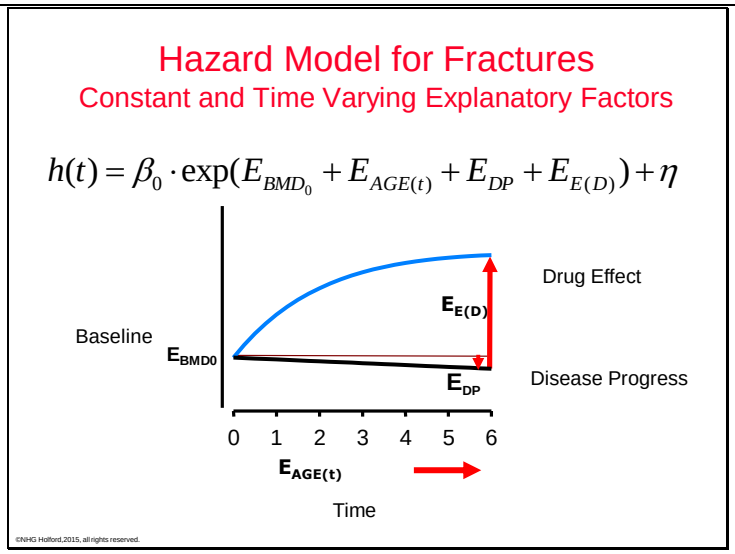
```
$INPUT ID TRT DVID TIME DV MDV
$ESTIM MAX=9990 NSIG=3 SIGL=9
METHOD=CONDITIONAL
LAPLACE
$SUBR ADVAN=6 TOL=9
$MODEL
COMP=(CUMHAZ)
$PK
IF (NEWIND.LE.1) THEN ; Initialize
   SURLAST=1
   CUMLAST=0
ENDIF
;-------------------------------
; Hazard
BASHAZ  = THETA(1) ; Baseline hazard
BETADP  = THETA(2) ; 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
CUMDIF=CUMHAZ-CUMLAST  ; CUMHAZ since last event
SUR=EXP(-CUMDIF)
;-------------------------------
DISPRG=INTRI + SLOPI*TIME
HAZARD = BASHAZ*EXP(BETADP*DISPRG)
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(-CUMDIF)
ENDIF
IF (DVID.EQ.2.AND.DV.EQ.1) THEN ; exact time
   F_FLAG = 1 ; Likelihood
   Y = SUR*HAZARD
   CUMLAST=CUMHAZ
ELSE
   CUMLAST=CUMLAST
ENDIF
IF (DVID.EQ.2.AND.DV.EQ.2) THEN ; interval censored
   F_FLAG = 1 ; Likelihood
   Y = SURLAST - SUR
   CUMLAST=CUMHAZ
ELSE
   CUMLAST=CUMLAST
ENDIF
IF (DVID.EQ.2.AND.DV.EQ.3) THEN
   SURLAST=SUR ; start event interval
ELSE
   SURLAST=SURLAST ; save recursive random variable
ENDIF
```


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.

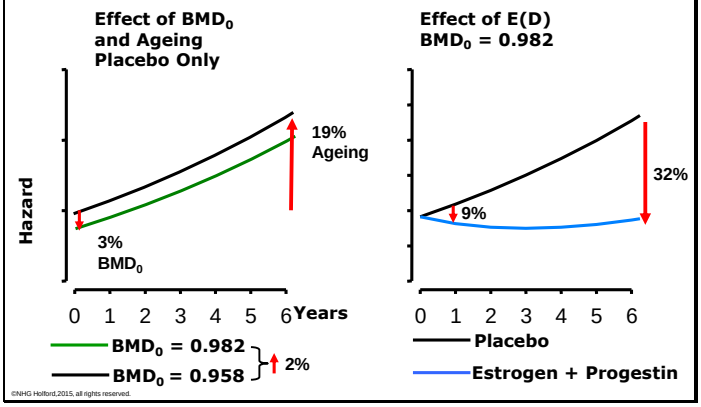
The F_FLAG variable is used to tell NONMEM how to use the predicted Y value. F_FLAG of 0 is the default i.e. Y is the prediction of a continuous variable. F_FLAG

		of 1 means the prediction is a likelihood. F_FLAG of 2 means the prediction is -2*ln(Likelihood). 2023-Aug-29 Correction: The right censored likelihood for repeated events has been changed to Y=EXP(-CUMDIF). Previously it was incorrect (Y=EXP(-CUMHAZ)). Thanks to Dr Hyeong-Seok Lim for bringing this to my attention.
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** 	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 	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		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

Baseline BMD, Age and Treatment Effect are Predictors of Fracture



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

Repeated Bone Fractures

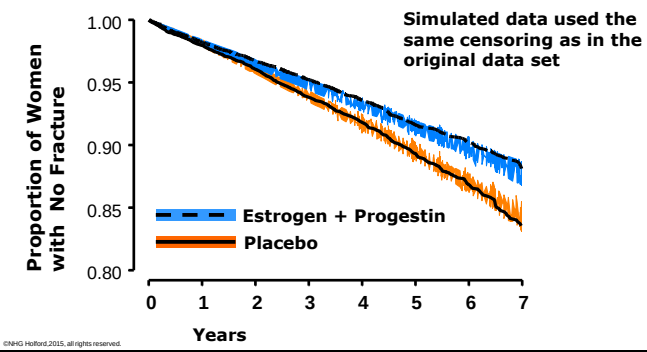
Model Parameters	Estimate (RSE%)
Baseline hazard for first fractures, y^{-1}	0.017 (5%)
Baseline BMD	-3.93 (16%)
Treatment effect on first fractures	-17.6 (16%)
Time	0.00025 (16%)
Baseline hazard for second fractures, y^{-1}	0.011 (16%)
Treatment effect on second fractures	-60 (33%)

Slide 32

Simulating RTTE

```
; Simulation Code
$SIM (1234) (45678 UNI) ONLYSIM NOPRED
NSUB=1

IF(ICALL.EQ.4) THEN
   IF (NEWIND.EQ.0) THEN
; max events to simulate
      MAXEVT=10000
   ENDIF
   IF(NEWIND.NE.2) THEN
      NEVT=0
      MDVX=0
      DVX=0
   ; new chance for each individual
      CALL RANDOM (2,R)
      RVAL=R
   ENDIF
```

```
IF(NEVT.LT.MAXEVT) THEN
   IF (RVAL.GT.SUR) THEN ;simulate event
         NEVT=NEVT+1
         DVX=1
         MDVX=0
      ; Save cumulative hazard for this event
         CUMLAST=CUMHAZ
      ; Resample so events are independent
         CALL RANDOM (2,R)
         RVAL=R
      ELSE ; not an event
         IF (DV.EQ.99) THEN ; last record
            ; right censored event
            DVX=0
            MDVX=0
         ELSE
            ; start of interval?
            DVX=3
            MDVX=1
            CUMLAST=CUMLAST
         ENDIF ;  DV=99?
      ENDIF ; event?
   ELSE
      DVX=2
      MDVX=1
   ENDIF ; max events?
ENDIF ; simulate?


$TABLE ID TIME DVX MDVX SUR NEVT
NOAPPEND NOPRINT ONEHEADER FILE=rtte.fit
```

Slide 33	## Estimation Method • NONMEM First Order method is fastest if there are no random effects in the model » E.g. Use empirical Bayes estimates to predict time varying covariates • Joint models (e.g. PPP+D method) are not usually required but if used then use the estimation method used for the continuous part of the joint model. 	
Slide 34	## Repeated Event Diagnostics • Consider each event as a new event • Simulate using hazard conditional on previous events • Use Kaplan-Meier VPC to assess model prediction for each event 	
Slide 35	## A Visual Predictive Check for Time to Event Based on Kaplan-Meier Estimates of S(t)  	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.