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Trial Innovation

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mixedpower - a new program for calculating power and sample size for longitudinal mixed models

UK Stata Conference 2026, London
4th September

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Outline

- Background
- Methods overview
- `mixedpower` command
 - Basic 2-level example with `mixedpower`
- More advanced models
 - Variance structure (marginal models, group heterogeneity)
 - Treatment effect specifications
- Incomplete follow-up (introducing `trialcounts` and `mvmixedpower`)
- Misspecification of treatment effect
- Future updates

Background

In Stata

- `slopepower`
 - analytic
 - only for proportionate slope effect and random slopes model
 - fits mixed model as part of the command – no user input of variance parameters
- `ipdpower`
 - simulation based (including GLMMs)

In R

- More options but mostly simulation-based or for slope effect only

Simulation versus analytic calculations

- Simulation can be used to replicate exactly the scenario you desire
- Analytic calculations:
 - more accurate – no Monte Carlo error
 - much (much) faster - essentially instantaneous in `mixedpower`
 - speed difference increases with n
 - can calculate sample size explicitly
- More scope for analytic calculations than may be apparent

Methods - basic idea*

- For a linear mixed model for outcome y :

$$\mathbf{Y}|\mathbf{u} \sim N(\mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u}; \mathbf{R}) \text{ with } \mathbf{u} \sim N(0; \mathbf{G})$$

- Marginally,

$$\mathbf{Y} \sim N(\mathbf{X}\boldsymbol{\beta}; \boldsymbol{\Sigma}) \text{ with } \boldsymbol{\Sigma} = \mathbf{R} + \mathbf{Z}\mathbf{G}\mathbf{Z}'$$

$$\text{Var}(\hat{\boldsymbol{\beta}}) = (\mathbf{X}'\boldsymbol{\Sigma}^{-1}\mathbf{X})^{-1}$$

- **Key idea** – subjects in RCTs typically only necessarily **differ** in terms of a few model parameters – often just in terms of **treatment received**
 - → Calculate the $\text{Var}(\hat{\boldsymbol{\beta}})$ matrix for a “two-person” trial and use the treatment effect variance element (s^2) from $\text{Var}(\hat{\boldsymbol{\beta}})$ to calculate power/sample size in usual way
 - Just need to reweight s^2 for appropriate sample size

Example: 4 measurements at 0, 1, 2 and 3 years

X matrix 8x3

X1	X2	X3
1	0	0
1	1	0
1	2	0
1	3	0
1	0	0
1	1	1
1	2	2
1	3	3

R matrix 8x8

R1	R2	R3	R4	R5	R6	R7	R8
3	0	0	0	0	0	0	0
0	3	0	0	0	0	0	0
0	0	3	0	0	0	0	0
0	0	0	3	0	0	0	0
0	0	0	0	3	0	0	0
0	0	0	0	0	3	0	0
0	0	0	0	0	0	3	0
0	0	0	0	0	0	0	3

Z matrix 8x4

Z1	Z2	Z3	Z4
1	0	0	0
1	1	0	0
1	2	0	0
1	3	0	0
0	0	1	0
0	0	1	1
0	0	1	2
0	0	1	3

G matrix 4x4

G1	G2	G3	G4
20	2	0	0
2	5	0	0
0	0	20	2
0	0	2	5

$$\Sigma = R + ZGZ'$$

$$Var(\hat{\beta}) = (X'\Sigma^{-1}X)^{-1}$$

$$s^2 = Var(\hat{\beta})[3, 3] = 11.1$$

n=200 patients per arm

Control group mean slope=2.0

30% reduction → Trt effect=0.6

Alpha=0.025 one-sided

$$\text{Power} = \Phi \left[\mu - \Phi^{-1} \left(1 - \frac{\alpha}{2} \right) \right]$$

$$\text{Power} = \Phi \left[0.6 \sqrt{200/11.1} - \Phi^{-1}(1 - 0.025) \right]$$

$$\text{Power} = 0.722$$

mixedpower syntax

```
mixedpower, trtspec(trtspec_type) schedule(numlist)  
[alpha(#) twosided power(#) n(#) altcont(altcont_type)  
actualcont(altcont_type) actualtrt(trtspec_type) cbeta(#  
[# ...]) difference(# [# ...]) effectiveness(#)  
contslope(#) lctest(# # ...) jtttest(# # ...)  
covariance(matrix) errorvar(#) auto covhet(input_type[(  
matrix)]) marginal errxt(input_type[(xerror_type[# ...  
|mat_name])]) errhet(input_type[(xerror_type[# ...  
|mat_name])]) scale(#) aratio(# #) dropouts(numlist)  
drop2(numlist) strecruitment(numlist) noheader nosyntax  
xmat(#) rmat(#) zmat(#) gmat(#) bvarn(#)]
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```

`trtspec (trtspec_type)`

- `slope` proportionate slope effect i.e. constrained to equal control slope at baseline
- `intercept` intercept effect i.e. parallel shift
- `lateslope #` slope effect that only starts to differ from control slope at time #
- `2slope #` two separate slope effects with changepoint at time #
- `slint` separate slope and intercept treatment effects
- `factor` factorised i.time#1.treatment interactions but constrained to be equal to control at 'baseline'
- `factor0` fully factorised i.time#1.treatment interactions including at 'baseline'
- `user (f1 (t) [ ; f2 (t) ] )` allows user to specify up to 2 functions of 'schedule time'

Example from the Statablog*

"imagine that you are planning a longitudinal study of childrens' weight and you are interested in the interaction of age and sex"

- $\text{weight}_{it} = \beta_0 + \beta_1(\text{age}_{it}) + \beta_2(\text{female}_i) + \beta_3(\text{age}_{it} \times \text{female}_i) + u_{0i} + u_{1i}(\text{age}) + e_{it}$
- Here i indexes children, t indexes time (age), and we assume that $u_{0i} \sim N(0, \tau_0^2)$, $u_{1i} \sim N(0, \tau_1^2)$, $e_{it} \sim N(0, \sigma^2)$ and $\text{cov}(\tau_0^2, \tau_1^2) = 0$.
- Parameter values chosen:
 $\beta_0 = 5.35, \beta_1 = 3.6, \beta_2 = -0.5, \beta_3 = -0.25, \tau_0^2 = 0.0625, \tau_1^2 = 0.36, \text{ and } \sigma^2 = 1.44$

- Also:

$P(\text{female}) \sim \text{Bin}(1, 0.5)$

age is controlled by design i.e. 5 (or 6) 6-monthly measures from birth

sample size range from 100 to 500 in increments of 100

```
ssc install mixedpower
```

```
mixedpower, trtspec(slint) sched(0(0.5)2) n(100) diff(-0.5 -0.25)  
cov(0.0625, 0\0, 0.36) error(1.44) lctest(0 1)
```

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```

mixedpower output

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lctest(0 1)
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mixedpower - power and sample size calculator for linear mixed models (version 1.0): author M.Burnell
MRC Centre of Research Excellence in Clinical Trial Innovation, UCL, London WC1V 6LJ, UK

Mixed model syntax:

```
mixed depvar c.time i.trt c.time#1.trt || id_level2: time , cov(independent) resid(independent , t(time))
```

Calculating power for a 2-level mixed model with slint treatment effect parameterisation:

```
visit schedule      = 0 0.5 1 1.5 2  
treatment effect(s) = -0.5 -0.25  
alpha              = 0.050  
total sample size   = 100  
n in control arm    = 50  
n in treatment arm  = 50  
power              = 0.2521
```



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mixedpower output

```
mixedpower, trtspec(slint) sched(0(0.5)2) n(100) diff(-0.5 -0.25) cov(0.0625,0\0,0.36)  
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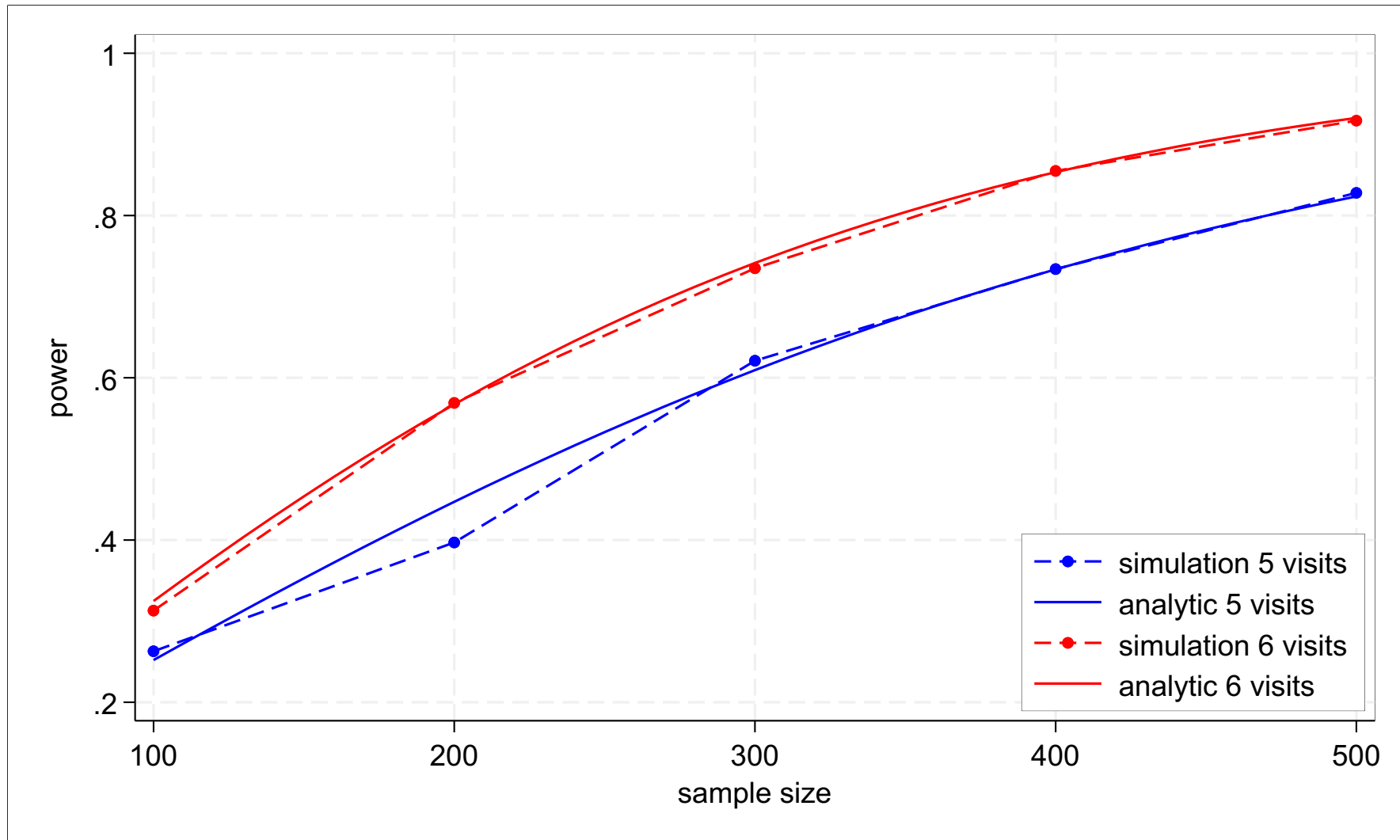


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Comparison with simulation (1000 replications)



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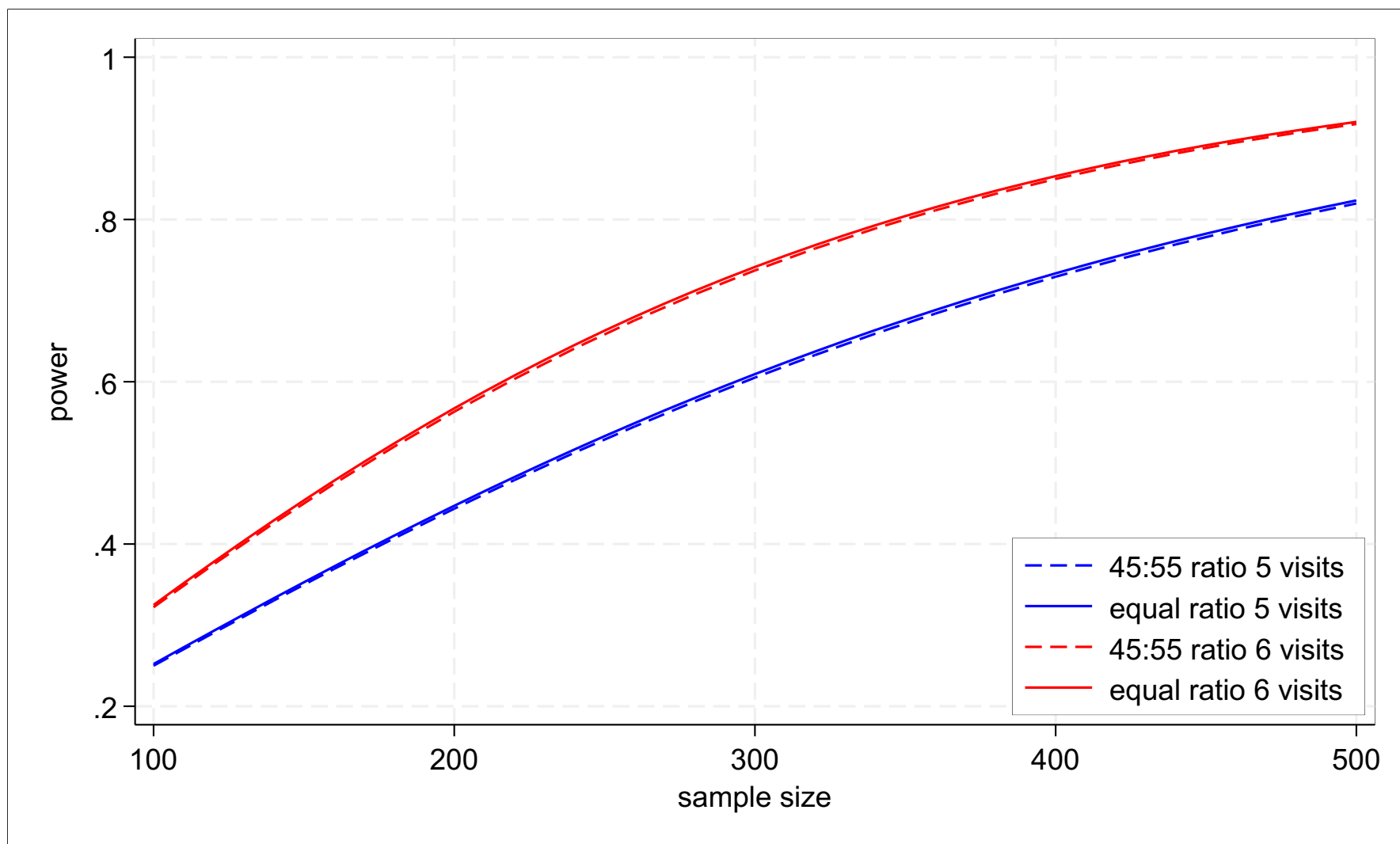


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Equal ratio versus 45:55 ratio



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NIHR

National Institute for
Health and Care Research

Complex covariance and error structure

- No random effects – ‘marginal’ model with AR(2) structure:
- `mixed weight c.week c.week#1.trt if week<=4 || id: ,nocons resid(ar 2, t(week)) reml`

weight	Coefficient	Std. err.	z	P> z	[95% conf. interval]	
week	6.353491	.1414451	44.92	0.000	6.076264	6.630718
trt#c.week 1	-.1416163	.191331	-0.74	0.459	-.5166181	.2333855
_cons	25.07109	.5260814	47.66	0.000	24.03999	26.10219

Random-effects parameters		Estimate	Std. err.	[95% conf. interval]	
id:	(empty)				
Residual: AR(2)					
	phi1	1.009429	.0744062	.8635957	1.155263
	phi2	-.0943942	.0783788	-.2480139	.0592254
	var(e)	13.29269	2.373062	9.368136	18.86134

- `mixedpower, trtspec(slope) sched(0 1 2 3 4) diff(0.5) alpha(0.05) n(48) marginal
errxt(auto) rmat(5)`
- `power` = 0.7432

Complex covariance and error structure

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- `mixedpower, trtspec(slope) sched(0 1 2 3 4) diff(0.5) alpha(0.05) n(48) marginal
errxt(input(ar 13.29 1.009 -.0943)) rmat(5)`
- `power` = 0.7422

Complex covariance and error structure

- No random effects – ‘marginal’ model with AR(2) structure:
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- `mixedpower, trtspec(slope) sched(0 1 2 3 4) diff(0.5) alpha(0.05) n(48) marginal
errxt(auto) rmat(5)`
- `di r(se_trial)`
- `.19133096`

Complex covariance and error structure

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 - `mixed weight c.week c.week#1.trt if week<=4 || id: ,nocons resid(ar 2, t(week)) reml`
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errxt(input(ar 13.29 1.009 -.0943)) rmat(5)`
 - `mat li r(rmat)`

	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10
t0_v1	13.29									
t0_v2	12.254053	13.29								
t0_v3	11.111092	12.254053	13.29							
t0_v4	10.055535	11.111092	12.254053	13.29						
t0_v5	9.0982588	10.055535	11.111092	12.254053	13.29					
t1_v1	0	0	0	0	0	13.29				
t1_v2	0	0	0	0	0	12.254053	13.29			
t1_v3	0	0	0	0	0	11.111092	12.254053	13.29		
t1_v4	0	0	0	0	0	10.055535	11.111092	12.254053	13.29	
t1_v5	0	0	0	0	0	9.0982588	10.055535	11.111092	12.254053	13.29

Complex covariance and error structure

- mixed model for repeated measures (MMRM):
- `mixed weight i.week i.week#1.trt if week<=4 || id: , nocons resid(unstr, t(week)) reml`
- `mixedpower, trtspec(factor) altcont(factor) sched(0 1 2 3 4) diff(0.5(0.5)2) lctest(0 0 0 1) n(100) marginal errxt(auto) rmat(5)`

Complex covariance and error structure

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Residual: Unstructured

var(e0)	6.17301	1.287097	4.102212	9.289148
var(e1)	7.936371	1.654705	5.274114	11.94248
var(e2)	12.83311	2.675662	8.528235	19.311
var(e3)	14.2423	2.969469	9.46472	21.43151
var(e4)	20.99887	4.378229	13.95474	31.59876
cov(e0,e1)	6.412595	1.399525	3.669576	9.155614
cov(e0,e2)	7.173466	1.685304	3.870331	10.4766
cov(e0,e3)	7.476909	1.768024	4.011645	10.94217
cov(e0,e4)	8.600099	2.103534	4.477248	12.72295
cov(e1,e2)	9.218073	2.015073	5.268603	13.16754
cov(e1,e3)	9.660103	2.117767	5.509355	13.81085
cov(e1,e4)	11.40512	2.539557	6.42768	16.38256
cov(e2,e3)	12.96083	2.761115	7.549141	18.37251
cov(e2,e4)	15.23573	3.301904	8.764122	21.70735
cov(e3,e4)	16.65738	3.539964	9.719183	23.59558

Complex covariance and error structure

- mixed model for repeated measures (MMRM):
 - `mixed weight i.week i.week#1.trt if week<=4 || id: , nocons resid(unstr, t(week)) reml`
 - `mixedpower, trtspec(factor) altcont(factor) sched(0 1 2 3 4) diff(0.5(0.5)2) lctest(0 0 0 1) n(100) marginal errxt(auto) rmat(5)`

Mixed model syntax:

`constraint 1 _b[0.time#1.trt]=0`

`mixed depvar c.time i.time#1.trt , constraints(1) || id_level2: , nocons resid(unstructured , t(time))`

Calculating power for a 2-level mixed model with factor treatment effect parameterisation:

```
visit schedule      = 0 1 2 3 4
treatment effect(s) = 0.5 1 1.5 2
alpha               = 0.050
total sample size   = 100
n in control arm    = 50
n in treatment arm  = 50
power               = 0.9337
```

Complex covariance and error structure

- Heterogenous random effects and MA(2) errors
- ```
mixed weight c.week c.week#1.trt if week<=6 || id: c.week#0.trt 0.trt , cov(uns) nocons
|| id: c.week#1.trt 1.trt, cov(uns) nocons reml resid(ma 2 , t(week) by(trt))
```

|                            |                       |          |          |           |          |
|----------------------------|-----------------------|----------|----------|-----------|----------|
| id: Unstructured           |                       |          |          |           |          |
|                            | var(0.trt#week)       | .0898904 | .0682003 | .020319   | .3976714 |
|                            | var(0.trt)            | 6.44481  | 2.40953  | 3.097206  | 13.41066 |
|                            | cov(0.trt#week,0.trt) | .2241268 | .2819883 | -.3285601 | .7768137 |
| id: Unstructured           |                       |          |          |           |          |
|                            | var(1.trt#week)       | .4494937 | .1543419 | .2293232  | .8810474 |
|                            | var(1.trt)            | 4.50217  | 1.665568 | 2.180327  | 9.296555 |
|                            | cov(1.trt#week,1.trt) | 1.1412   | .402475  | .3523635  | 1.930037 |
| Residual: MA(2),<br>by trt |                       |          |          |           |          |
|                            | 0: theta1             | .6403558 | .101935  | .4405668  | .8401448 |
|                            | theta2                | .2033059 | .1221    | -.0360056 | .4426174 |
|                            | var(e)                | 2.28888  | .4557201 | 1.549342  | 3.381418 |
|                            | 1: theta1             | .450745  | .1268837 | .2020575  | .6994324 |
|                            | theta2                | .0211289 | .1569821 | -.2865503 | .3288082 |
|                            | var(e)                | 1.466889 | .3301105 | .9437167  | 2.280093 |

# Complex covariance and error structure

- Heterogenous random effects and heterogenous MA(2) errors
  - `mixed weight c.week c.week#1.trt if week<=6 || id: c.week#0.trt 0.trt , cov(uns) nocons || id: c.week#1.trt 1.trt, cov(uns) nocons reml resid(ma 2 , t(week) by(trt))`
  - `mixedpower, trtspec(slope) sched(0(1)4) diff(0.5) alpha(0.05) n(100) auto covhet(auto) errxt(auto) errhet(input(ma 1.466888 .4507447 .0211286)) rmat(5) gmat(5)`

---

Mixed model syntax:

```
mixed depvar c.time c.time#1.trt || id_level2: c.time#0.trt 0.trt, cov(unstr) nocons || id_level2: c.time#1.trt 1.t
> rt, cov(unstr) nocons resid(ma 2, t(time) by(trt))
```

---

Calculating power for a 2-level mixed model with slope treatment effect parameterisation:

```
visit schedule = 0 1 2 3 4
treatment effect(s) = 0.5
alpha = 0.050
total sample size = 100
n in control arm = 50
n in treatment arm = 50
power = 0.9440
```



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# Incomplete follow-up

- Two sources:
  - Dropout
  - Staggered recruitment – an interim analysis at a given point in calendar time will include subjects with differing amounts of follow-up
- Mathematically equivalent impact
- But `mixedpower` can adjust for both sources simultaneously
  - options `dropout` and `strecruitment`
- Can also specify alternate dropout function for treatment group
  - Option `drop2`

# Example of incomplete follow-up

- mixedpower , trtspec(slope) schedule(0 1 2 3 4) **conts(-2.0) eff(0.25) cov(100,3.5\3.5,2.5)**  
error(12) power(0.9) **ara(1 2)**

Calculating sample size for a 2-level mixed model with slope treatment effect parameterisation:

```
visit schedule = 0 1 2 3 4
treatment effect(s) = 0.5
alpha = 0.050
total sample size = 699
n in control arm = 233
n in treatment arm = 466
power = 0.9005
```

- mixedpower , trtspec(slope) schedule(0 1 2 3 4) conts(-2.0) eff(0.25) cov(100,3.5\3.5,2.5)  
error(12) power(0.9) ara(1 2) **strec(0.05 0.1 0.15 0.2 0.4) drop(0.1 0.05 0.05 0.05 0.75)**

```
total sample size = 1338
n in control arm = 446
n in treatment arm = 892
power = 0.9006
```

Table of control and treatment group numbers (rounded) reaching each visit:

|           | visit 1<br>time=0 | visit 2<br>time=1 | visit 3<br>time=2 | visit 4<br>time=3 | visit 5<br>time=4 |
|-----------|-------------------|-------------------|-------------------|-------------------|-------------------|
| control   | 401               | 341               | 284               | 214               | 134               |
| treatment | 803               | 682               | 569               | 428               | 268               |

# Introducing `trialcounts` and `mvmixedpower`

- `trialcounts` companion program to `mixedpower`
  - Helps one calculate the number of subjects recruited to a trial at any point in trial-time based on piecewise linear recruitment function and (parametric survival) dropout functions
  - Also calculates those  $p$  weights needed to pass easily to `mixedpower`
- `mvmixedpower` and `dmmixedpower` are additional programs that come with `mixedpower` package
  - `mvmixedpower` calculates power and sample size for a multivariate mixed model
  - `dmmixedpower` calculates power and sample size for a 'direct measures' mixed model\*



# Example from real MS trial

- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`

| month_name | month | recr_2mth | recr2 |
|------------|-------|-----------|-------|
| Mar-23     | 2     | 3         | 1.5   |
| May-23     | 4     | 4         | 2     |
| Jul-23     | 6     | 4         | 2     |
| Sep-23     | 8     | 8         | 4     |
| Nov-23     | 10    | 14        | 7     |
| Jan-24     | 12    | 9         | 4.5   |
| Mar-24     | 14    | 23        | 11.5  |
| May-24     | 16    | 17        | 8.5   |
| Jul-24     | 18    | 17        | 8.5   |
| Sep-24     | 20    | 19        | 9.5   |
| Nov-24     | 22    | 21        | 10.5  |
| Jan-25     | 24    | 21        | 10.5  |
| Mar-25     | 26    | 23        | 11.5  |
| May-25     | 28    | 23        | 11.5  |
| Jul-25     | 30    | 25        | 12.5  |
| Sep-25     | 32    | 27        | 13.5  |
| Nov-25     | 34    | 27        | 13.5  |
| Jan-26     | 36    | 28        | 14    |
| Mar-26     | 38    | 30        | 15    |
| May-26     | 40    | 30        | 15    |
| Jul-26     | 42    | 32        | 16    |
| Sep-26     | 44    | 33        | 16.5  |
| Nov-26     | 46    | 33        | 16.5  |
| Jan-27     | 48    | 33        | 16.5  |
| Mar-27     | 50    | 33        | 16.5  |
| May-27     | 52    | 33        | 16.5  |
| Jul-27     | 54    | 33        | 16.5  |

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# Example from real MS trial

- trialcounts, sched(0(6)36) **ends(month) rates(recr2 1(1)21 27)** time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr

| month_name | month | recr_2mth | recr2 |
|------------|-------|-----------|-------|
| Mar-23     | 2     | 3         | 1.5   |
| May-23     | 4     | 4         | 2     |
| Jul-23     | 6     | 4         | 2     |
| Sep-23     | 8     | 8         | 4     |
| Nov-23     | 10    | 14        | 7     |
| Jan-24     | 12    | 9         | 4.5   |
| Mar-24     | 14    | 23        | 11.5  |
| May-24     | 16    | 17        | 8.5   |
| Jul-24     | 18    | 17        | 8.5   |
| Sep-24     | 20    | 19        | 9.5   |
| Nov-24     | 22    | 21        | 10.5  |
| Jan-25     | 24    | 21        | 10.5  |
| Mar-25     | 26    | 23        | 11.5  |
| May-25     | 28    | 23        | 11.5  |
| Jul-25     | 30    | 25        | 12.5  |
| Sep-25     | 32    | 27        | 13.5  |
| Nov-25     | 34    | 27        | 13.5  |
| Jan-26     | 36    | 28        | 14    |
| Mar-26     | 38    | 30        | 15    |
| May-26     | 40    | 30        | 15    |
| Jul-26     | 42    | 32        | 16    |
| Sep-26     | 44    | 33        | 16.5  |
| Nov-26     | 46    | 33        | 16.5  |
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| Mar-27     | 50    | 33        | 16.5  |
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# Example from real MS trial

- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`

| month_name | month | recr_2mth | recr2 |
|------------|-------|-----------|-------|
| Mar-23     | 2     | 3         | 1.5   |
| May-23     | 4     | 4         | 2     |
| Jul-23     | 6     | 4         | 2     |
| Sep-23     | 8     | 8         | 4     |
| Nov-23     | 10    | 14        | 7     |
| Jan-24     | 12    | 9         | 4.5   |
| Mar-24     | 14    | 23        | 11.5  |
| May-24     | 16    | 17        | 8.5   |
| Jul-24     | 18    | 17        | 8.5   |
| Sep-24     | 20    | 19        | 9.5   |
| Nov-24     | 22    | 21        | 10.5  |
| Jan-25     | 24    | 21        | 10.5  |
| Mar-25     | 26    | 23        | 11.5  |
| May-25     | 28    | 23        | 11.5  |
| Jul-25     | 30    | 25        | 12.5  |
| Sep-25     | 32    | 27        | 13.5  |
| Nov-25     | 34    | 27        | 13.5  |
| Jan-26     | 36    | 28        | 14    |
| Mar-26     | 38    | 30        | 15    |
| May-26     | 40    | 30        | 15    |
| Jul-26     | 42    | 32        | 16    |
| Sep-26     | 44    | 33        | 16.5  |
| Nov-26     | 46    | 33        | 16.5  |
| Jan-27     | 48    | 33        | 16.5  |
| Mar-27     | 50    | 33        | 16.5  |
| May-27     | 52    | 33        | 16.5  |
| Jul-27     | 54    | 33        | 16.5  |

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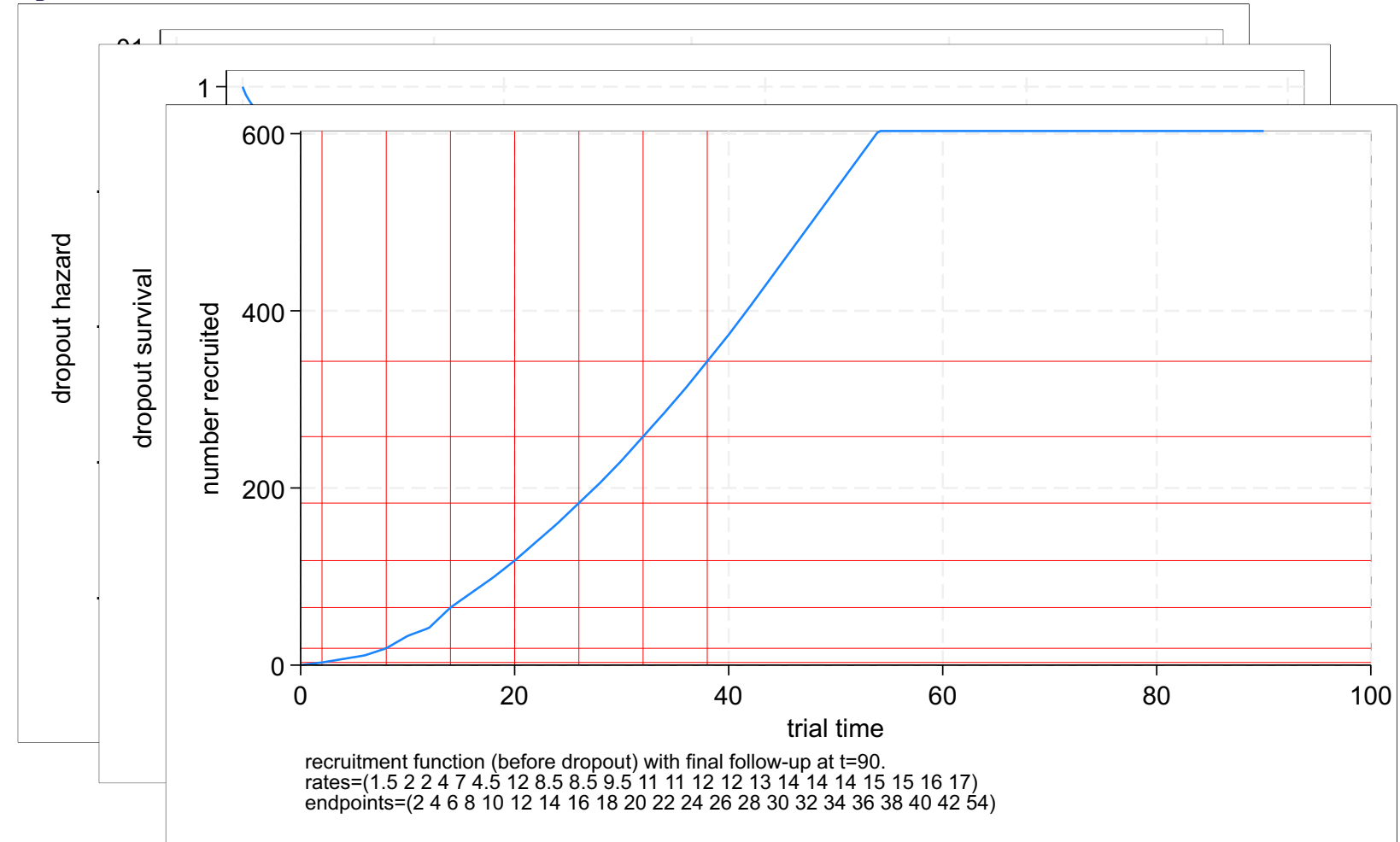
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# Example from real MS trial

- trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) **drfunction(weibull, p(0.75) s(0.9))** dgr rgr

| month_name | month | recr_2mth | recr2 |
|------------|-------|-----------|-------|
| Mar-23     | 2     | 3         | 1.5   |
| May-23     | 4     | 4         | 2     |
| Jul-23     | 6     | 4         | 2     |
| Sep-23     | 8     | 8         | 4     |
| Nov-23     | 10    | 14        | 7     |
| Jan-24     | 12    | 9         | 4.5   |
| Mar-24     | 14    | 23        | 11.5  |
| May-24     | 16    | 17        | 8.5   |
| Jul-24     | 18    | 17        | 8.5   |
| Sep-24     | 20    | 19        | 9.5   |
| Nov-24     | 22    | 21        | 10.5  |
| Jan-25     | 24    | 21        | 10.5  |
| Mar-25     | 26    | 23        | 11.5  |
| May-25     | 28    | 23        | 11.5  |
| Jul-25     | 30    | 25        | 12.5  |
| Sep-25     | 32    | 27        | 13.5  |
| Nov-25     | 34    | 27        | 13.5  |
| Jan-26     | 36    | 28        | 14    |
| Mar-26     | 38    | 30        | 15    |
| May-26     | 40    | 30        | 15    |
| Jul-26     | 42    | 32        | 16    |
| Sep-26     | 44    | 33        | 16.5  |
| Nov-26     | 46    | 33        | 16.5  |
| Jan-27     | 48    | 33        | 16.5  |
| Mar-27     | 50    | 33        | 16.5  |
| May-27     | 52    | 33        | 16.5  |
| Jul-27     | 54    | 33        | 16.5  |



# Example from real MS trial

- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`

## Trial Summary

total number (planned) = 603  
at time=38 total recruited = 343

## Table of visit probability weights and counts

|                | visit 1<br>time=0 | visit 2<br>time=6 | visit 3<br>time=12 | visit 4<br>time=18 | visit 5<br>time=24 | visit 6<br>time=30 | visit 7<br>time=36 | sum   |
|----------------|-------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------|
| final weights  | .1526             | .1265             | .106               | .0841              | .071               | .0243              | .0045              | .5688 |
| f_wgts rescale | .2682             | .2224             | .1863              | .1478              | .1248              | .0427              | .0079              | 1     |
| unique counts  | 92                | 76.3              | 63.9               | 50.7               | 42.8               | 14.6               | 2.7                | 343   |
| sum counts     | 343               | 251               | 174.7              | 110.8              | 60.1               | 17.3               | 2.7                |       |

# Example from real MS trial

- trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr

| Random-effects parameters  | Estimate  | Std. err. | [95% conf. interval] |           |
|----------------------------|-----------|-----------|----------------------|-----------|
| pat_idd: Unstructured      |           |           |                      |           |
| var(subscale_1)            | .2746418  | .0319136  | .2187039             | .344887   |
| var(subscale_2)            | .0712169  | .017981   | .043418              | .1168142  |
| var(subscale_3)            | .2327295  | .0260943  | .1868152             | .2899283  |
| var(yearsV_1)              | .0878073  | .009588   | .0708901             | .1087618  |
| var(yearsV_2)              | .0185581  | .0046185  | .0113945             | .0302253  |
| var(yearsV_3)              | .040874   | .0052704  | .0317462             | .0526263  |
| cov(subscale_1,subscale_2) | -.0272549 | .017995   | -.0625245            | .0080148  |
| cov(subscale_1,subscale_3) | .0050262  | .0207667  | -.0356757            | .0457281  |
| cov(subscale_1,yearsV_1)   | -.0569389 | .0142773  | -.0849219            | -.0289558 |
| cov(subscale_1,yearsV_2)   | .012509   | .0085141  | -.0041784            | .0291963  |
| cov(subscale_1,yearsV_3)   | -.0075305 | .0090986  | -.0253634            | .0103025  |
| cov(subscale_2,subscale_3) | -.0000471 | .015518   | -.0304618            | .0303675  |
| cov(subscale_2,yearsV_1)   | -.0198483 | .0097219  | -.0389028            | -.0007938 |
| cov(subscale_2,yearsV_2)   | .0041978  | .0074215  | -.0103481            | .0187436  |
| cov(subscale_2,yearsV_3)   | .0112102  | .0069591  | -.0024293            | .0248498  |
| cov(subscale_3,yearsV_1)   | -.0172578 | .0115987  | -.0399909            | .0054752  |
| cov(subscale_3,yearsV_2)   | -.0037198 | .007919   | -.0192407            | .0118011  |
| cov(subscale_3,yearsV_3)   | -.0523668 | .0099512  | -.0718708            | -.0328628 |
| cov(yearsV_1,yearsV_2)     | -.0182902 | .0048974  | -.0278888            | -.0086915 |
| cov(yearsV_1,yearsV_3)     | -.0091811 | .0051572  | -.0192889            | .0009268  |
| cov(yearsV_2,yearsV_3)     | .0114564  | .0035614  | .0044762             | .0184366  |
| occ: (empty)               |           |           |                      |           |
| Residual: Unstructured     |           |           |                      |           |
| var(e1)                    | .2145785  | .007399   | .2005559             | .2295816  |
| var(e2)                    | .1321472  | .006492   | .1200165             | .1455039  |
| var(e3)                    | .0866155  | .0043431  | .078508              | .0955603  |
| cov(e1,e2)                 | -.0109482 | .0058638  | -.0224411            | .0005446  |
| cov(e1,e3)                 | -.0083194 | .00493    | -.0179821            | .0013434  |
| cov(e2,e3)                 | .0075267  | .0038081  | .000063              | .0149904  |

# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079) eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`



# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079) eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`

# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079) eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`

# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079)  
eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`

# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079) eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`



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# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079) eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`

# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079) eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`

# Example from real MS trial

- `est use mvmixed_ms.ster`
- `trialcounts, sched(0(6)36) ends(month) rates(recr2 1(1)21 27) time(38) drfunction(weibull, p(0.75) s(0.9)) rgr dgr`
- `mvmixedpower, trtspec(slope) sched(0 0.5 1 1.5 2 2.5 3) contslope(.107 -.126 -.079) eff(0.4) auto multi(3) weighting(nivw) n(686) alpha(0.6) dropout(`=r(fw_rescale)`)`

Mixed model syntax:

```
mixed depvar subscale_1 subscale_2 subscale_3 c.time_1 c.time_2 c.time_3 c.time_1#1.trt c.time_2#1.trt c.time_3#1.
> trt , nocons || id_level2: subscale_1 subscale_2 subscale_3 time_1 time_2 time_3, nocons || visit: , nocons residuals
> (unstr, t(subscale))
```

Calculating power for a multivariate model with slope treatment effect parameterisation:

```
visit schedule = 0 0.5 1 1.5 2 2.5 3
n joint outcomes = 3
treatment effect(s) = -0.04; 0.05; 0.03
outcome weighting = nivw
alpha = 0.600
total sample size = 686
n in control arm = 343
n in treatment arm = 343
power = 0.9057
```

Table of control and treatment group numbers (rounded) reaching each visit:

|           | visit 1<br>time=0 | visit 2<br>time=.5 | visit 3<br>time=1 | visit 4<br>time=1.5 | visit 5<br>time=2 | visit 6<br>time=2.5 | visit 7<br>time=3 |
|-----------|-------------------|--------------------|-------------------|---------------------|-------------------|---------------------|-------------------|
| control   | 343               | 251                | 175               | 111                 | 60                | 17                  | 3                 |
| treatment | 343               | 251                | 175               | 111                 | 60                | 17                  | 3                 |

# Misspecification of the treatment effect

- Based on the generalised least-squares estimator for the fixed effects:

$$\hat{\beta} = \{X' \Sigma^{-1} X\}^{-1} X' \Sigma^{-1} y$$

- Calculate sigma as before and plug into above estimator along with design  $X$  from analysis model and  $y$  from based on 'actual'  $X$
- The new  $\hat{\beta}$  is then used in the power or sample size calculations
  - an estimate of the beta vector you will obtain if you were to fit this 'misspecified' model
- The variance values taken from this 'misspecified' model would though be slightly different
  - does it matter?

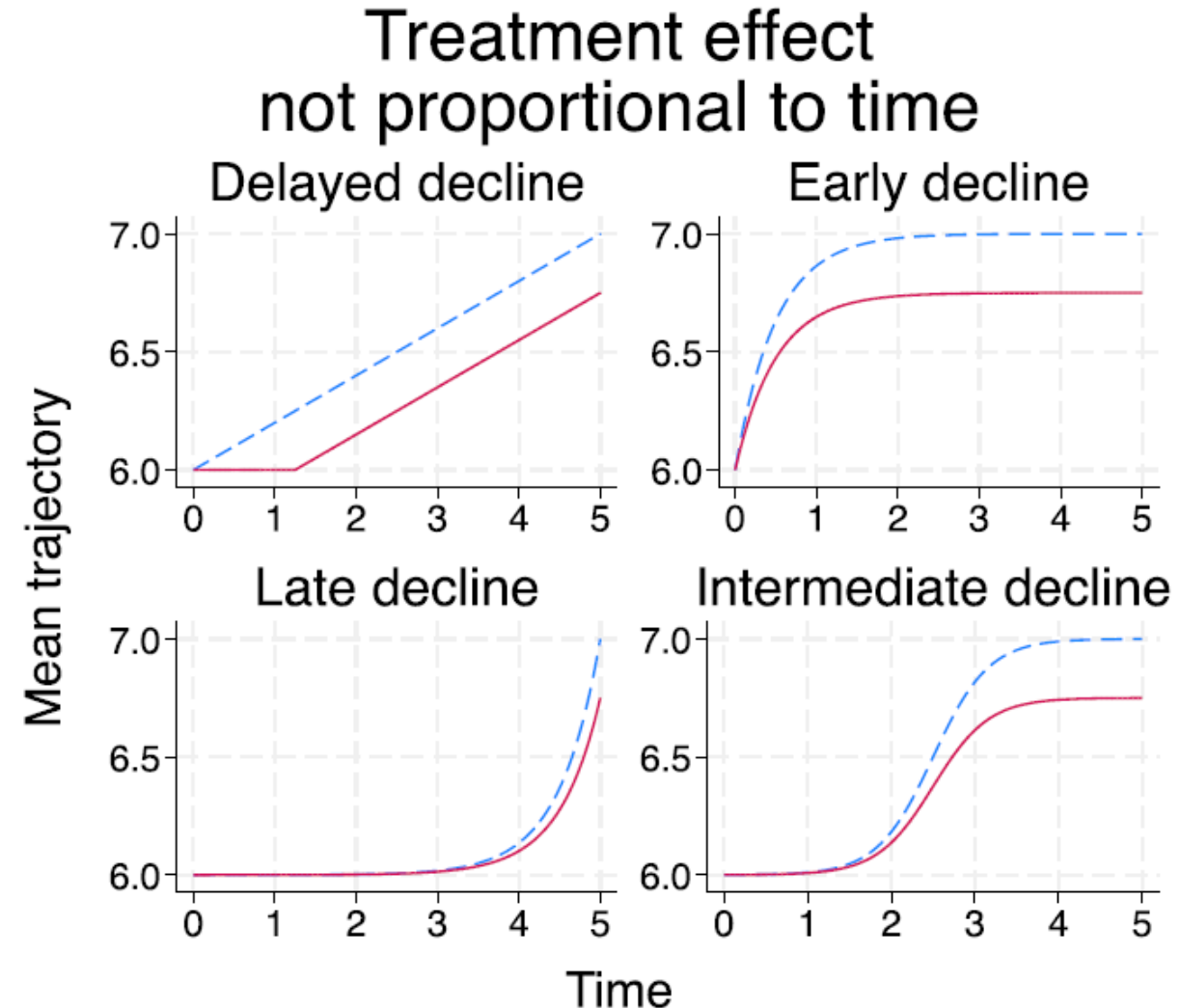
# Power when incorrectly assume linear slope effects

- Replicate results from a simulation study by Morgan et al\*
  - look at the effect on power and other trial operating characteristics when actual non-linear effects were modelled with a proportionate slope effect
- Demonstrate the 'user' function sub-option of *trtspec()*
- If true treatment effect was a proportionate slope ( $= -0.05$ ):
  - then required sample size would be 230 with power=0.8
  - regardless of the control arm trajectory and assuming a slope and intercept (or factorised time) is used
- The non-linear effects examples therefore use a sample size of 230 as a comparison

# Power when incorrectly assume linear slope effects

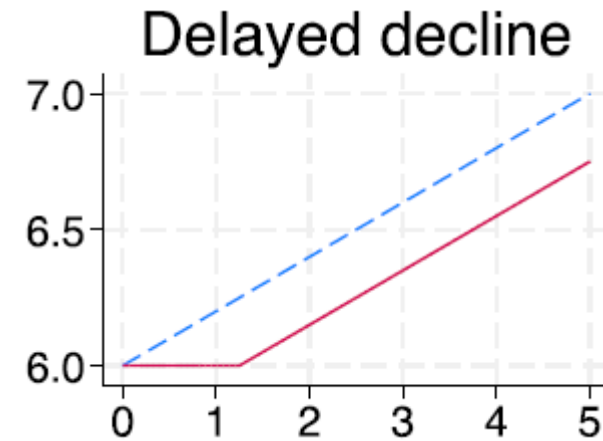
- “Steady decline”:  $f(t_j) = t_j$  (i.e. a linear trajectory)
- “Early decline”:  $f(t_j) = -5\exp(-2t_j) + 5$
- “Late decline”:  $f(t_j) = \frac{1}{4400}\exp(2t_j)$
- “Intermediate decline”:  $f(t_j) = \frac{-5}{1+\exp(-3(2.5-t_j))} + 5$

- All functions are defined so that:
  - except for ‘Steady decline’, treatment is proportional to the control function of time
  - both arms start baseline with a mean value of 6
  - control arm reaches 7 at year 5
  - treatment reaching 6.75, given the treatment difference of 0.05



# Comparing results with `mixedpower`

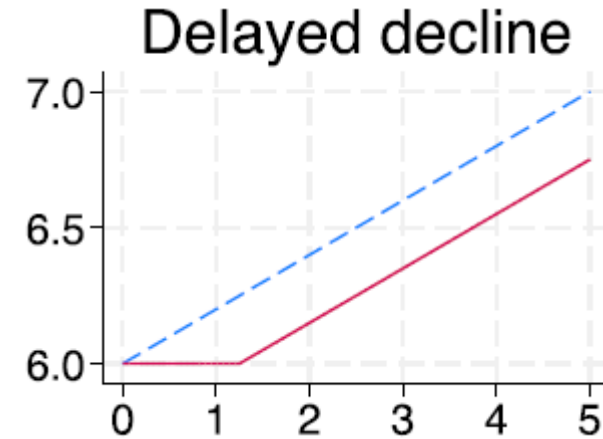
- Steady (delayed) decline
- “Steady decline”:  $f(t_j) = t_j$  (i.e. a linear trajectory)



- `mixedpower, trtspec(slope) sched(0(1)5) diff(-0.2 -0.25) cov(0.5, .0354\.0354, 0.01) error(0.15) n(230) actualcont(user(x)) cbeta(6 0.2) actualtrt(user(x; cond(x>=1.25,x-1.25,0)))`

# Comparing results with `mixedpower`

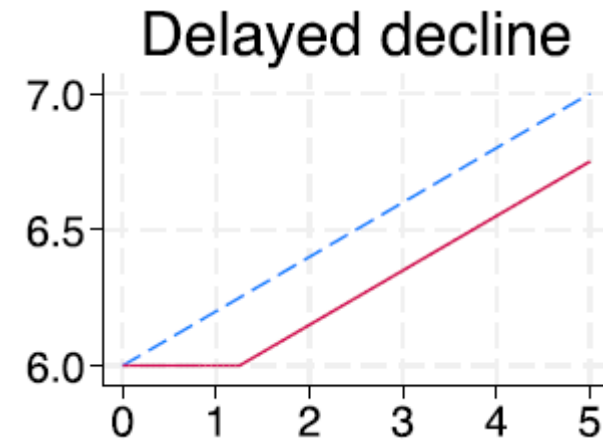
- Steady (delayed) decline
- “Steady decline”:  $f(t_j) = t_j$  (i.e. a linear trajectory)



- `mixedpower, trtspec(slope) sched(0(1)5) diff(-0.2 0.2) cov(0.5, .0354\ .0354, 0.01)`  
`error(0.15) n(230) actualcont(user(x)) cbeta(6 0.2) actualtrt(user(x; cond(x>=1.25,x-`  
`1.25,0)))`

# Comparing results with `mixedpower`

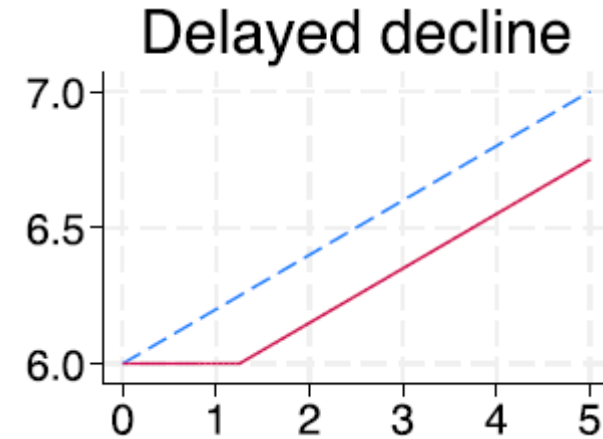
- Steady (delayed) decline
- “Steady decline”:  $f(t_j) = t_j$  (i.e. a linear trajectory)



- `mixedpower, trtspec(slope) sched(0(1)5) diff(-0.2 0.2) cov(0.5, .0354\|.0354, 0.01)  
error(0.15) n(230) actualcont(user(x)) cbeta(6 0.2) actualtrt(user(x; cond(x>=1.25,x-  
1.25,0)))`

# Comparing results with `mixedpower`

- Steady (delayed) decline
- “Steady decline”:  $f(t_j) = t_j$  (i.e. a linear trajectory)

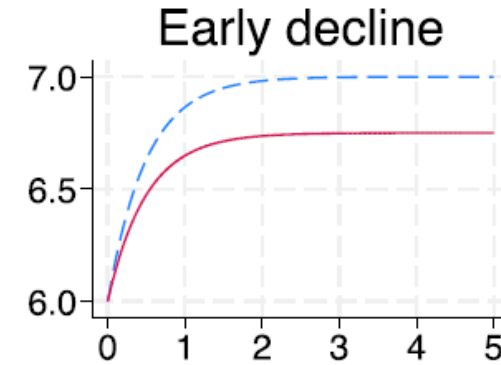


- `mixedpower, trtspec(slope) sched(0(1)5) diff(-0.2 -0.25) cov(0.5, .0354\ .0354, 0.01)  
error(0.15) n(230) actualcont(user(x)) cbeta(6 0.2) actualtrt(user(x; cond(x>=1.25,x-  
1.25,0)))`
- `power` = 0.5599

# Comparing results with `mixedpower`

- ‘Early’ decline

“Early decline”:  $f(t_j) = -5\exp(-2t_j) + 5$



- `mixedpower, trtspec(slope) sched(0(1)5) diff(-0.05) cov(0.5, .0354\.0354, 0.01)`  
`error(0.15) n(230) actualcont(user(-5*exp(-2*x)+5)) cbeta(6 0.2) actualtrt(user(-5*exp(-`  
`2*x)+5))`

- `power` = 0.5287

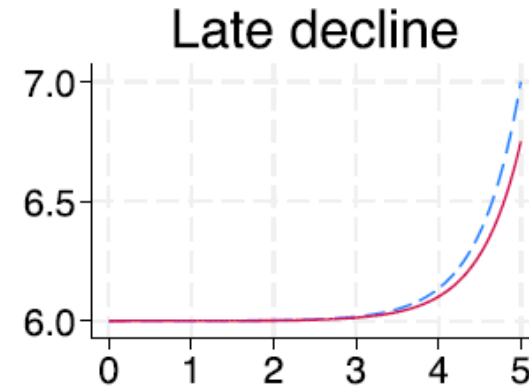
- `mat li r(exp_y_true)`

```
r(exp_y_true)[12,1]
r1
t0_v1 6
t0_v2 6.8646647
t0_v3 6.9816844
t0_v4 6.9975212
t0_v5 6.9996645
t0_v6 6.9999546
t1_v1 6
t1_v2 6.6484985
t1_v3 6.7362633
t1_v4 6.7481409
t1_v5 6.7497484
t1_v6 6.749966
```

# Comparing results with `mixedpower`

- ‘Late’ decline

“Late decline”:  $f(t_j) = \frac{1}{4400} \exp(2t_j)$



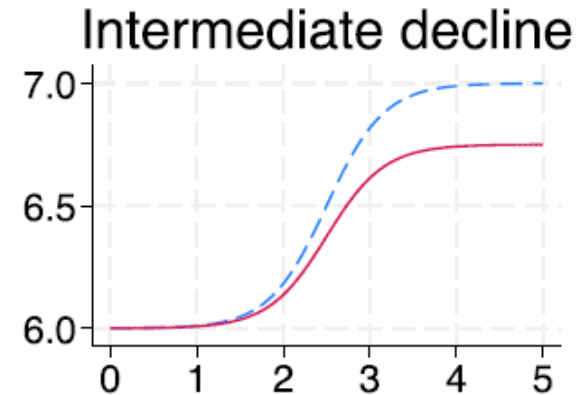
- `mixedpower, trtspec(slope) sched(0(1)5) diff(-0.05) cov(0.5, .0354\ .0354, 0.01)`  
`error(0.15) n(230) actualcont(user(1/4400*exp(2*x))) cbeta(6 0.2)`  
`actualtrt(user(1/4400*exp(2*x)))`
- `power` = 0.6114
- `mat li r(trtbeta_model)`

```
symmetric r(trtbeta_model)[1,1]
X3
r1 -.03994044
```

# Comparing results with `mixedpower`

- ‘Intermediate’ decline

“Intermediate decline”:  $f(t_j) = \frac{-5}{1+\exp(-3(2.5-t_j))} + 5$



- `mixedpower, trtspec(slope) sched(0(1)5) diff(-0.05) cov(0.5,.0354\ .0354,0.01)`  
`error(0.15) n(230) actualcont(user(-5/(1+exp(-3*(2.5-x)))+5)) cbeta(6 0.2)`  
`actualtrt(user(-5/(1+exp(-3*(2.5-x)))+5)) xmat(6)`

- `power = 0.9348`

- `mat li r(trtbeta_model)`  
`symmetric r(trtbeta_model)[1,1]`  
`X3`  
`r1 -.06184358`

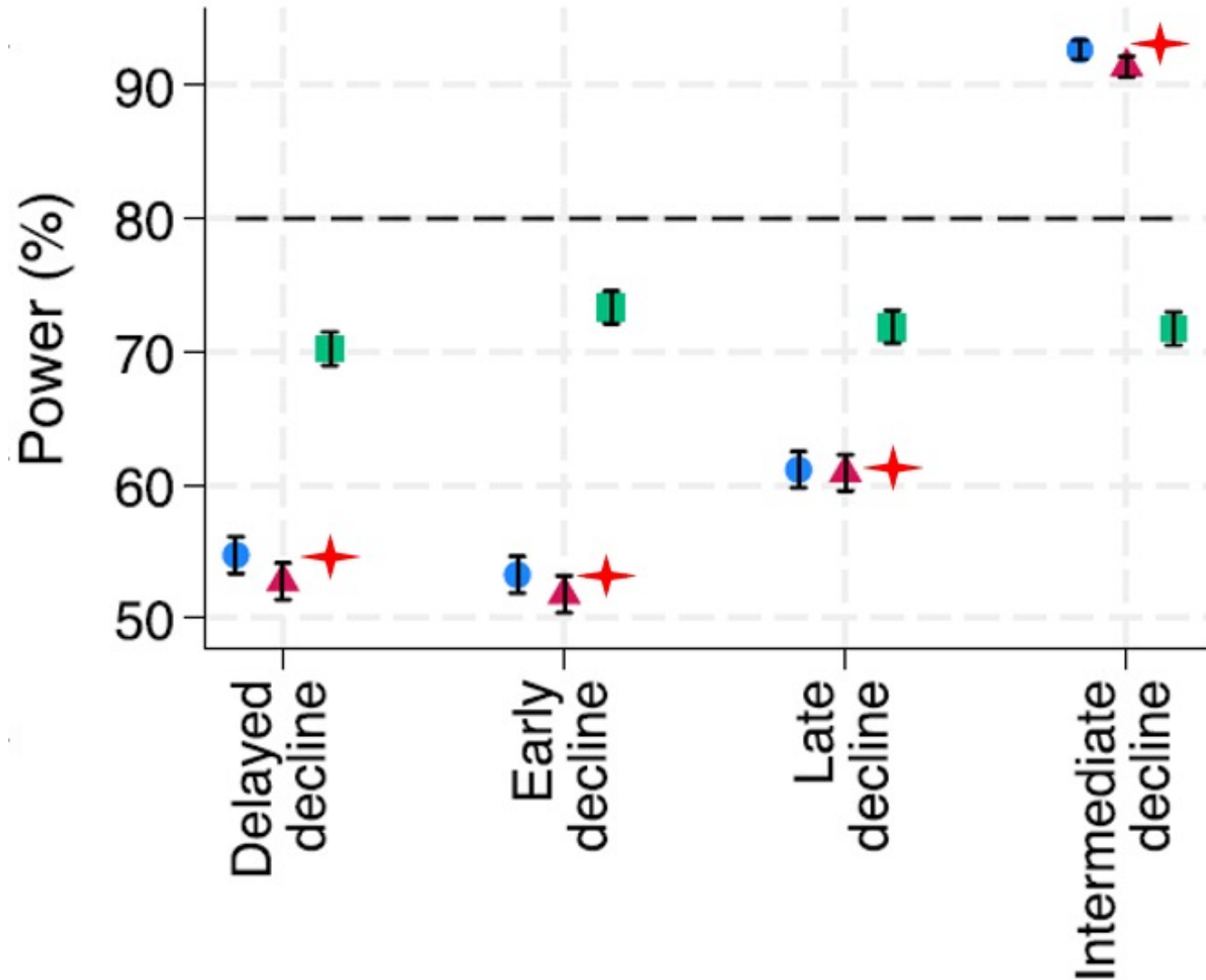
- `mat li r(exp_y_model)`

```
r(exp_y_model)[12,1]
r1
t0_v1 5.9022688
t0_v2 6.1472831
t0_v3 6.3922973
t0_v4 6.6373116
t0_v5 6.8823259
t0_v6 7.1273402
t1_v1 5.9022688
t1_v2 6.0854395
t1_v3 6.2686102
t1_v4 6.4517809
t1_v5 6.6349516
t1_v6 6.8181223
```

# Comparing results with mixedpower

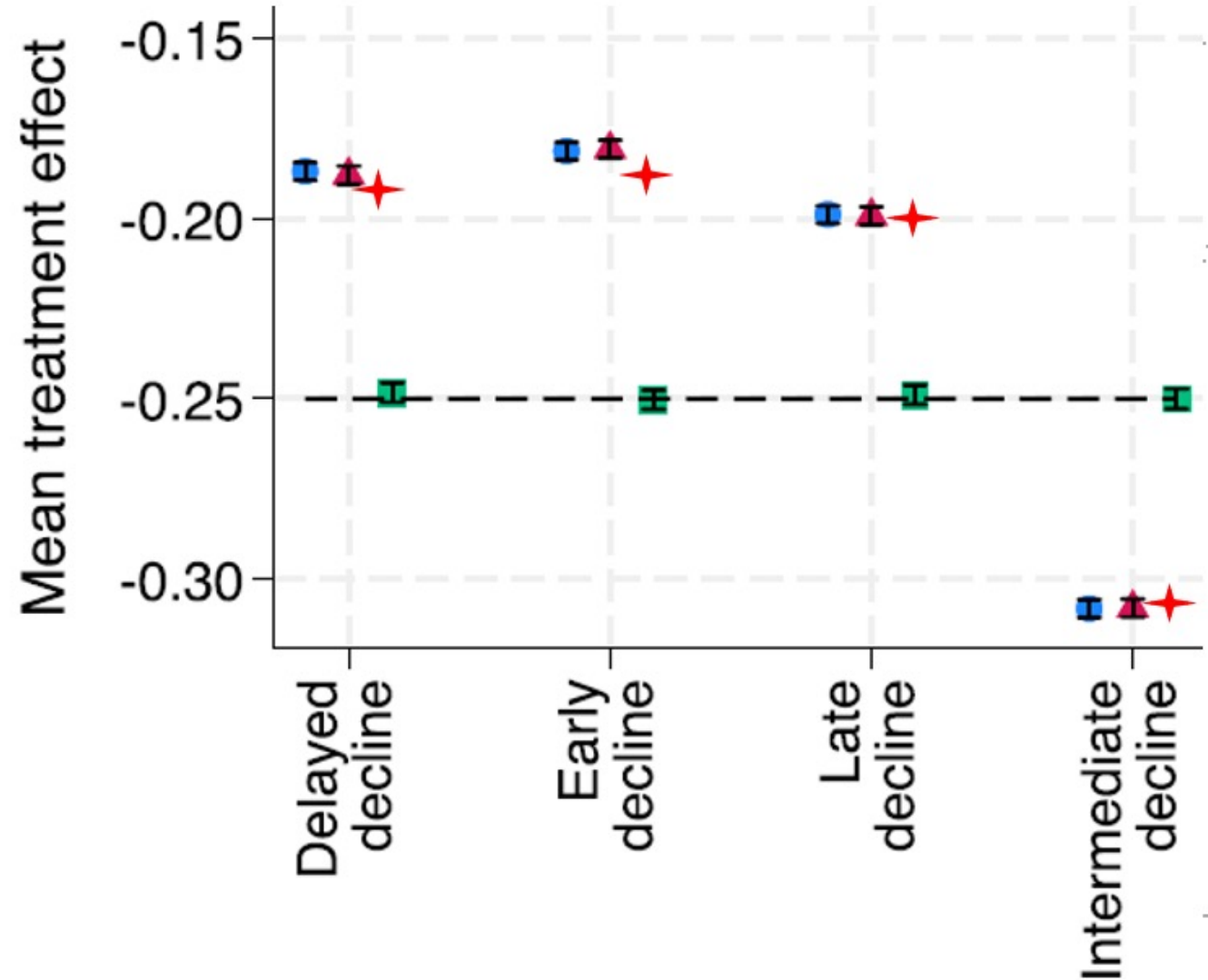
- power

compare with blue circles



# Comparing results with mixedpower

- mean treatment effect  
slope coefficient  $\times 5$   
compare with blue circles



# Future work

- Additional covariates
  - factorial designs?
  - subgroup effects?
- 3-level models
  - higher level cluster e.g. site
  - cluster randomised designs with repeated measures
- Program integrating Stata's `gsbounds` to perform group sequential testing
  - Information fraction not linearly related sample size/events like other models
- Incorporate uncertainty of variance parameters → effect on power

# THANK YOU



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# Additional detail on incomplete follow-up



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# Incomplete follow-up

- Sample is divided into  $m$  'cohorts' of patients each having reached a different point in trial. If trial has 4 measures then  $m \leq 4$ , for example:
  - cohort 1: measure at  $t=\{0\}$  with  $p_1$  (probability weight 1)
  - cohort 2: measure at  $t=\{0,1\}$  with  $p_2$
  - cohort 3: measure at  $t=\{0,1,2\}$  with  $p_3$
  - cohort 4: measure at  $t=\{0,1,2,3\}$  with  $p_4$
- If dealing with dropout:  $\sum_{p_k}^m = 1$
- If dealing with staggered recruitment:  $\sum_{p_k}^m \leq 1$
- If both dropout and staggered recruitment 'present' then need to integrate the 2 sets of  $p_k$  weights into one single set for the 4 cohorts

# Combining dropout and staggered recruitment

- dropout weights:  $\{d_1, d_2, d_3 \dots d_m\}$  and  $\sum_{d_k}^m = 1$
- staggered recruitment weights:  $\{s_1, s_2, s_3 \dots s_m\}$  and  $\sum_{s_k}^m \leq 1$
- then ‘integrated’ cohort weights:

$$p_k = \sum_{j=1 \geq k}^m s_k d_j + s_{(j+1)} d_k$$

# Calculate overall $Var(\hat{\beta})$ from cohort-specific $Var(\hat{\beta}_k)$

- `slopepower` combined cohort-specific z-scores with  $p_k$  weights, used back-calculation for overall variance.
- Only gives overall variance for slope term
  - Could apply same principle for other coefficients, but inaccuracies creep in and cannot obtain covariances
- `mixedpower` combines cohort-specific covariance matrices
  - Accurate for all terms and gives the covariances needed for linear combinations of effects

$$Var(\hat{\beta}) = \left( \sum_k^m p_k Var(\hat{\beta}_k)^{-1} \right)^{-1}$$

# Bonus examples



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# Generalisability of mixedpower

- two sample z-test
- `power twomeans 1 1.5, sd1(2) sd2(3) knownsds n(600) onesided alpha(0.025) nrat(2)`
- `power = 0.6792`
- `mixedpower, schedule(0 1) trtspec(intercept) altcont(noslope) difference(0.5) marginal  
errxt(input(independent 4)) errhet(input(independent 9)) n(600) aratio(1 2) dropout(1 0)`

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errxt(input(independent 4)) errhet(input(independent 9)) n(600) aratio(1 2) dropout(1 0)`
- `power = 0.6792`
- `mixedpower, schedule(0 1) trtspec(intercept) altcont(noslope) difference(0.5) marginal  
errxt(input(independent 4)) errhet(input(independent 9)) n(300) aratio(1 2)`
- `power = 0.6792`

# Generalisability of `mixedpower`

- Cluster-randomised trial

- `power twomeans 0 0.4, power(0.9) m1(25) m2(25) sd(2) rho(0.1) kratio(2)`

Estimated numbers of clusters and sample sizes:

```
K1 = 54
K2 = 108
N1 = 1,350
N2 = 2,700
```

- `mixedpower, schedule(1(1)25) trtspec(intercept) altcont(noslope) difference(0.4) marginal  
errxt(input(exchangeable 4 0.1)) power(0.9) arat(1 2)`

# Generalisability of `mixedpower`

- Cluster-randomised trial

- `power twomeans 0 0.4, power(0.9) m1(25) m2(25) sd(2) rho(0.1) kratio(2)`

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# Generalisability of mixedpower

- Cluster-randomised trial

- `power twomeans 0 0.4, power(0.9) m1(25) m2(25) sd(2) rho(0.1) kratio(2)`

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```
K1 = 54
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N1 = 1,350
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```

- `mixedpower, schedule(1(1)25) trtspec(intercept) altcont(noslope) difference(0.4) marginal  
errxt(input(exchangeable 4 0.1)) power(0.9) arat(1 2)`

Calculating sample size for a 2-level mixed model with intercept treatment effect parameterisation:

```
visit schedule = 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
treatment effect(s) = 0.4
alpha = 0.050
total sample size = 162
n in control arm = 54
n in treatment arm = 108
power = 0.9022
```

# Generalisability of mixedpower

- Cluster-randomised trial

- `power twomeans 0 0.4, power(0.9) m1(25) m2(25) sd(2) rho(0.1) kratio(2)`

Estimated numbers of clusters and sample sizes:

```
K1 = 54
K2 = 108
N1 = 1,350
N2 = 2,700
```

- `forvalues n=1/25 {`

```
 local prob=0
```

```
 if mod(`n',5)==0 & `n'>=10 local prob=0.25
```

```
 local dlist "`dlist' `prob'"
```

```
}
```

- `local dlist="0 0 0 0 0 0 0 0 0 0 .25 0 0 0 0 .25 0 0 0 0 .25 0 0 0 0 .25"`

# Generalisability of mixedpower

- Cluster-randomised trial

- `power twomeans 0 0.4, power(0.9) m1(25) m2(25) sd(2) rho(0.1) kratio(2)`

Estimated numbers of clusters and sample sizes:

```
K1 = 54
K2 = 108
N1 = 1,350
N2 = 2,700
```

- `mixedpower, schedule(1(1)25) trtspec(intercept) altcont(noslope) difference(0.4) marginal  
errxt(input(exchangeable 4 0.1)) power(0.9) dropout(`dlist') arat(1 2)`

Calculating sample size for a 2-level mixed model with intercept treatment effect parameterisation:

```
visit schedule = 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
treatment effect(s) = 0.4
alpha = 0.050
total sample size = 186
n in control arm = 62
n in treatment arm = 124
power = 0.9038
```