Attenuation of Treatment Effect Due to Measurement Variability in Assessment of Progression-Free Survival

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- *Nicola Schmitt is an employee of AstraZeneca LP. The views and opinions expressed herein are my own and cannot and should not necessarily be construed to represent those of AstraZeneca or its affiliates.*

Definitions

- PFS is defined as the time from randomisation to the earliest of objective progressive disease or death due to any cause

- Measurement variability defined for the purposes of this talk as within patient, within reader variability
  - Variability between repeat measurements for a patient, made by the same Reader

Background

- For normally distributed data, increased precision of measurements reduces the magnitude of the difference in means that is statistically significant

- However, for time-to-event variables such as progression-free survival (PFS), the effect of measurement variability is less well understood

Measurement variability is not considered in sample size calculations for PFS

- *On a standard treatment the median PFS time is 8 months and an improvement to 12 months is expected. Calculate the required sample size for 90% power in a 5% level test*
- Under the exponential assumption the HR is equal to the ratio of the medians:
  - HR = 8 / 12 = 0.67

$$No.Events = \frac{4}{\{\log(0.67)\}^2} \times 10.51 = 256$$

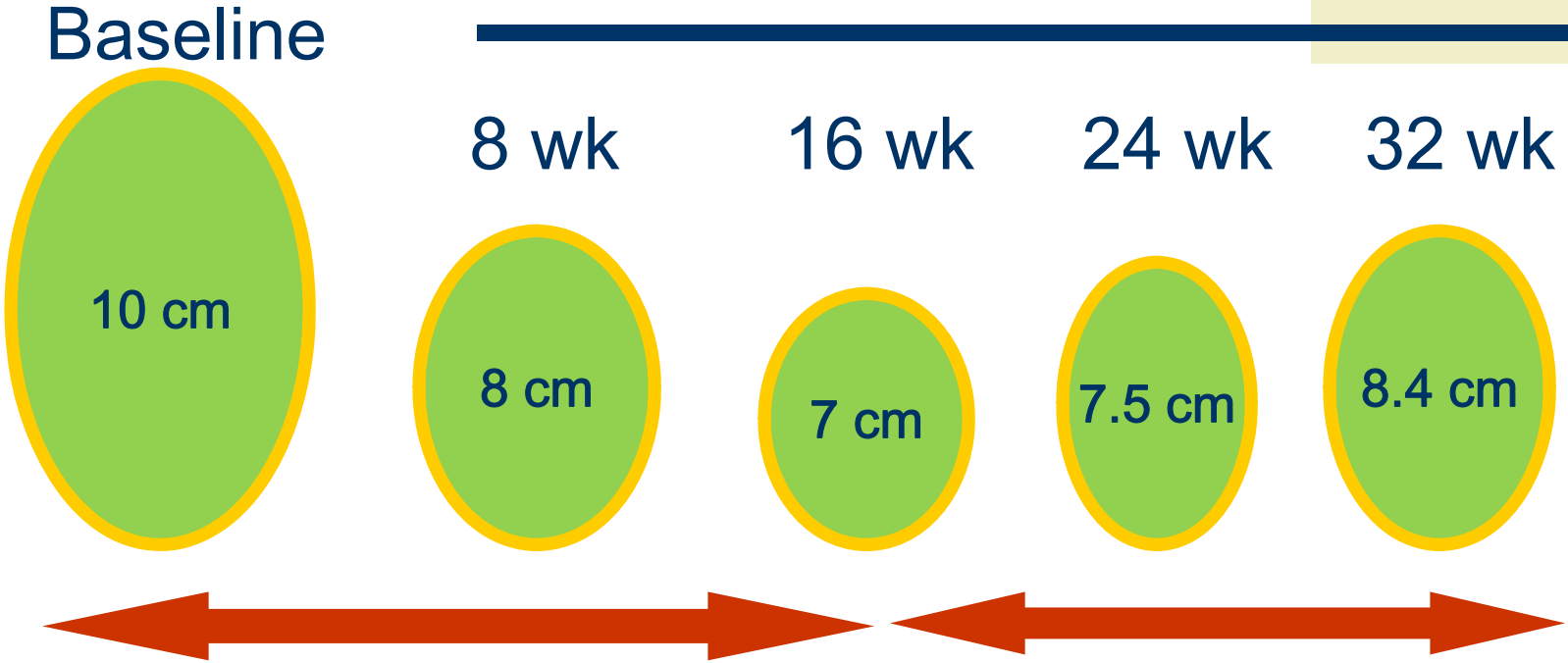
$$\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 = 10.51$$

Question addressed

- In a comparative trial with a PFS endpoint, does measurement variability in the RECIST assessment impact the treatment effect Hazard Ratio (HR)?

RECIST: Response Evaluation Criteria in Solid Tumours

Assessment of target lesions (as per RECIST criteria) is subject to measurement variability



30% ↓ in sum of the LD = PR

20% ↑ in sum of LD (from nadir) = PD

Tumour assessment is subject to measurement variability

What degree of measurement variability might we expect in RECIST assessment?

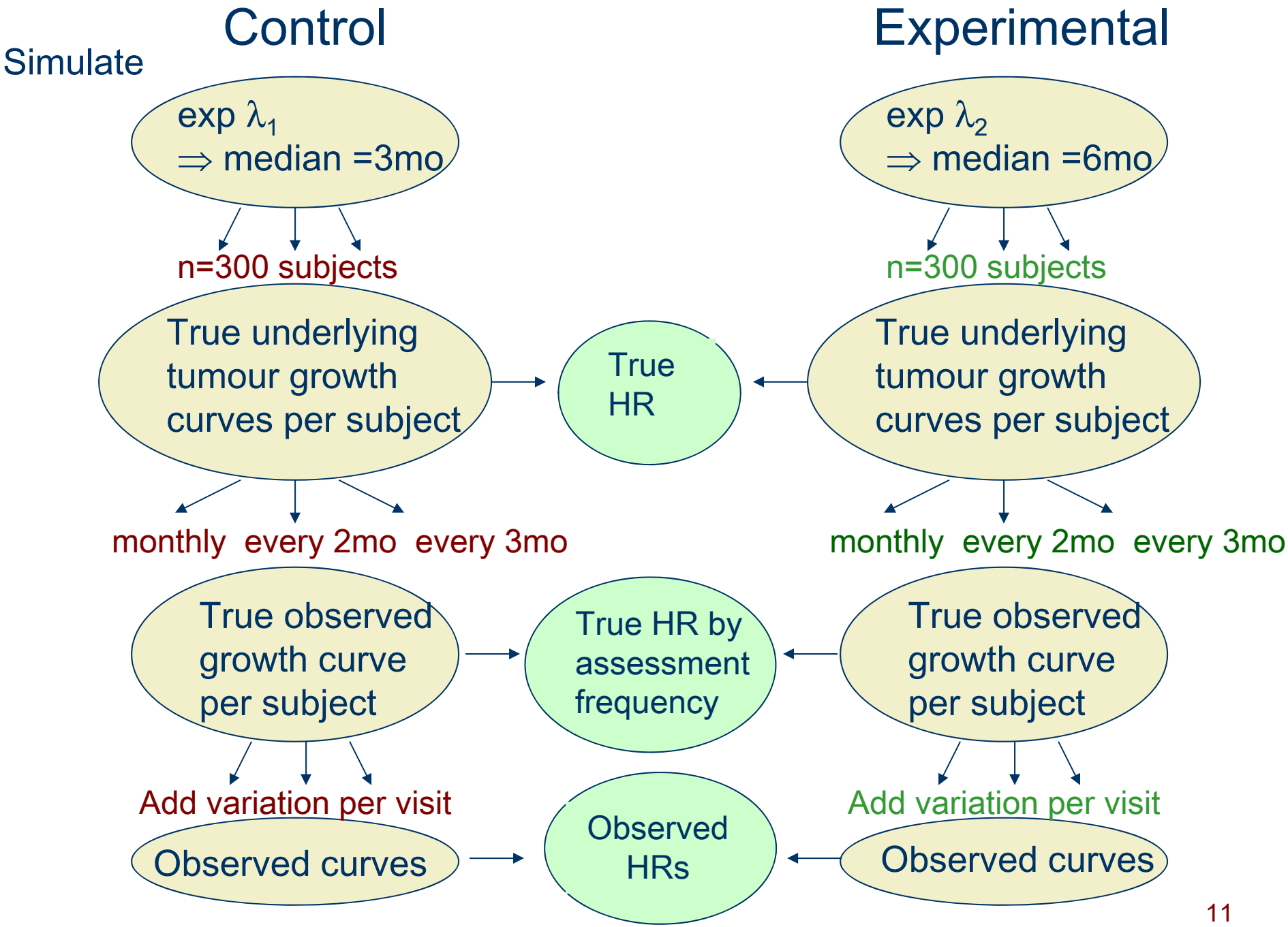
- In Non Small Cell Lung Cancer within subject variability was SD = 0.077cm (log scale) for repeat measurements (Zhao 2009)
  - E.g. For a mean tumour burden of 2 cm, a second scan will yield a measurement of approx 1.7 to 2.3 cm, 95% of the time
- SD=0.077 cm may be an underestimate as this study only looked at single lesions
- We therefore investigated multiples of this SD (2x and 3x)
- A review of SDs across tumour types was performed and is reported in the paper
- Studies looking at the sum of target lesions were not found

Reproducibility of scan measurements (some examples from the published literature)

Author, year	Tumour type	Number of patients, lesions and Readers	Assessment type	within subject standard deviation
Zhao et al, 2009	Non-small cell lung cancer	Patients: 32 Lesions: 32 Readers:3	CT, digital imaging, manual measurements Repeat CT scans (<15 minutes apart) and measurements	0.077 cm (log scale) Mean Lesion size: ?0.69cm (log scale)
Erasmus et al, 2003	Non-small cell lung cancer	Patients:33 Lesions: 40 Readers: 5	CT film, measured using manual rulers/calipers Measurements repeated 5-7 days apart	0.54 cm Mean Lesion size: 4 cm
Hopper et al, 1996	Metastatic disease, thoracic and abdominal	Patients:26 Lesions:105 Readers: 3	CT film, measured using manual rulers/calipers Repeat measurements	Approx 0.12 cm (log scale) Mean Lesion size: 1.95cm (log scale)

Methods – A Simulation Study

Question addressed: In a comparative trial with a PFS endpoint, does measurement variability in the RECIST assessment impact the treatment effect HR?


Simulate
Control
Experimental
exp λ_1
⇒ median =3mo
exp λ_2
⇒ median =6mo
n=300 subjects
n=300 subjects
True underlying tumour growth curves per subject
True HR
True underlying tumour growth curves per subject
monthly every 2mo every 3mo
monthly every 2mo every 3mo
True observed growth curve per subject
True HR by assessment frequency
True observed growth curve per subject
Add variation per visit
Add variation per visit
Observed curves
Observed HRs
Observed curves

Model used to determine underlying tumour growth curves for each subject

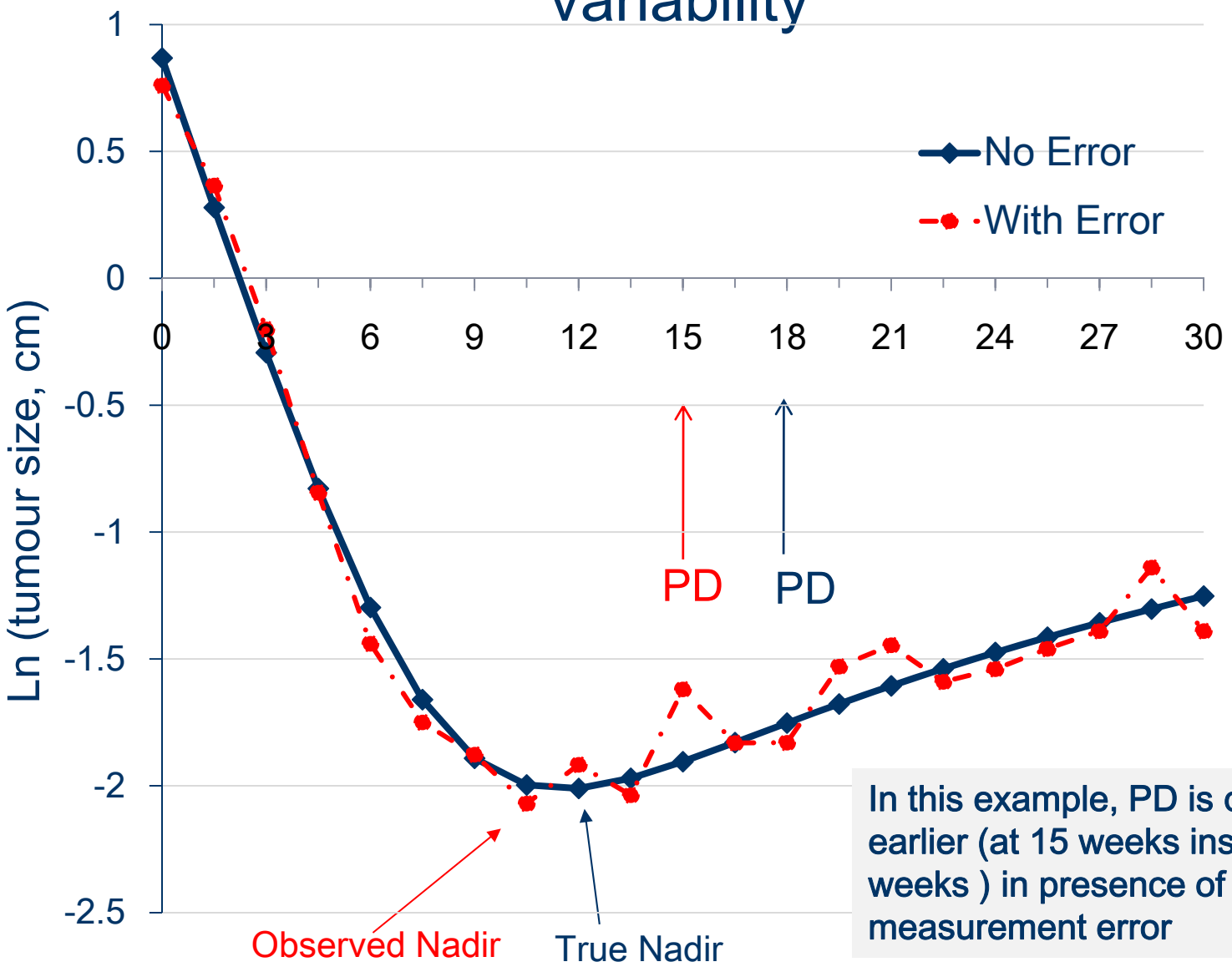
$$y_{ij}(t) = v_{ij}(e^{-b_{ij}t} + a_{ij}b_{ij}t)$$

- y_{ij}=Longest Diameter for the ith patient in arm j;
- v_{ij} is the baseline tumor size (longest diameter) for subject i in Arm j,
  - log(vij)~N(1.29, 0.453)), i.e mean baseline value of 4 cm and SD of 1.9 cm
- t = time, in months.
- The parameters a_{ij} and b_{ij} (both >0) control the shrinkage and recovery of the tumor growth curve, respectively
  - 'b' fixed at 0.4; 'a' is calculated such that the PFS time (20% increase in y)for the ith patient in the growth model matches the individual PFS time generated from the underlying exponential distributions
- Random normally distributed variation (SD=0, 0.077, 0.155, 0.232) applied to each underlying longest diameter at each visit

Reference: Wang Y, 2009

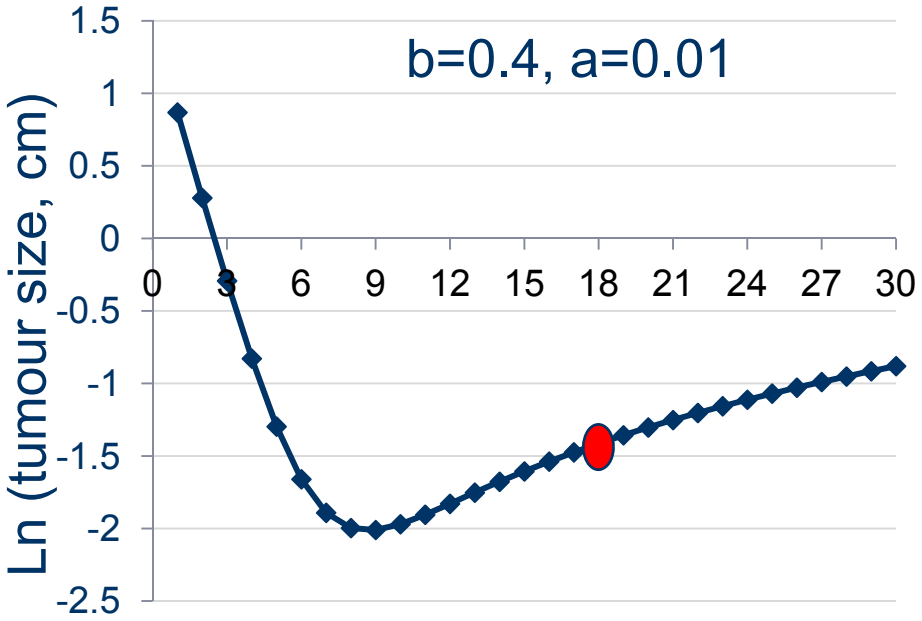
$$\log(O_{ij}(t)) = \log(y_{ij}(t)) + e_{ij}(t), \quad t = 0, w, 2w, \cdots$$

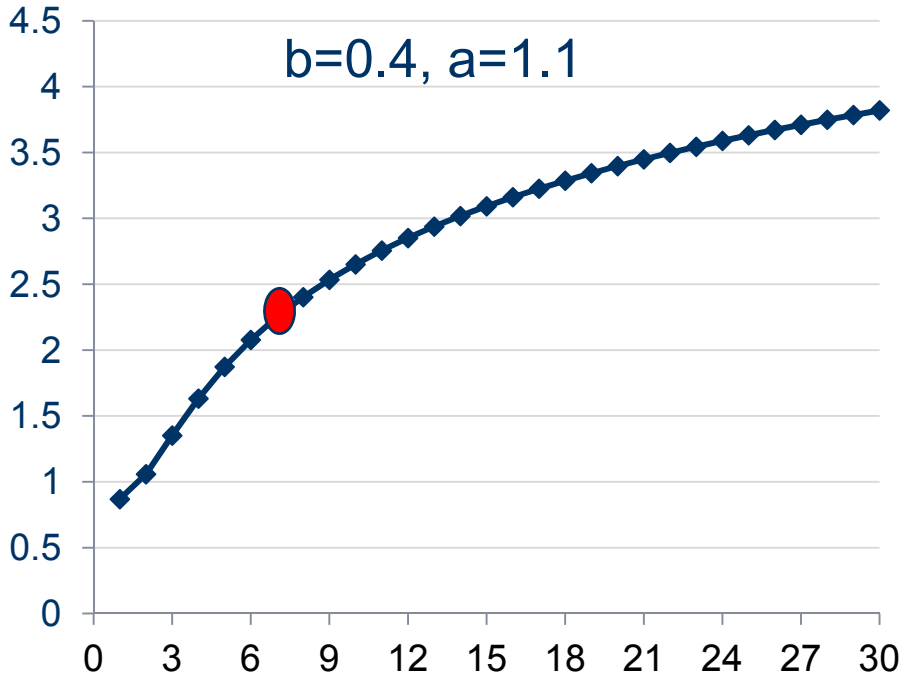
A tumour growth curve for an individual patient, with and without measurement variability



In this example, PD is declared earlier (at 15 weeks instead of 18 weeks) in presence of measurement error

Example Individual tumor growth curves with parameter a<1 and >1, respectively

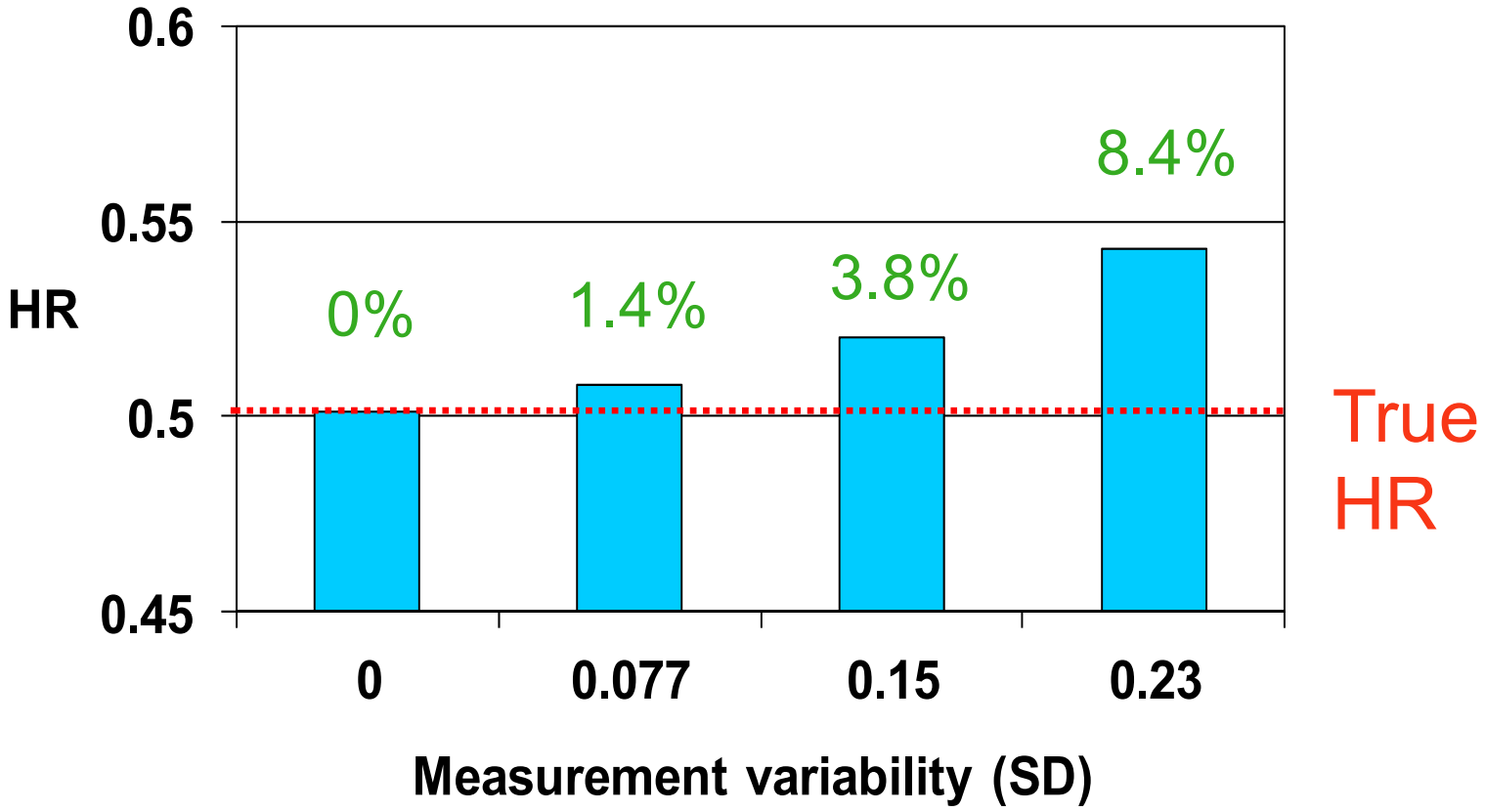




Time (months)

Results

Impact of measurement error on PFS HR
(assessment frequency of every 1.5mo)



% attenuation calculated as 100*(observedHR-0.501)/(1-0.501)

Attenuation of the HR leads to a loss of statistical power (i.e. an increase in type II error)

- For example, for a trial that is to be sized with 90% power to detect a true HR=0.5, would have only 82% power to detect an attenuated HR=0.55 i.e. a loss of about 8% in power
- Increasing levels of attenuation, lead to increased loss in statistical power

Table II. Estimated median PFS, HRs, and attenuation rates for simulated model (HR = 0.5).

		$N = 50$ per arm			
w	σ	Median PFS (95% CI)	HR (95% CI)	AR (%)	Percent of times log rank $p < 0.05$
1.0	0	3.57 (2.00, 5.00) 6.63 (4.00, 10.0)	0.497 (0.308, 0.767)		88.0
	0.07746	3.22 (2.00, 4.00) 5.87 (4.00, 8.00)	0.505 (0.315, 0.780)	1.6	86.8
	0.15492	2.69 (2.00, 4.00) 4.53 (3.00, 6.00)	0.528 (0.330, 0.814)	6.2	83.6
	0.23238	2.27 (2.00, 3.00) 3.38 (2.00, 5.00)	0.585 (0.372, 0.889)	17.5	70.2
1.5	0	3.99 (3.00, 4.50) 6.89 (4.50, 10.5)	0.498 (0.308, 0.770)		87.6
	0.07746	3.65 (3.00, 4.50) 6.48 (4.50, 9.00)	0.505 (0.315, 0.778)	1.4	86.7
	0.15492	3.35 (3.00, 4.50) 5.72 (4.50, 7.50)	0.517 (0.326, 0.801)	3.8	84.3
	0.23238	3.14 (3.00, 4.50) 4.95 (3.00, 7.50)	0.541 (0.343, 0.836)	8.6	79.7
2.0	0	4.10 (2.00, 6.00) 7.34 (4.00, 10.0)	0.500 (0.310, 0.773)		87.2
	0.07746	4.09 (3.00, 6.00) 6.96 (4.00, 10.0)	0.507 (0.314, 0.785)	1.4	86.4
	0.15492	4.04 (4.00, 6.00) 6.55 (4.00, 8.00)	0.517 (0.323, 0.796)	3.4	84.2
	0.23238	4.00 (3.00, 4.00) 6.03 (4.00, 8.00)	0.531 (0.333, 0.820)	6.2	81.9

The extent of attenuation may be increased with more frequent scan assessments

Conclusions

- Scan measurement variability can cause attenuation of the treatment effect (i.e. the HR is closer to one)
- Scan measurement variability should be minimised in order to:
  - reveal a treatment effect that is closest to the truth
  - Increase our the ability to identify valuable new therapies
- In disease settings where the measurement variability is shown to be large, consideration may be given to
  - inflating the sample size of the study to maintain power
  - Consider change of primary endpoint to overall survival?
- The extent of attenuation may be increased with more frequent scan assessments

Some practical things we can do in our trials

- Rigorous training of radiologists to ensure high-quality scans
- The same radiologist should be used to read all scans from all patients at a particular site (or as a minimum all scans for an individual patient)
- Are there ways to minimise the dilution requiring additional reads?
- Note: RECIST guidance may ultimately help reduce measurement variability as fewer lesions (up to 5, reduced from 10) will be selected

Limitations

- The model only considers progression of target (measurable) lesions and not new lesions
  - For some tumour types, a proportion of patients typically progress due to the appearance of new lesions
- The model used may oversimplify the complexity of tumor growth
- Choice of values for parameters a and b – are these realistic? This could be tested on existing clinical data
- Have we underestimated the level of variability?
  - variability typically calculated for repeat measurements of individual lesions rather than for the sum of the longest diameters.

References

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Q?

Back-up

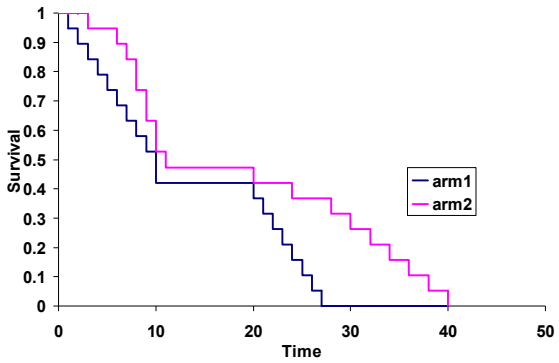
Definitions: Hazard Ratio

- HR is the ratio of the hazard (progression) rates of the two groups
  - HR=1 means no difference between treatment in terms of progression rates
  - HR=0.8 rate of progression decreased by 20%, or (take reciprocal) delays rate of progression by 25% (1/0.8=1.25)
  - HR=2 means risk on active group is twice that on control

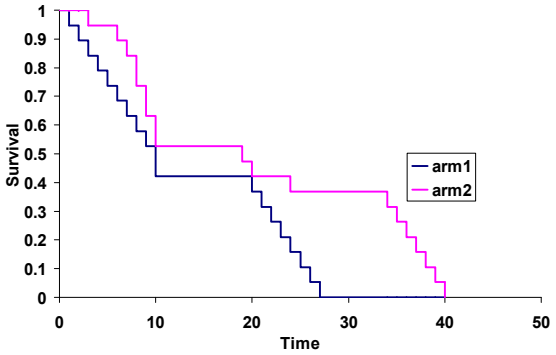
Concordance of PD Times between Different Measurement Variability for Simulated Model

w	σ_1	σ_2	Arm 0			Arm 1		
			% of PD time for σ_1 <PD time for σ_2	% of PD time for σ_1 =PD time for σ_2	% of PD time for σ_1 >PD time for σ_2	% of PD time for σ_1 <PD time for σ_2	% of PD time for σ_1 =PD time for σ_2	% of PD time for σ_1 >PD time for σ_2
1.5	0.0775	0	22.7	65.7	11.6	29.9	59.8	10.3
	0.1549	0.0775	31.5	48.3	20.2	38.3	44.1	17.6
	0.2324	0.1549	34.2	40.9	24.9	39.4	37.7	22.9

Standard analyses use ranks not the times themselves



Data
Arm1: 1 2 3 4 5 6 7 8 9 10 10 20 21 22 23 24 25 26 27
Arm2: 3 6 7 8 8 9 9 10 10 11 20 24 28 30 32 34 36 38 40

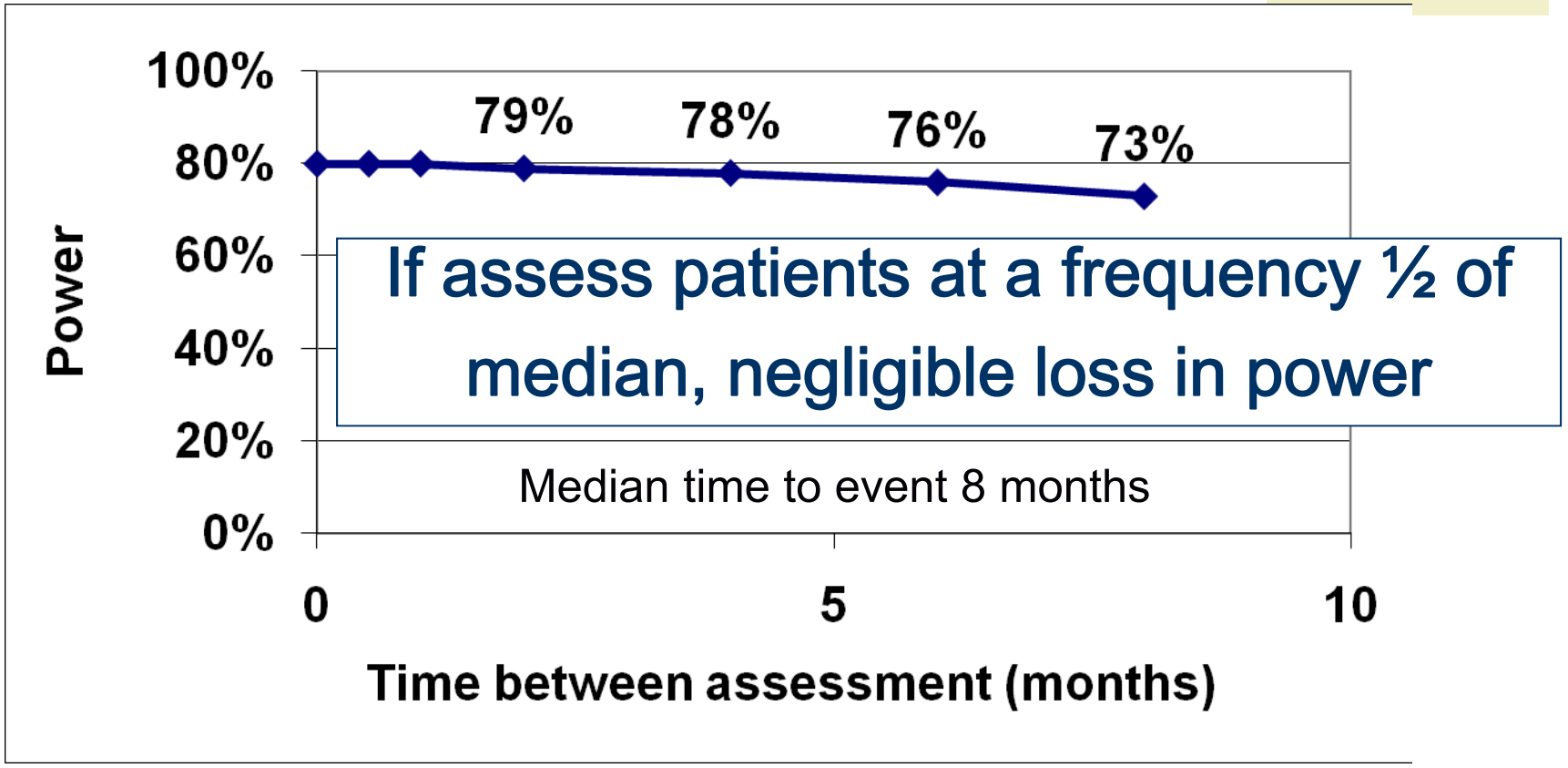


Data
Arm1: 1 2 3 4 5 6 7 8 9 10 10 20 21 22 23 24 25 26 27
Arm2: 3 6 7 8 8 9 9 10 10 **19** 20 24 **34 35 36 37 38 39** 40

Dataset 1	Dataset 2
Median difference 1m (11 v 10)	Median difference 9m (19 v 10)
Mean difference 5.8m (19.1 v 13.3)	Mean difference 7.3m (20.6 v 13.3)
HR=0.445	HR=0.445
Log-rank p=0.027	Log-rank p=0.027

Ranks identical, times different but p-value and HR identical

Patients can be assessed at a frequency that is consistent with clinical practice



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