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Frequency and timing of self-reported quality of life measurement in trials: emerging issues

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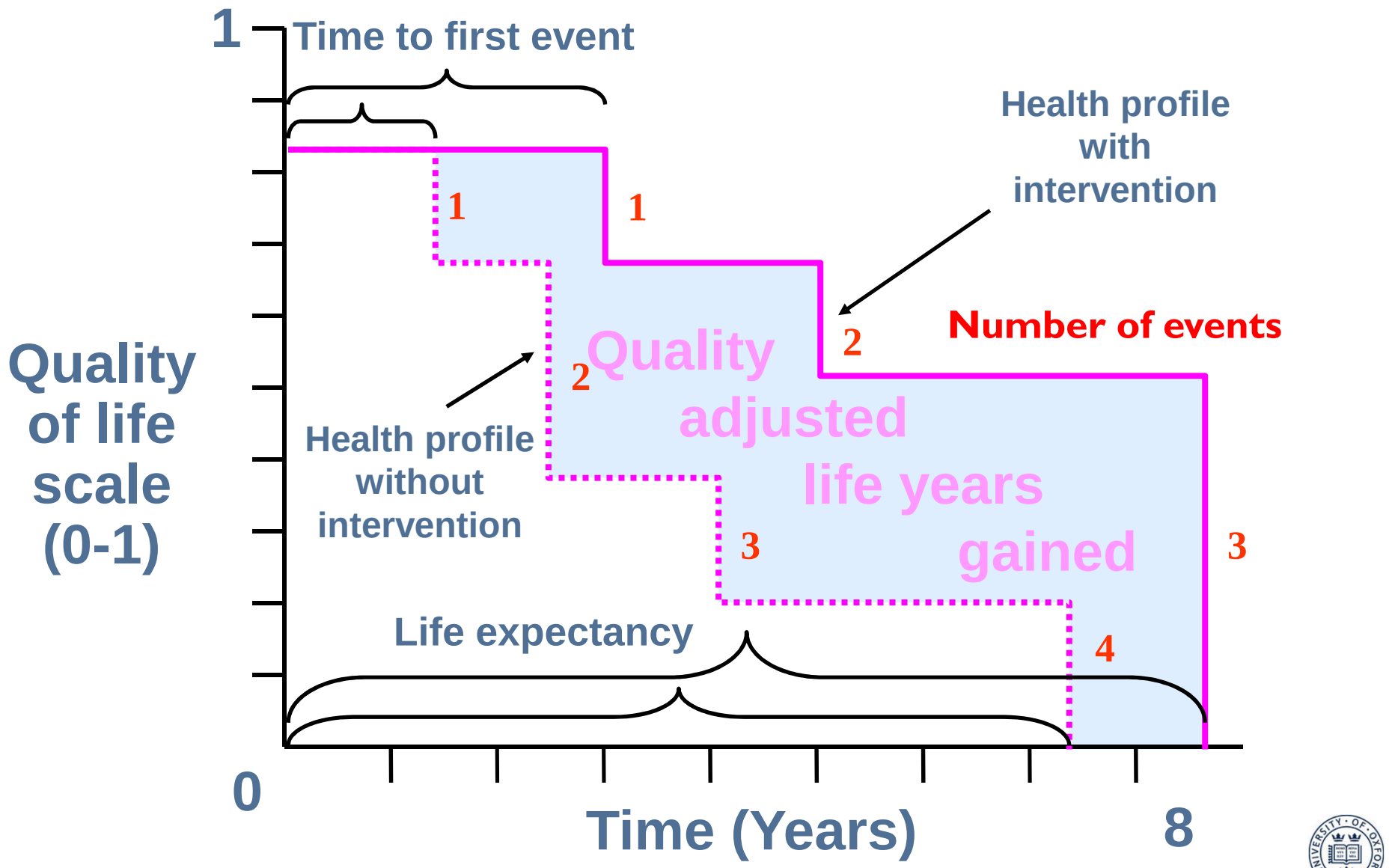
What measures of outcome are useful to health economists?

- Using cost-effectiveness to aid decision-making requires comparing c-e of different interventions
- Therefore we need an effectiveness/outcome measure that can be used in a wide range of settings:
  - Events or event-free time:
    - But events have different severity, cost, consequences
  - Life-years gained
    - but only where survival is main outcome
  - Quality adjusted life years (QALYs)
    - Composite of survival and quality of life

Using QALYs to measure health gain



Measuring quality of life impact of events - Two broad alternatives in trial-based studies:

1. Distribute quality of life instrument to trial participants (all or sample) and averaging
    1. eg at final follow-up
    2. or baseline and final follow-up
    3. or at baseline, intermediate points and follow-up

    Then calculate mean difference/mean profiles
2. Attach quality of life decrements to non-fatal events observed in trial
    1. typically from external estimates

Examples of each approach: 1

Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A on behalf of the Diabetes Glycaemic Education and Monitoring Trial Group. Cost-effectiveness of self-monitoring of blood glucose in the management of patients with non-insulin treated type 2 diabetes: economic evaluation of data from the randomised controlled DiGEM trial. BMJ 2008; 336(7654):1177-80. PMID: 18420663

type 2 diabetes receiving standardised usual care, less intensive self monitoring of blood glucose, or more intensive self monitoring of blood glucose

		Utility			Difference	
Intervention	No	Baseline	12 month follow-up	Change	Less intensive group *v* standardised usual care	More intensive group *v* standardised usual care
Standardised usual care group	152	0.799 (0.023)	0.798 (0.034)	−0.001 (−0.060 to 0.059)	—	—
Less intensive self monitoring group	150	0.781 (0.022)	0.755 (0.024)	−0.027 (−0.069 to 0.015)	−0.029 (−0.084 to 0.025)	−0.072 (−0.127 to −0.017)*
More intensive self monitoring group	151	0.807 (0.024)	0.733 (0.024)	−0.075 (−0.119 to −0.031)*	—	—

*P<0.05.

Examples of each approach: 2

Decrements estimated using cross-sectional data, linear or tobit regression

Complication	Effect on utility
No complications	0.785
MI	-0.055 (-0.042, -0.067)
IHD (angina)	-0.090 (-0.054,-0.126)
Stroke	-0.164 (-0.105, -0.222)
Heart Failure	-0.108 (-0.048, -0.169)
Amputation	-0.280 (-0.170, -0.389)
Loss of sight in one eye	-0.074 (-0.025,-0.124)

Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D. Medical Decision Making 2002; 22(4):340-349. PMID: 12150599

Advantages and disadvantages of each approach:

1) Distributing quality of life instrument to trial participants

Pro: May capture treatment effects, side effect

No other QoL data may exist on events/patient group

Minus: Respondent burden

Missingness – eg respondents may be healthier

Events might be important but rare: EG ACST-2 stroke

2) Attach external quality of life decrements

Pro: Low cost/respondent burden

Decrements may be widely accepted/used, from large sample

Minus: May not exist, may not match trial population

May miss therapy effects, side effects, differences in event severity

…….Decrements may overstate quality of life impact……..

Quality of life as a risk factor:

- Eg analysis of 7348 patients in FIELD trial (fenofibrate in diabetes). EQ-5D administered X-sectionally to all patients
- Multivariate Cox proportional hazard regression models used to estimate hazard ratio associated with EQ-5D on:
  1. cardiovascular events
  2. other major diabetes-related complications
  3. death from any cause.
- Results: EQ-5D scores independent predictor of risk
- Each 10 points higher on EQ-5D score =
  7% lower rates of cardiovascular events
  13% lower rates of other major diabetes-related complications
- 2-14% lower rate of all cause mortality

Clarke PM, Hayes AJ, Glasziou PG, Scott R, Simes J, Keech AC. Using the EQ-5D Index Score as a Predictor of Outcomes in Patients With Type 2 Diabetes. Med Care 2009;47: 61–68

Quality of life as a risk factor:

TABLE 2. Hazard Ratios of Risk Factors and EQ-5D Index Score for Vascular Events, Other Complications of Diabetes, and All Cause Mortality Based on Multivariate Proportional Hazard Models

					All Cause Mortality			
	Vascular Events All Individuals		Diabetic Complications All Individuals		With Prior Complications or Cancer		Without Prior Complications or Cancer	
No. individuals	7348		7348		1693		5655	
No. events	453		193		151		133	
P_H test: χ^2 statistic (P value)	11.40 (0.25)		11.72 (0.30)		9.70 (0.21)		3.31 (0.65)	
Variable	**HR**	***P***	**HR**	***P***	**HR**	***P***	**HR**	***P***
EQ-5D index score per 0.10 point	0.93	<0.001	0.87	<0.001	0.88	<0.001	0.86	<0.001
Female	0.75	0.007	0.54	<0.001	0.58	0.006	—	—
Age per 10 yrs	1.47	<0.001	1.70	<0.001	1.72	<0.001	2.12	<0.001
Diabetes duration per 10 yrs	—	—	1.39	0.002	—	—	—	—
HbA_{1c} per 1% increase	1.19	<0.001	1.42	<0.001	1.15	0.045	1.21	0.009
Total/HDL cholesterol ratio per 1%	1.13	0.006	—	—	—	—	—	—
Body mass index	—	—	1.04	<0.001	—			—
Systolic blood pressure	1.17	<0.001	1.13	0.026	—	—	1.13	0.056
Current smoker	1.57	0.002	2.32	<0.001	1.78	0.017	3.21	<0.001
Prior vascular events	3.06	<0.001	1.86	<0.001	—	—	—	—
Prior diabetic complications	2.36	<0.001	10.69	<0.001	2.64	<0.001	—	—
Cancer					3.75	<0.001	—	—

Hazard ratios (HRs) for variables that were not significant at $P < 0.1$ have been omitted from the table.

If quality of life is a risk factor…

- The quality of life of those having events may be systematically lower before the event occurs
- Therefore analyses averaging across everyone may be overstating the impact
- To test this:
  - Used additional data from UK Prospective Diabetes Study (UKPDS) post study follow-up
  - Up to 7 EQ-5D questionnaires administered. One in1996/7; 5 annually 2003-2007, plus one final questionnaire to all surviving participants
  - 11,614 fully completed questionnaires from 3,380 participants

  - Working with Maria Alva, Boby Mihaylova on this

Averages: 1997-2007

Unconditional averages

	Event	No event	
	Mean Tariff (S.D.)	Mean Tariff (S.D.)	**Difference in means (S.E.)**
MI (year before)	0.595 (0.33)	0.693 (0.30)	-0.098 (0.04)**
MI (prior history)	0.658 (0.30)	0.695 (0.30)	-0.038 (0.01)**
IHD	0.614 (0.32)	0.702 (0.30)	-0.087 (0.01)**
Stroke	0.487 (0.37)	0.700 (0.30)	-0.213 (0.02)**
Heart Failure	0.501 (0.34)	0.698 (0.30)	-0.197 (0.02)**
Amputation	0.475 (0.34)	0.695 (0.30)	-0.220 (0.03)**
Blindness in 1 eye	0.617 (0.31)	0.696 (0.30)	-0.079 (0.01)**

** P-value<0.01

The models:

1. **Ordinary Least Squares** (OLS):
   - each observation is an independent draw,
   - Having controlled for age gender etc, patients assumed identical…does not account for heterogeneity across patients

- But decomposition indicates that variation between patients is considerably greater than variation within…..

	Mean Tariff	Std. Dev.	Variance
Overall	0.692	0.30	0.09
Between		0.27	0.07
Within		0.16	0.03

- That is, considerable heterogeneity. If correlated with events, OLS will be biased. Therefore….

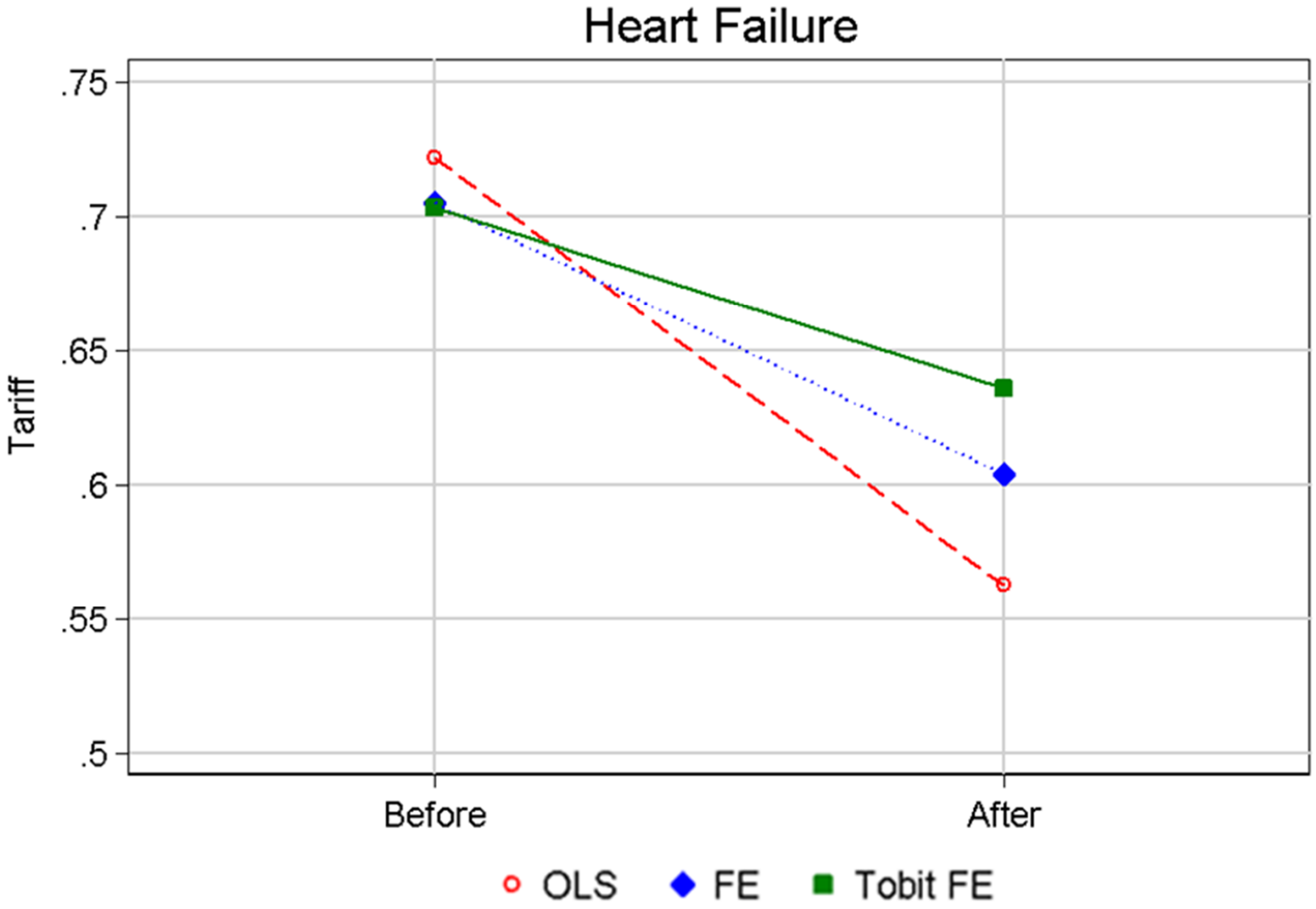
2. **Fixed Effects** (FE):
   - removes time-invariant missing or unobservable variables
   - produces more consistent estimates of the parameters of interest
   - But relies on within variation. Hence may be less efficient, bigger SEs

Results:

	OLS		FE		Tobit FE	
	Coeff	Robust SE	Coeff	Robust SE	Coeff (MFX)	Robust SE
Constant	0.839**	(0.035)	1.774**	(0.046)		
Current age	-0.002**	(0.001)	-0.016**	(0.001)	-0.012**	(0.001)
Male=1	0.081**	(0.010)				
events						
MI (year before)	-0.088*	(0.036)	-0.066*	(0.030)	-0.036	(0.020)
MI (prior history)	-0.037*	(0.018)	0.008	(0.024)	0.011	(0.016)
IHD	-0.084**	(0.016)	-0.029	(0.022)	-0.020	(0.015)
Stroke	-0.189**	(0.029)	-0.165**	(0.035)	-0.111**	(0.029)
Heart Failure	-0.159**	(0.031)	-0.101**	(0.032)	-0.047*	(0.022)
Amputation	-0.203**	(0.039)	-0.172**	(0.045)	-0.106**	(0.035)
Blindness in 1 eye	-0.049*	(0.022)	0.031	(0.027)	0.025	(0.017)
Observations	11614		Observations	11614	11614	
			Number of participants	3380	3380	
R-squared	0.067		R-squared	0.130	0.130	

** p<0.01, * p<0.05

Predictions for average participant with no other complication



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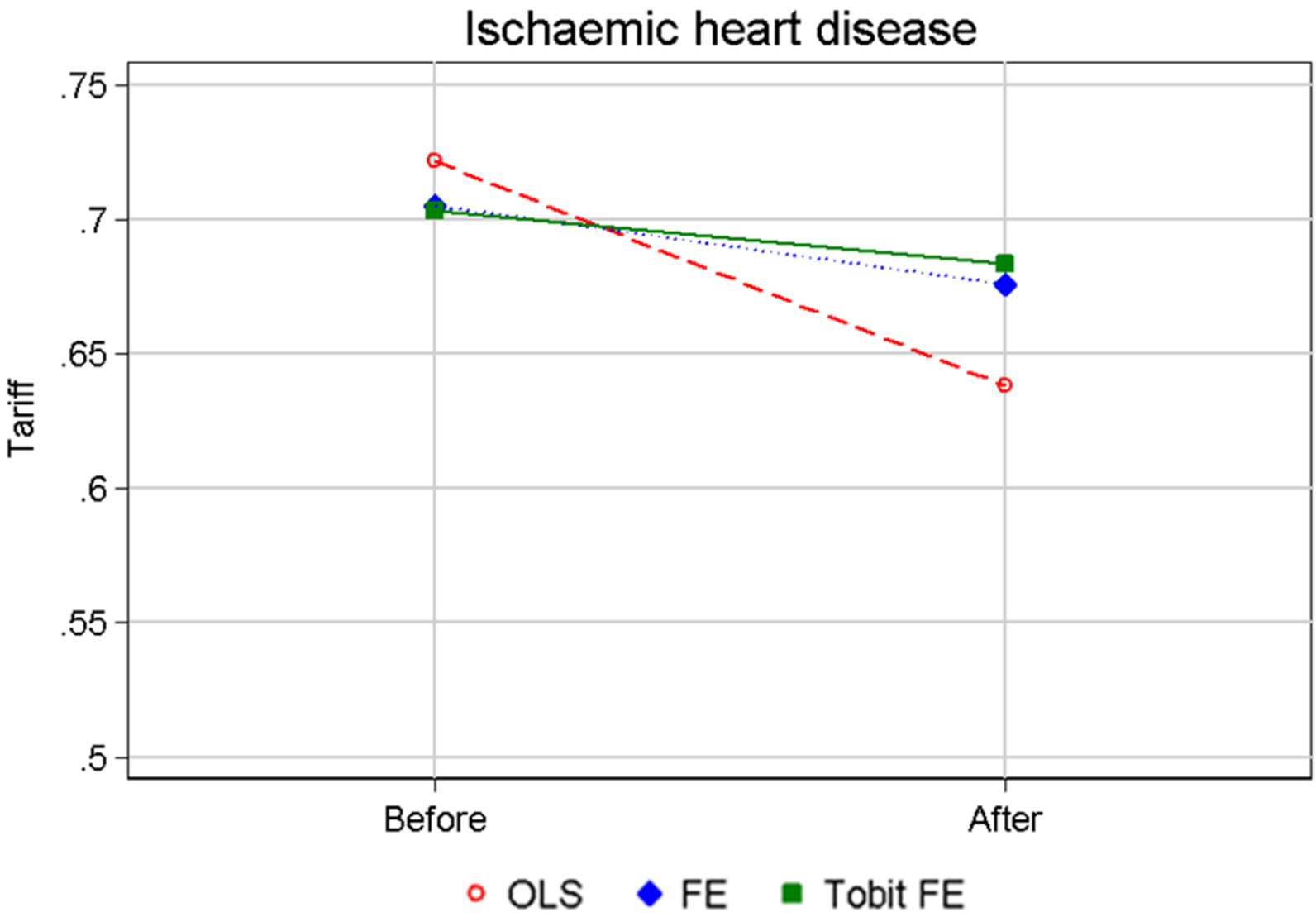
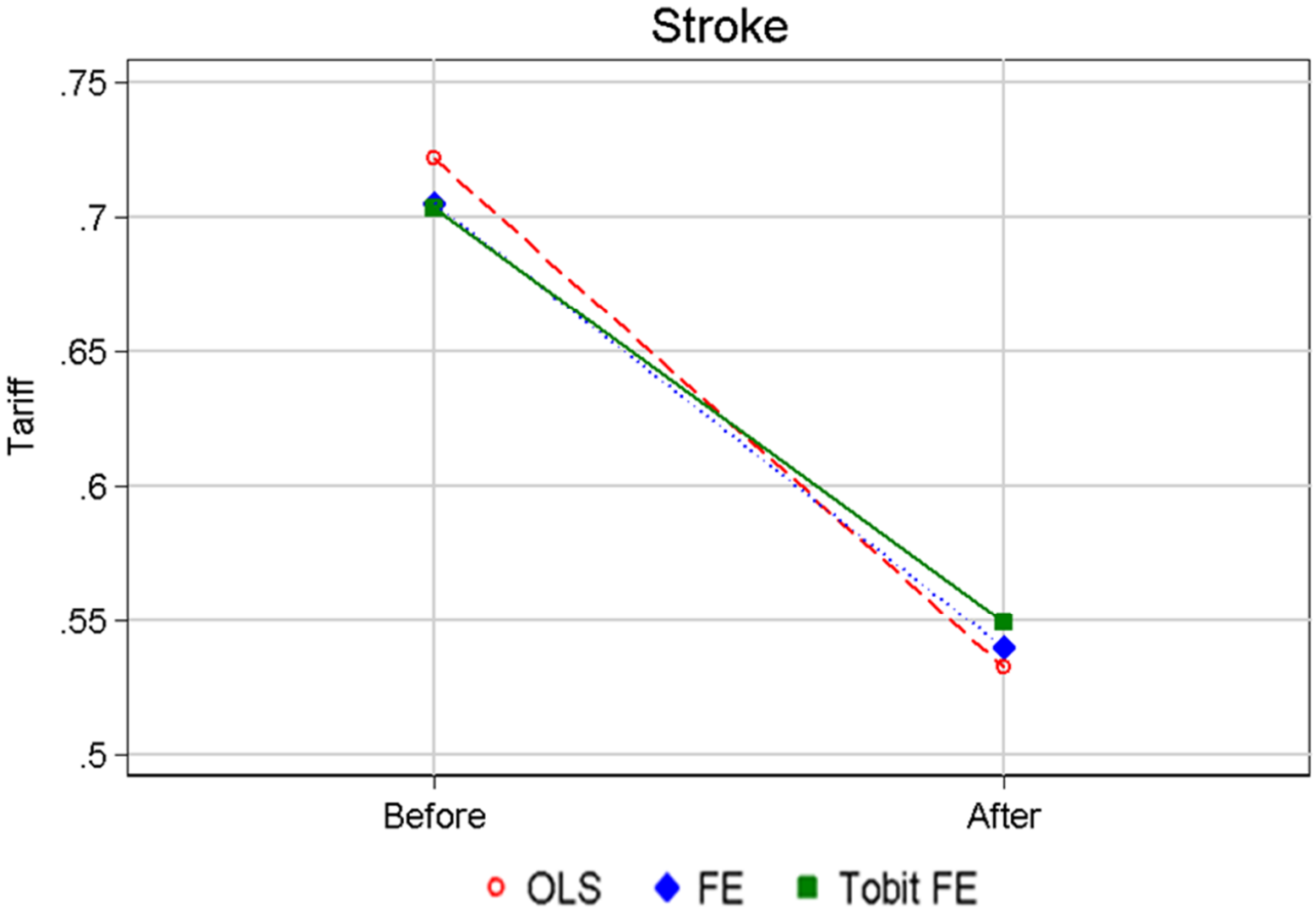


Predictions for average participant with no other complication



Summary and Conclusion

- Obtaining quality of life information from trial participants is often valuable:
  - Repeated QoL observations across time provide added information
  - May be able to rely on average QoL/QoL profile differences
  - But may need to use decrements from elsewhere, or calculate them
- Evidence that there is a lot of individual heterogeneity
  - Some evidence that patient specific characteristics including QoL may be correlated with the likelihood of events.
  - Patients who have an event may have a lower QoL beforehand
  - Therefore method of calculating decrements important:
    - Longitudinal data better than cross-sectional
    - OLS may be inadequate – work required on better methods, other datasets