Data Supplement:

Worked example in of applying the proposed methods

Consider a hypothetical dataset comprising of 30 patients, 15 receiving the intervention (coded 1) and 15 control (coded 0). Three QoL domains are of interest D1, D2, D3 and patient visits occur at 1, 3, 6, 9 and 12 months. The data are given in table S2.1 below

Table DS1: Hypothetical time to MCID for 30 patients

ID	Treat	Time to MCID†	Domain*	ID	Treat	Time to MCID†	Domain*
1	0	12	0	16	1	3	1
2	0	3	2	17	1	12	2
3	0	9	1	18	1	6	1
4	0	1	0	19	1	6	3
5	0	6	2	20	1	1	1
6	0	9	3	21	1	1	3
7	0	12	1	22	1	9	1
8	0	6	2	23	1	6	2
9	0	3	1	24	1	6	3
10	0	3	2	25	1	12	3
11	0	12	3	26	1	9	0
12	0	9	0	27	1	6	1
13	0	1	2	28	1	1	1
14	0	9	0	29	1	3	2
15	0	6	0	30	1	12	0

* Domain in which first MCID was observed, 0 indicating no MCID observed in any domain
†Time to MCID or last follow-up

(a) Fit a polytomous logistic regression model of treatment and log(time) to just the 23 cases where a MCID was observed The ln(time) term component allows for estimates of probabilities in each domain at the time points where the MCID was observed.

Polytomous Model: Reference category D3

			95% Confidence Interval		
Domain		Odds Ratio	Lower	Upper	p-value
D1	Intervention:control	0.859	0.091	8.117	0.894
	ln(time)	0.521	0.124	2.195	0.374
D2	Intervention:control	0.246	0.024	2.508	0.236
	ln(time)	0.448	0.099	2.039	0.299

Odds ratio >1: higher MCID rate for in the intervention group

(b) From the above model, probability estimates for each patient in which an MCID was observed. These are readily obtained from most statistical packages and are given in table DS2

Table DS2: Modelled probabilities from polytomous logistic regression

ID	Treat	Time	D1	D2	D3	ID	Treat	Time	D1	D2	D3
13	0	1	0.302	0.635	0.063	20	1	1	0.541	0.326	0.133
2	0	3	0.311	0.555	0.134	21	1	1	0.541	0.326	0.133
9	0	3	0.311	0.555	0.134	28	1	1	0.541	0.326	0.133
10	0	3	0.311	0.555	0.134	16	1	3	0.497	0.254	0.249
5	0	6	0.304	0.490	0.206	29	1	3	0.497	0.254	0.249
8	0	6	0.304	0.490	0.206	18	1	6	0.445	0.205	0.351
3	0	9	0.294	0.446	0.260	19	1	6	0.445	0.205	0.351
6	0	9	0.294	0.446	0.260	23	1	6	0.445	0.205	0.351
7	0	12	0.284	0.413	0.303	24	1	6	0.445	0.205	0.351
11	0	12	0.284	0.413	0.303	27	1	6	0.445	0.205	0.351
						22	1	9	0.406	0.176	0.417
						17	1	12	0.377	0.156	0.467
						25	1	12	0.377	0.156	0.467

The unique instances of time, treatment and modelled probabilities, are summarized in table DS3

Table DS3: Unique instances of modelled probabilities for each domain over time

	Control			Intervention			
Time	D1	D2	D3		D1	D2	D3
1	0.302	0.635	0.063	1	0.541	0.326	0.133
3	0.311	0.555	0.134	3	0.497	0.254	0.249
6	0.304	0.490	0.206	6	0.445	0.205	0.351
9	0.294	0.446	0.260	9	0.406	0.176	0.417
12	0.284	0.413	0.303	12	0.377	0.156	0.467

(c) Separately, we calculate the hazard ratio (HR) for the time to first MCID (in any domain) to obtain an estimate of the benefit/delay of achieving an MCID of intervention:control. In this context, a HR > 1 favours intervention (more events or MCID's);

A proportional hazards model fitting intervention effect to time to achieve any MCID; censoring code 0 for the 7 patients not achieving a MCID and event code 1,2,3 for the 23 achieving an MCID gives

	Hazard	95% Confidence Interval		
	Ratio	Lower	Upper	p-value
Intervention	1.383	0.606	3.158	0.4415

(d) The estimate of the 'hazard' of achieving an MCID at each time point using the method of Nelson-Aalen can be obtained from as output from statistical packages

Table DS4: Hazard estimate at 1, 3, 6, 9 and 12 months

Time (mths)	Number of MCID's	Number at Risk	Hazard
1	4	30	0.133
3	5	25	0.200
6	7	20	0.350†
9	3	12	0.250
12	4	6	0.667

† 0.35 = 7/20. Hazard is zero outside these time points

(e) The final step is to form the product of these probabilities at each event time point and transform them to cumulative probabilities.

For the control group:

Entries under the headings D1, D2, D3 are the modelled probabilities from the polytomous regression for the respective QoL domains.

QoL Domain D1

Time	haz	D1	haz*D1	Cumulative Sum (H)	Cumulative prob =1-e^{-H}
1	0.133	0.302	0.0401	0.0401	0.0393
3	0.2	0.311	0.0622	0.1023	0.0972
6	0.35	0.304	0.1064	0.2087†	0.1884‡
9	0.25	0.294	0.0736	0.2823	0.2459
*10	0	u/k	0	0.2823	0.2459
12	0.667	0.284	0.1897	0.4720	0.3762

† Cumulative sum of haz*D1=0.0401+0.0622+0.1064

‡ probability achieving a MCID in D1 at or prior to 6 months in the control group; 1-e^{-2087} =18.8%

* time values not observed have cumulative hazard and probabilities the same as at the previous observed time

QoL Domain D2

Time	haz	D2	haz*D2	Cumulative Sum (H)	Cumulative prob =1-e^{-H}
1	0.133	0.635	0.0845	0.0845	0.0810
3	0.2	0.555	0.1111	0.1956	0.1776
6	0.35	0.490	0.1715	0.3670	0.3072
9	0.25	0.446	0.1116	0.4786	0.3803
12	0.667	0.413	0.2754	0.7540	0.5295

QoL Domain D3

Time	haz	D2	haz*D2	Cumulative Sum (H)	Cumulative prob =1-e^{-H}
1	0.133	0.635	0.0845	0.0845	0.0084
3	0.2	0.555	0.1111	0.1956	0.0346
6	0.35	0.490	0.1715	0.3670	0.1017
9	0.25	0.446	0.1116	0.4786	0.1581
12	0.667	0.413	0.2754	0.7540	0.3121

For the intervention group:

Entries under the headings D1, D2, D3 are the modelled probabilities from the polytomous regression for the respective QoL domains.

Calculations are similar except the hazard in also multiplied by the hazard ratio HR=1.383 from the proportional hazards regression in (c)

QoL Domain D1

Time	haz	D1	haz*D1*HR	Cumulative Sum (H)	Cumulative prob $=1-e^{-H}$
1	0.133	0.541	0.0996	0.0996	0.0948
3	0.2	0.497	0.1374	0.2370	0.2110
6	0.35	0.445	0.2152	0.4522	0.3638
9	0.25	0.406	0.1405	0.5927	0.4472
12	0.667	0.377	0.3475	0.9402	0.6094

QoL Domain D2

Time	haz	D2	haz*D2*HR	Cumulative Sum (H)	Cumulative prob $=1-e^{-H}$
1	0.133	0.326	0.0600	0.0600	0.0582
3	0.2	0.254	0.0703	0.1303	0.1221
6	0.35	0.205	0.0992	0.2294	0.2050
9	0.25	0.176	0.0609	0.2904	0.2520
12	0.667	0.156	0.1443	0.4346	0.3525

QoL Domain D3

Time	haz	D3	haz*D3*HR	Cumulative Sum (H)	Cumulative prob $=1-e^{-H}$
1	0.133	0.133	0.0244	0.0244	0.0241
3	0.2	0.249	0.0689	0.0933	0.0891
6	0.35	0.351	0.1697	0.2630	0.2313
9	0.25	0.417	0.1443	0.4073	0.3346
12	0.667	0.467	0.4307	0.8380	0.5674