Reporting uncertainty as standard errors around point estimates of values - a standard method and worked example.

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Note: This short note and accompanying tool is part of a wider piece of work by the authors addressing uncertainty around HRQoL values, from which two manuscripts are currently being prepared for submission. We are happy to share this aspect of our work in advance of those papers, and encourage all those reporting HRQoL values to incorporate the methods described here as standard practice in their reporting of value sets, as a small first step toward better accounting for wider sources of uncertainty relating to HRQoL values.

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1. Reporting uncertainty as standard errors around point estimates of values - a worked example.

We identified a wide range of sources of uncertainty around HRQoL values, deriving from study design, stated preference methods and choice of methods for modelling of values (Devlin et al 2023). Our scoping review (Abangma et al 2023) identified a small number of studies that have analysed and quantified some of these aspects of uncertainty, but in general these do not directly provide useful information to users of health state values in cost effectiveness analysis (CEA). For example, Ara and Wailoo (2011) have provided information on uncertainty around dimension and level-specific parameters for the UK EQ-5D-3L value set. However, to allow that information to be used in CEA requires uncertainty to be reported for health *states*, that is, for EQ-5D profiles that combine dimensions and levels.

Where health state values have been estimated using a regression model, an obvious solution, which does not appear to have been used or reported elsewhere, is to apply the standard formula for the standard error of a linear combination of coefficients from independent variables, SE = $x'\Sigma x$, where x is a vector of regression coefficients and Σ is the variance/covariance matrix. In principle, this can be used to estimate standard errors for any health state described by the HRQoL instrument, not just for the health states for which values have been observed . These estimates are no different conceptually to out-of-sample predictions made in other statistical models. Such standard errors represent only one form of uncertainty and are conditional on the underlying model being correctly specified. However, the general point is that this conditional parameter uncertainty is straightforward to quantify.

To illustrate this, we used the original data from the MVH study, downloaded from the UK Data Archive at the University of Essex (Williams *et al.* 1995). We replicated the MVH valuation data set and estimation model (MVH Group, 1995) and generated its variance/covariance matrix, reported in an Appendix, available from the authors. This replicated exactly the estimation model reported by Gray *et al.* (2011) and the covariance matrix reported by Ara and Wailoo (2011). However, there were some small differences compared to the MVH Group estimates, also noted by Gray *et al*. From this, we calculated standard errors (SEs) for all 243 profiles generated from the variance/covariance matrix, detailed in the Appendix.

The SEs are in the range 0.008171 to 0.012203, which is small compared to the range of values from -0.594 to 1. As noted, these SEs are conditional on the model being correctly specified and may be sensitive to alternative model specifications. We are exploring this, and implementing a Bayesian model averaging procedure to demonstrate how model uncertainty (Draper 1995) and parameter uncertainty can be combined. In addition, these are SEs of the mean values and do not relate to the uncertainty in predicting the next observation. This may be important because in many cases the value sets are used in subsequent statistical analysis and therefore averaging occurs at two levels which inappropriately reduces the uncertainty. This may suggest a role for missing data (multiple imputation) approaches and the two-stage approach reported in the Gray *et al.* (2012) paper.

2. Model replication and covariance matrix for the MVH TTO value set.

The Measuring and Valuing Health (MVH) valuation data were downloaded from the University of Essex UK Data Archive (Williams *et al*., 1995). The data set includes data from interviews of 3395 people, consisting of 370 variables. After exclusions for data considered not to be reliable, the TTO data contains 2995 observations of 43 variables, one for each of the health states valued by respondents. These data are reshaped to generate observations by health state with the EQ-5D profiles converted to binary variables including N3, a data set containing 35 964 observations of 13 variables.

The 2995 observations used in the modelling data cannot be directly identified from publicly available information. The main MVH study report (MVH Group 1995) has some ambiguities and inaccuracies in the description of how observations were excluded. We had access to the correct data set through a historical file, but comparing these cases with the descriptions in the MVH report, we found 5 cases that should have been excluded according to the description but were not and 23 that were excluded but should not have been. Gray *et al.* (2011) reported the same issue in replicating the MVH results.

The model was estimated using the *nlme* package in R (version 4.2.2 (2022-10-31) - "Innocent and Trusting"), with the coefficients and standard errors shown in the following table:

Table 1: Coefficients and standard errors from replicated MVH Group valuation model

Variable	Coefficient	Standard Error
Mobility Level 2	0.0686	0.0051

Mobility Level 3	0.3133	0.0065
Self Care Level 2	0.1035	0.0054
Self Care Level 3	0.2133	0.0066
Usual Activities Level 2	0.0360	0.0062
Usual Activities Level 3	0.0944	0.0073
Pain & Discomfort Level 2	0.1226	0.0051
Pain & Discomfort Level 2	0.3847	0.0057
Anxiety & Depression Level 2	0.0711	0.0053
Anxiety & Depression Level 3	0.2365	0.0059
N3[a]	0.2693	0.0071
Intercept[b]	0.0806	0.0078

Notes: (a) N3 is defined as a binary variable identifying health states that contain a Level 3 in at least one dimension. (b) the intercept can be interpreted as a binary variable identifying health states that contain a Level 2 or 3 in at least one dimension.

This is identical to the estimates calculated by Gray *et al.* (2011), but has some small discrepancies with the published MVH model, which may be the result of using different statistical software: the MVH original used LIMDEP, while Gray *et al*. used Stata, which produces results identical to the R package used here. The following table shows the variance/covariance matrix that we calculated, which is also identical to that published by Ara and Wailoo (2011).

Table 2: Variance/covariance matrix from replicated MVH Group valuation model

	(Intercept)	MO2	MO3	SC2	SC3	UA2	UA3	PD2	PD3	AD2	AD3	N3
(Intercept)	6.07E-05	-3.66E-06	1.74E-06	-1.03E-05	-4.93E-06	-3.25E-06	-3.53E-06	-8.99E-06	-4.22E-06	-1.03E-05	-4.29E-06	-9.85E-06
MO2	-3.66E-06	2.61E-05	1.61E-05	-3.53E-06	7.80E-07	-2.01E-06	-6.51E-06	-4.19E-06	-4.79E-06	-4.10E-06	-2.96E-06	-8.00E-07
MO3	1.74E-06	1.61E-05	4.26E-05	-9.81E-06	-1.26E-05	-6.15E-06	-8.18E-06	-1.60E-06	-6.52E-06	-3.07E-07	-5.35E-06	-3.68E-06
SC2	-1.03E-05	-3.53E-06	-9.81E-06	2.90E-05	1.82E-05	-8.94E-06	-5.62E-06	-3.84E-06	-7.03E-07	4.54E-06	2.20E-06	3.62E-06
SC3	-4.93E-06	7.80E-07	-1.26E-05	1.82E-05	4.35E-05	-8.30E-06	-1.64E-05	-2.09E-06	-2.41E-06	-1.24E-06	3.20E-06	-2.97E-06
UA2	-3.25E-06	-2.01E-06	-6.15E-06	-8.94E-06	-8.30E-06	3.80E-05	2.80E-05	-9.45E-07	4.34E-06	-7.63E-06	2.87E-06	-1.59E-05
UA3	-3.53E-06	-6.51E-06	-8.18E-06	-5.62E-06	-1.64E-05	2.80E-05	5.29E-05	-1.80E-06	7.86E-06	1.43E-06	2.38E-06	-2.49E-05
PD2	-8.99E-06	-4.19E-06	-1.60E-06	-3.84E-06	-2.09E-06	-9.45E-07	-1.80E-06	2.63E-05	1.13E-05	-6.97E-07	-5.13E-06	5.56E-06
PD3	-4.22E-06	-4.79E-06	-6.52E-06	-7.03E-07	-2.41E-06	4.34E-06	7.86E-06	1.13E-05	3.21E-05	-1.44E-06	-1.63E-06	-1.28E-05
AD2	-1.03E-05	-4.10E-06	-3.07E-07	4.54E-06	-1.24E-06	-7.63E-06	1.43E-06	-6.97E-07	-1.44E-06	2.81E-05	1.36E-05	-1.30E-06
AD3	-4.29E-06	-2.96E-06	-5.35E-06	2.20E-06	3.20E-06	2.87E-06	2.38E-06	-5.13E-06	-1.63E-06	1.36E-05	3.50E-05	-1.59E-05
N3	-9.85E-06	-8.00E-07	-3.68E-06	3.62E-06	-2.97E-06	-1.59E-05	-2.49E-05	5.56E-06	-1.28E-05	-1.30E-06	-1.59E-05	5.00E-05

3. Generating standard errors for the MVH value set

Using the standard equation SE = $x'\Sigma x$ (where Σ is the covariance matrix), standard errors can be calculated for the MVH value set for all 243 profiles defined by the EQ-5D-3L – see Table 3.

Table 3: Values and standard errors for profiles from replicated MVH Group valuation model

	Value	**SE**
11112	0.848	0.008261
11113	0.414	0.009253
11121	0.796	0.008308
11122	0.725	0.00867
11123	0.291	0.009737
11131	0.264	0.009434
11132	0.193	0.009543
11133	0.028	0.008966
11211	0.883	0.009601
11212	0.812	0.009191
11213	0.378	0.00954
11221	0.76	0.009931
11222	0.689	0.009462
11223	0.255	0.009915
11231	0.228	0.009865
11232	0.157	0.009173
11233	-0.008	0.009719
11311	0.556	0.009331
11312	0.485	0.009741
11313	0.32	0.009299
11321	0.433	0.010145
11322	0.362	0.010456
11323	0.197	0.009594
11331	0.17	0.010041
11332	0.099	0.010283
11333	-0.066	0.009847
12111	0.815	0.00831
12112	0.744	0.009257
12113	0.31	0.010278

12121	0.692	0.008349
12122	0.621	0.009217
12123	0.187	0.010351
12131	0.16	0.010159
12132	0.089	0.010694
12133	-0.076	0.009949
12211	0.779	0.009093
12212	0.708	0.009169
12213	0.274	0.009652
12221	0.656	0.009024
12222	0.585	0.009024
12223	0.151	0.009632
12231	0.124	0.009678
12232	0.053	0.009464
12233	-0.112	0.009757
12311	0.452	0.009564
12312	0.381	0.010409
12313	0.216	0.00976
12321	0.329	0.009982
12322	0.258	0.01073
12323	0.093	0.009652
12331	0.066	0.010188
12332	-0.005	0.010854
12333	-0.17	0.010214
13111	0.436	0.010894
13112	0.365	0.011007
13113	0.2	0.010941
13121	0.313	0.011574
13122	0.242	0.01162
13123	0.077	0.011168
13131	0.05	0.010577
13132	-0.021	0.010557
13133	-0.186	0.010471
13211	0.4	0.010086
13212	0.329	0.009431
13213	0.164	0.010417
13221	0.277	0.010729
13222	0.206	0.010047
13223	0.041	0.010566
13231	0.014	0.010179
13232	-0.057	0.009378
13233	-0.222	0.01035
13311	0.342	0.009049
13312	0.271	0.009339
13313	0.106	0.009364
13321	0.219	0.009672
13322	0.148	0.009873
13323	-0.017	0.009438
13331	-0.044	0.009529
13332	-0.115	0.009657

13333	-0.28	0.009661
21111	0.85	0.008917
21112	0.779	0.00888
21113	0.345	0.009845
21121	0.727	0.008914
21122	0.656	0.008799
21123	0.222	0.009886
21131	0.195	0.009831
21132	0.124	0.009513
21133	-0.041	0.009061
21211	0.814	0.010343
21212	0.743	0.009543
21213	0.309	0.009914
21221	0.691	0.010249
21222	0.62	0.009367
21223	0.186	0.00986
21231	0.159	0.010047
21232	0.088	0.008919
21233	-0.077	0.0096
21311	0.487	0.009554
21312	0.416	0.009533
21313	0.251	0.009205
21321	0.364	0.009937
21322	0.293	0.009846
21323	0.128	0.009053
21331	0.101	0.009769
21332	0.03	0.0096
21333	-0.135	0.009255
22111	0.746	0.00899
22112	0.675	0.009447
22113	0.241	0.010482
22121	0.623	0.00855
22122	0.552	0.008951
22123	0.118	0.010149
22131	0.091	0.010188
22132	0.02	0.010331
22133	-0.145	0.009677
22211	0.71	0.009509
22212	0.639	0.009143
22213	0.205	0.009662
22221	0.587	0.008989
22222	0.516	0.00852
22223	0.082	0.009199
22231	0.055	0.009499
22232	-0.016	0.008827
22233	-0.181	0.009264
22311	0.383	0.009413
22312	0.312	0.009863
22313	0.147	0.009298
22321	0.26	0.009402

22322	0.189	0.009782
22323	0.024	0.008717
22331	-0.003	0.009558
22332	-0.074	0.009857
22333	-0.239	0.009272
23111	0.367	0.011724
23112	0.296	0.011477
23113	0.131	0.011514
23121	0.244	0.012015
23122	0.173	0.011714
23123	0.008	0.011367
23131	-0.019	0.011003
23132	-0.09	0.010604
23133	-0.255	0.010626
23211	0.331	0.010793
23212	0.26	0.009772
23213	0.095	0.010833
23221	0.208	0.011023
23222	0.137	0.009956
23223	-0.028	0.010587
23231	-0.055	0.01043
23232	-0.126	0.009215
23233	-0.291	0.010314
23311	0.273	0.009362
23312	0.202	0.009207
23313	0.037	0.009355
23321	0.15	0.009536
23322	0.079	0.009309
23323	-0.086	0.008974
23331	-0.113	0.009326
23332	-0.184	0.009013
23333	-0.349	0.009143
31111	0.336	0.01139
31112	0.265	0.011578
31113	0.1	0.010661
31121	0.213	0.012082
31122	0.142	0.012203
31123	-0.023	0.010938
31131	-0.05	0.010709
31132	-0.121	0.010777
31133	-0.286	0.009766
31211	0.3	0.01082
31212	0.229	0.010303
31213	0.064	0.010332
31221	0.177	0.011464
31222	0.106	0.010914
31223	-0.059	0.010529
31231	-0.086	0.010522
31232	-0.157	0.009845
31233	-0.322	0.009857

31311	0.242	0.010461		32221	0.073	0.010094		33131	-0.264	0.0106
31312	0.171	0.0108		32222	0.002	0.009932		33132	-0.335	0.010552
31313	0.006	0.009906		32223	-0.163	0.009258		33133	-0.5	0.009972
31321	0.119	0.011049		32231	-0.19	0.009351		33211	0.086	0.010148
31322	0.048	0.011309		32232	-0.261	0.009096		33212	0.015	0.009465
31323	-0.117	0.010026		32233	-0.426	0.008847		33213	-0.15	0.009953
31331	-0.144	0.010495		32311	0.138	0.009707		33221	-0.037	0.010637
31332	-0.215	0.010698		32312	0.067	0.010511		33222	-0.108	0.009918
31333	-0.38	0.009776		32313	-0.098	0.009344		33223	-0.273	0.009948
32111	0.232	0.011213		32321	0.015	0.009959		33231	-0.3	0.009581
32112	0.161	0.011796		32322	-0.056	0.01068		33232	-0.371	0.00869
32113	-0.004	0.01068		32323	-0.221	0.009056		33233	-0.536	0.009199
32121	0.109	0.011589		32331	-0.248	0.00967		33311	0.028	0.008891
32122	0.038	0.012096		32332	-0.319	0.010339		33312	-0.043	0.009153
32123	-0.127	0.010601		32333	-0.484	0.009129		33313	-0.208	0.008611
32131	-0.154	0.010454		33111	0.122	0.011499		33321	-0.095	0.009355
32132	-0.225	0.010946		33112	0.051	0.011579		33322	-0.166	0.009531
32133	-0.39	0.009714		33113	-0.114	0.011071		33323	-0.331	0.008506
32211	0.196	0.009757		33121	-0.001	0.012012		33331	-0.358	0.008656
32212	0.125	0.009662		33122	-0.072	0.012031		33332	-0.429	0.008761
32213	-0.04	0.009449		33123	-0.237	0.011152		33333	-0.594	0.008171

While this worked example pertains to the UK value set for the EQ-5D-Y-3L, these same methods can be applied to the value sets for any HRQoL instrument.

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