Investigating the use of the difference method for sampling more than two ordered variables

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Background and Objectives

- In an appraisal by the National Institute for Health and Care Excellence (NICE) (HST28: birch bark extract [BBE] for epidermolysis bullosa), patient and carer's health state utility values (HSUVs) were inappropriately sampled within probabilistic sensitivity analysis (PSA), as highlighted by the external assessment group (EAG).[1]
- Each sampled HSUV was capped at the value of the adjacent, less severe state if a better utility was implied for the more severe state, illustrated in **Figure 1**. Six alive patient health states and three carer health states are used to model the disease, with capping applied to each pair.
- Alternative methodology exists for retaining distributional properties of ordered variables (OVs) using the difference method (DM), developed by Ren *et al*.[2] If parameters have a known order (such as HSUVs) the DM avoids possible inconsistent sampling via PSA by maintaining ordering while not distorting summary statistics of each variable.
- The DM was created for only two OVs. This work aims to extend the DM to more than two OVs.

***Figure 1**: Illustration showing the HSUV capping method applied by the company in HST28*

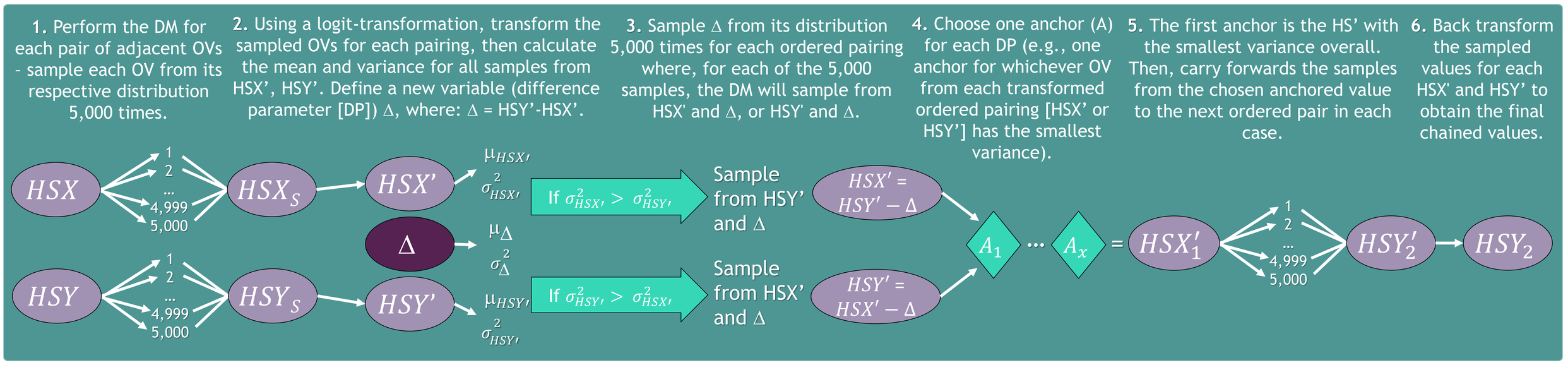
Deterministic	HSUV 1 (less severe health state)	0.70
	HSUV 2 (more severe health state)	0.65
	HSUVs probabilistically sampled	
Probabilistic	HSUV 1 (less severe health state)	0.68
	HSUV 2 (more severe health state)	0.71
	HSUVs capped after sampling	
Capped	HSUV 1 (less severe health state)	0.68
	HSUV 2 (more severe health state)	0.68

Key: HST, highly specialised technology; HSUV, health state utility value

Methods

- A cost-effectiveness model was developed to replicate a simplified version of the model used in HST28. The goal of the original model was to perform a cost-effectiveness analysis between the intervention (BBE) and comparator, standard-of-care.[1] Using the re-created model, differences in incremental cost-effectiveness ratios (ICERs) between the company's results, results calculated using a regular 'uncapped' PSA (at risk of inconsistent sampling errors) and those created when switching to the DM could be compared, along with differences in health benefit.
- To extend the DM to more than two OVs, a 'chained' version of the method was created where the DM was applied to each pair of ordered HSUVs with the previous sample carried forwards. By chaining together each application of the DM, sampled values remained consistent along with the original distributional properties (mean, μ and variance, σ) for each HSUV. The chaining methodology was implemented as illustrated in **Figure 2**.

***Figure 2**: Figure to show the implementation of the extended difference method (DM) for more than two ordered variables (OVs)*



Key: A, anchor; DM, difference method; DP, difference parameter; HS, health state; OV, ordered variable

- 'Capped' and 'uncapped' PSA methods were implemented in the recreated, simplified model. Consistency between the initial and sampled summary statistics for each HSUV distribution was assessed for each sampling method. This generated probabilistic results (incremental costs, quality-adjusted life years [QALYs] and ICERs) using each method and the expected value of perfect information (EVPI).

Results and conclusions

- Summary statistics for HSUVs were largely maintained when using the chained DM, as well as the ordering of the sampled HSUVs, shown in **Figure 3**.
- This method maintained the published mean and variance across seven out of the nine total health states (six patient and three carer), whereas the capped approach only managed to maintain the summary statistics for one health state.
- The mean incremental cost-effectiveness ratio had over £4,000 difference, and the EVPI was reduced from £13,376 to £9,359 when using the chained DM.
- In conclusion, the DM may be chained across more than two OVs. Using this approach, the summary statistics of original inputs are maintained, and parameter uncertainty is not over-inflated. Despite reducing this uncertainty, further research is needed to establish how the chained DM affects the sampled values themselves.

***Figure 3**: Summary statistics for each patient and carer HS after sampling 1,000 times via each method; PSA, capped PSA and using the DM.*

	Method	HS1	HS2	HS3	HS4	HS5	HS6
Patient	HST28 mean, μ	0.5600	0.5150	0.4610	0.3450	0.2290	0.0770
	Uncapped PSA mean, μ	0.5583	0.5148	0.4617	0.3466	0.2263	0.0799
	Capped PSA mean, μ	0.5596	0.5086	0.4555	0.3466	0.2198	0.0555
	DM PSA mean, μ	0.5608	0.5159	0.4622	0.3462	0.2295	0.0809
	HST28 Var(μ), σ^2	0.0013	0.0012	0.0013	0.0032	0.0078	0.0169
	Uncapped PSA Var(μ), σ^2	0.0013	0.0011	0.0014	0.0031	0.0075	0.0188
	Capped PSA Var(μ), σ^2	0.0013	0.0010	0.0010	0.0028	0.0054	0.0059
	DM PSA Var(μ), σ^2	0.0013	0.0012	0.0014	0.0031	0.0065	0.0059*
Carer	HST28 mean, μ	0.85		0.76		0.64	
	Uncapped PSA mean, μ	0.8500	0.8510	0.7615	0.7601	0.6385	0.6400
	Capped PSA mean, μ	0.8499	0.8331	0.7592	0.7419	0.6380	0.6172
	DM PSA mean, μ	0.8500		0.7603		0.6398	
	HST28 Var(μ)**, σ^2	0.0009		0.0011		0.0015	
	Uncapped PSA Var(μ), σ^2	0.0009	0.0009	0.0010	0.0011	0.0015	0.0014
	Capped PSA Var(μ), σ^2	0.0009	0.0007	0.0010	0.0007	0.0015	0.0010
	DM PSA Var(μ), σ^2	0.0008		0.0011		0.0014	

Key: DM, difference method; HS, health state; HST, highly specialised technology; PSA, probabilistic sensitivity analysis. Note: HSUVs ≤0.001 of the published mean are green, and >0.001 away are red. Variances lying ≤0.0001 of the published/calculated variance are green, and >0.0001 away are red.

References: [1]NICE. Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. 2023; Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10654/documents. [2]Ren S, Minton J, Whyte S, Latimer N, Stevenson M. A New Approach for Sampling Ordered Parameters in Probabilistic Sensitivity Analysis. Pharmacoeconomics. 2018;36(3):341–7.

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