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## Putting the 'Q' in quality adjusted life years (QALYs) for advanced ovarian cancer – An approach using data clustering methods and the internet

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### ABSTRACT

There are few clearly described utility studies in advanced ovarian cancer, despite the public health importance of condition and the need for preference based measures of quality of life in economic evaluation of the new treatments. We used data clustering techniques to develop health state descriptions based on data from 66 women who completed the EORTC QLQ-C30 over a six month period while receiving chemotherapy for ovarian cancer. The health state descriptions were presented to a group of members of the general public ( $n = 38$ ), via the internet, and preferences elicited using the standard gamble technique. Mean utility values ranged from 0.685 to 0.977, although the range of individual preferences was wider, including values as low as 0.125. This is the first study to use data clustering methods combined with internet preference elicitation in oncology. The resulting health state model is parsimonious, data driven, and incorporates quality of life items tailored to cancer. The estimates therefore meet the needs of policy makers while reflecting more accurately the experience of disease than those based on generic preference measures.

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### 1. Introduction

Ovarian cancer is the most common gynaecological cancer, with an annual incidence of 22 per 100,000 women in England (2000 figures). The prognosis is generally poor, due to the typically advanced stage of disease at detection, and the UK 5

year survival rate is only around 36%. There were over 4500 deaths from ovarian cancer in England and Wales in 2000.<sup>1</sup>

Ovarian cancer's impact on quality of life (QoL) may be measured using both cancer-specific (e.g. EORTC-QLQ-C30) and generic (e.g. SF36 or SIP) scales. QoL measures are of established value in the assessment of treatments in clinical

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<sup>g</sup> Galina Velikova provided the EORTC quality of life, clinical and demographic patient data and contributed to the manuscript.

<sup>h</sup> Dan Stark contributed to the design of the study and development of the health state descriptions, advised on all clinical aspects of the study and contributed to the manuscript.

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trials, and there is an increasing evidence supporting their use in informing doctor–patient interactions during routine care of people living with cancer.<sup>2</sup>

Health economic analyses also apply QoL, in particular to assess cost utility. This is the preferred economic approach of policy makers and their advisors in the UK<sup>3</sup> and North America.<sup>4,5</sup> In order to carry out cost utility analyses (CUA), quality of life must be estimated using a single index where full health is scored as one and death as zero.

Estimating utility involves two steps: (a) description and (b) valuation of relevant states of health. A range of methods are available for each. Description should clearly be based on patients' experiences,<sup>6</sup> although there is no universally accepted approach either to defining health states or to creating the descriptions. There are three commonly used methods for valuation – time trade-off, standard gamble and rating scales.<sup>6</sup> Where the purpose of evaluations is to inform public policy decisions, it is recommended that valuation of health states should be carried out by members of the general population.<sup>3–5</sup>

There are very few estimates of utility in advanced ovarian cancer. A recent UK literature review<sup>7</sup> carried out for a review of treatment in relapsed ovarian cancer by the National Institute for Health and Clinical Excellence (NICE) identified only five papers<sup>8–12</sup> (see Table 1), of which one was a review including no new values.<sup>13</sup> The approaches taken to develop hypothetical health states in the ovarian cancer literature are inadequately reported according to guidelines established by consensus among methodologists in this field.<sup>14</sup> Most estimates were obtained as part of decision analytic modelling studies of the cost effectiveness of ovarian cancer drugs or ovarian cancer screening. Nevertheless, precise descriptions of methods are important as systematic differences between the results of different utility assessment techniques are well recognised.<sup>15–18</sup>

Multi-attribute utility scales assess the impact of health on QoL, expressed as a utility value. The major instruments in current use are the Health Utilities Index<sup>19</sup> and the EQ5D.<sup>20</sup> These provide systems in which a finite number of health states can be described (e.g. 243 for the EQ5D). Based on a general population survey, utilities for each of these discrete states have been estimated.<sup>20</sup> Researchers can therefore estimate utility without a new preference measurement study: a patients' condition is described by application of the EQ5D and values are obtained by consulting appropriate tables for general population estimates of utility. While this approach is

efficient, it has important limitations. First, the measure may not be sufficiently, finely grained to capture all important aspects of a condition.<sup>21</sup> At the same time, the orthogonal definition of health states, many of which may be clinically indistinguishable or which may not even exist in a specific disease, may make the model unwieldy in practical applications. Second, the EQ5D is of limited benefit when considering treatments and patient groups that have not been studied with this measure, e.g. there are no published EQ5D data for ovarian cancer. A wide range of alternative approaches to obtaining utility data are therefore in use.<sup>22</sup>

In this study, we applied a novel approach to developing health states in advanced ovarian cancer. We used cluster analysis to convert cancer-specific individual patient QoL data into a parsimonious set of clinically relevant descriptions,<sup>23,24</sup> which were then valued as hypothetical health states by a group of members of the UK general public. The resulting estimates of preference-based quality of life in advanced ovarian cancer, taken from a general population perspective, will be valuable to policy decision-making on emerging treatments for this important public health problem.

## 2. Patients and methods

### 2.1. Patient sample

Our sample consisted of women with advanced ovarian cancer on chemotherapy who had participated in a randomised controlled trial of routine quality of life measurement.<sup>2</sup> Patients completed the EORTC QLQ-C30 on touch-screen computer each time they attended the outpatient clinic at St. James's Hospital, Leeds, over a period of 6 months.

### 2.2. QoL Instrument

The EORTC-QLQ-C30 is a validated measure of QoL applicable in ovarian cancer, containing 30 items. These are grouped into a global health status scale, five functional scales (physical, role, emotional, cognitive and social functioning) and nine symptom scales/items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Since we were interested in estimating global quality of life using descriptors of specific impacts of disease, we excluded the global QoL questions. We also excluded the financial impact question since costs met

**Table 1 – Methodological features of previous utility studies in advanced ovarian cancer**

Author	Method for health state description	Valuation method	Population carrying out valuation
Ortega et al. <sup>9</sup>	Unclear	TTO	Women with ovarian cancer (n = 40) and female hospital employees (n = 20)
Grann et al. <sup>8</sup>	Unclear	TTO	Women at high risk of ovarian cancer due to genetic condition
Bennett et al. <sup>10</sup>	Unclear	TTO	Oncologists (n = 10) and women with ovarian cancer (n = 15)
Calhoun et al. <sup>11</sup>	'Crafted by an experienced health services researcher and oncologist'	TTO	Gynaecologic oncologists (n = 11), Women at high risk (n = 39), women with no risk factors for ovarian cancer (n = 39)

directly by patients are not generally included in economic evaluations of health technologies in the UK.<sup>3</sup>

### 2.3. Statistical approach

Initially, we carried out principle components analysis (PCA) and *k*-means clustering (KMC) to identify coherent subgroups within the EORTC data set. PCA is a statistical technique, akin to factor analysis, that identifies a smaller number of variables that account for most of the variance in a dataset. KMC is a clustering algorithm that divides the data space into a pre-specified number of groups. Where, as here, a data set covers a broad continuum of health status, clusters are unlikely to be highly distinct.<sup>24</sup> A model based on too few clusters will describe the variability within the data poorly; a model with too many clusters will not identify clinically distinct groups. We therefore examined the clinical characteristics of a sequence of cluster models, and stopped adding states when they could no longer be interpreted as statistically or

medically separate groups. Model stability is also an important issue. Adding additional clusters should result in subdividing the previously existing groups rather than creating an entirely new partition of the data space. We checked this by comparing cluster membership in successive models and also by looking at the cluster centres, or means, which represent the prototypical patients for the states.

### 2.4. Health state description

Health state descriptions for each cluster were developed from the distribution of EORTC QLQ-C30 item scores within domains (see [Appendix](#)). A balance needs to be struck between providing a description which is sufficiently rich to reflect the distribution of patients' responses within any one cluster and presenting so much information that the respondent is unable to process the description.

The written description of each QoL scale in each cluster had two elements. The score that was the mode for each

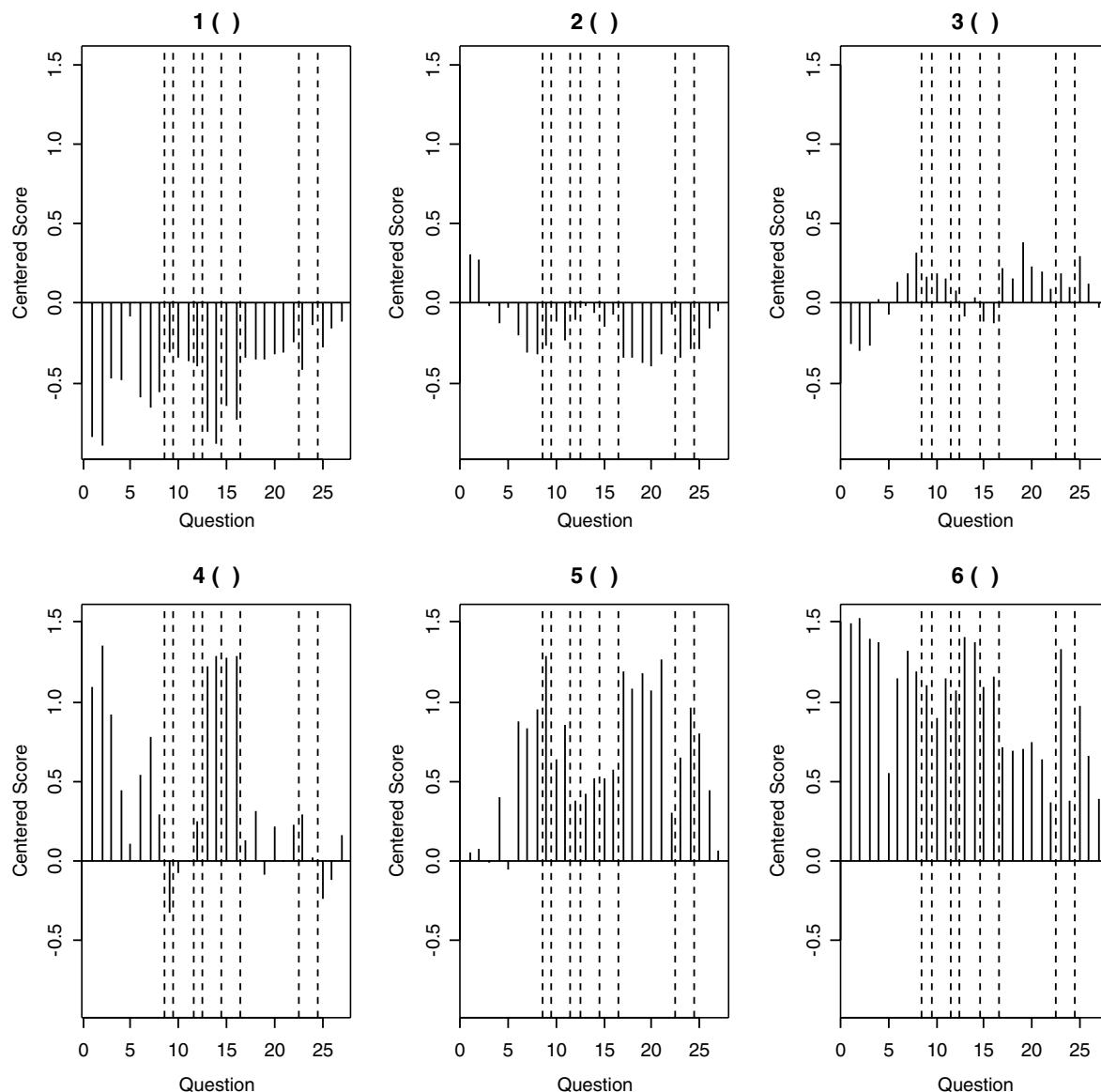


Fig. 1 – Standardised EORTC item scores for clusters ( $k = 46$ ).

domain was described as the 'usual' level of impairment that would be expected. Item scores which occurred in less than 10% of responses within a cluster were not mentioned in the description. Item scores with a frequency of 10–24% were described as 'rare' and those with a frequency of 25–49% were described as 'sometimes' to be expected (see [Appendix](#)).

## 2.5. Valuation by members of the public

Valuations of these descriptions were made by the Value of Health Panel (VHP). The VHP contains members of the public recruited from the electoral registers of four UK cities. Its purpose is to provide utility estimates in relation to defined health states where no appropriate estimates exist. Since October 2004, the panel has provided utility data on 18 sets

of health state descriptions; 106 states in total. The panel has a smaller proportion of people from areas of higher socio-economic deprivation and people from ethnic minorities than the UK population as a whole, but is representative in terms of age and sex. Health state descriptions were presented in tabular format<sup>25</sup> and in random order. The standard gamble was carried out using the titration approach,<sup>6</sup> via the World Wide Web.

We took two approaches to validation of utility estimates.<sup>26</sup> The first is based on unambiguous logical ordering of severity in the health states being valued. Logical inconsistency<sup>26</sup> is then described as the frequency with which respondents' utilities do not conform to the expected ordering of states.<sup>27–30</sup> In this study, inconsistent responses are described but excluded from the analysis.

**Table 2 – Cluster characteristics**

	Whole sample	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
N patients included	66	40	34	34	20	18	17
N time points included	486 <sup>a</sup>	147	117	101	56	32	33
<i>Age</i>							
Years (mean)	60.0	58.3	63.1	54.8	60.5	49.8	66.1
<i>Marital status (%)</i>							
Married	58.6	63.3	62.4	46.5	67.9	59.4	45.5
Cohabiting	3.7	0	0.9	4.95	16.1	9.4	0
Separated/divorced	7.6	11.6	1.7	12.9	1.8	12.5	0
Widowed	16.7	10.9	24.8	14.9	10.7	0	45.5
Single	9.7	13.6	2.6	15.8	1.8	18.8	3.1
Missing data	3.7	0.7	7.7	5.0	1.8	0	6.1
<i>Employment (%)</i>							
Working full time	9.9	4.8	4.3	17.8	17.9	15.6	9.1
Working part time	17.5	33.3	12.0	11.9	7.1	15.6	3.0
Unable to work due to illness	23.3	22.5	16.2	32.7	16.1	50	9.1
Retired	27.4	19.1	35.0	24.8	32.1	3.1	60.6
Homemaker	15.8	16.3	21.4	6.9	21.4	15.6	12.1
Unemployed looking for work	2.5	3.4	3.4	1	3.6	0	0
Other	3.7	0.7	7.7	5.0	1.8	0	3.7
<i>Disease stage (%)</i>							
1 (local)	22.6	21.8	17.9	27.7	21.4	37.5	15.2
2 (recur)	1.9	5.4	0	1	0	0	0
3 (metastatic)	75.5	72.8	82.1	71.3	78.6	62.5	84.8
<i>Time since diagnosis</i>							
Months (mean)	20.5	20.9	19.9	16.4	28.3	17.3	22.7
<i>Treatment type (%)</i>							
1 (chemo)	95.5	91.2	97.4	99	98.2	96.9	90.9
3 (hormone)	4.5	8.8	2.6	1	1.8	3.1	9.1
<i>Performance status (%)</i>							
0	13.8	26.5	3.4	16.8	1.8	18.8	0
1	46.1	47.6	45.3	56.4	35.7	43.8	30.3
2	33.7	22.5	47.0	24.8	51.8	37.5	30.3
3	6.4	3.4	4.3	2	10.7	0	39.4
<i>Response at 6 months (%)</i>							
Complete response	22.2	21.1	23.1	21.8	26.8	34.4	6.1
Partial response	32.3	37.4	33.3	28.7	33.9	12.5	33.3
No change	10.3	7.5	10.3	18.8	1.8	15.6	0.4
Progressive disease	32.7	32	33.3	29.7	32.1	37.5	39.4
Missing data	0.8	1.4	0	0	3.6	0	0

<sup>a</sup> The number of patients included in each cluster is greater than the overall sample size because of repeated measures.

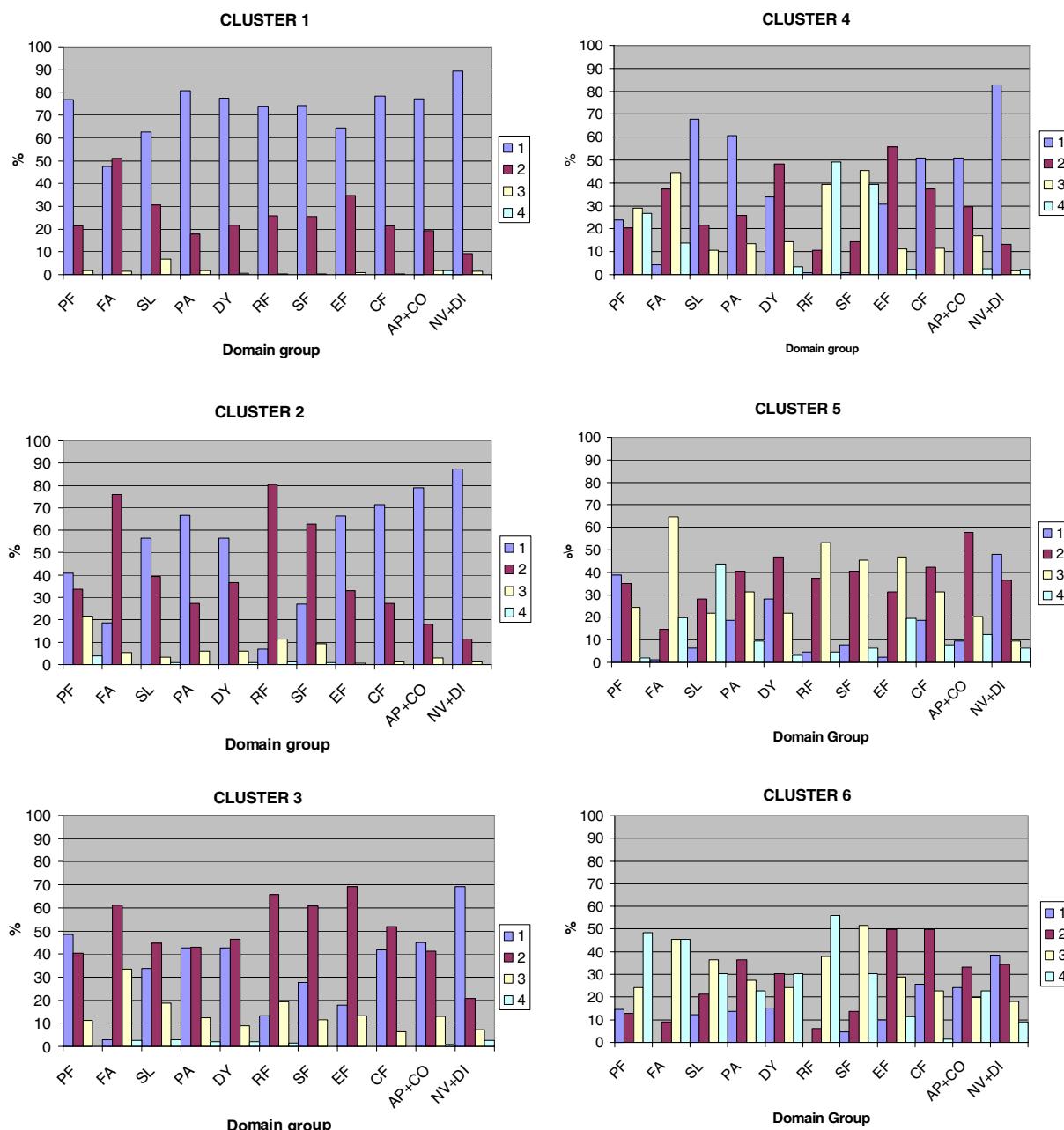
The second measure of validity in this context, procedural invariance,<sup>26</sup> compares the ranking of utility for health states using different methods of utility assessment. We compared the panel's utility estimates with the EORTC-QLQ-C30 global health status score for each cluster/health state, the latter having been excluded from the health state descriptions.

### 3. Results

The sample is described in Table 1. There were a median of seven QL measurements per patient (interquartile range 3), over a mean of 15.3 weeks (range 1.6–28.6).

In the initial PCA, the first component, a measure of overall function and impairment, explained nearly 40% of variability. The first five components accounted for 65.8% of variability and were used in the KMC procedure.

We generated models involving 2–8 clusters and scrutinised the standardised EORTC item scores for each cluster. The patient prototypes defined by the cluster centres clearly remained stable as additional states were added. Taking into account statistical, medical and QoL characteristics, the six cluster model contained the maximum number of clinically meaningful distinct groups (see Fig. 1). Where values for items are less than zero, cluster



**Fig. 2 – Distribution of item scores across clusters:** PF, physical function; FA, fatigue; SL, sleep disturbance; PA, pain; DY, dyspnoea; RF, role function; SF, social/family function; EF, emotional function; CF, cognitive function; AP + CO, appetite disturbance/constipation; NV + DI, nausea, vomiting or diarrhoea 1–4, response level.

respondents had fewer problems than the whole sample average.

### 3.1. Cluster characteristics

Clinical and demographic characteristics of the clusters are shown in Table 2. The clusters are labelled according to their score on the first principle component. Cluster 1 describes a QoL profile where performance status is good. Overall there are few limitations and responses on all items of the EORTC-QLQ-C30 that are better than the average for the overall study population. This is the largest cluster (40 women, 147 observations) and has the highest proportion of women with performance status (PS) zero (see Fig. 2).

In cluster 2, physical function is worse than average but most other aspects of quality of life are similar or better. Average age is older than cluster 1, at 63 years. More women have metastatic disease, and there is a larger proportion of women with PS = 2. Given these clinical indicators, this cluster represents a group of women whose quality of life is perhaps better than might be expected.

Cluster 3 is the inverse of cluster 2 – symptoms are generally slightly worse than the mean, except for physical function which is above average. This cluster is younger than average (55 years), closest to diagnosis (mean 16 months) and has a higher proportion of women living alone. The proportion of those in full time employment is higher than average (18%) and the proportion unable to work because of illness is highest.

Cluster 4 shows high degrees of fatigue, limitation of physical, role, and social functioning, but a lesser impact on emotional and cognitive function. As with cluster 3, this cluster has a higher than average proportion of women in full time employment, although average age is closer to the group mean at 60 years and a higher proportion of women are retired than cluster 3. Also in contrast to cluster 3, the time since diagnosis is longer.

In clusters 5 and 6, which describe the most severe problems, patterns differ. Cluster 5 is characterised by fatigue, relatively severe sleep disturbance and high levels of emotional and cognitive symptoms. Physical function is relatively less severely impaired. Gastrointestinal disturbances (anorexia, constipation, nausea and vomiting) are worse than average. Although cluster 5 includes women at a younger age (mean 49.8 years), with higher educational status, higher proportion of local disease and better performance status, this group also has the highest proportion of women who are unable to work because of illness. This cluster represents

women who are disproportionately affected by psychological aspects of disease.

Cluster 6 describes high levels of physical, role and social impairment, though the latter are less severely affected than in cluster 5. Emotional and cognitive function is worse than all other clusters except cluster 5. The average age is older than the overall mean, at 66 years with the highest proportion of metastatic disease. Cluster 6 describes a greater impact on physical ability, fatigue and the ability to carry out activities of daily living, but a less impact on sleep, psychological symptoms and cognition than cluster 5.

### 3.2. Results of preference elicitation

Thirty-nine (35%) panel members participated. The characteristics of respondents are reported in Table 3.

Table 4 reports the utility values obtained for each of the health states after removal of inconsistent responses. The

**Table 3 – Characteristics of preference study respondents**

Characteristic	N (%) <sup>a</sup>
Sex	
Male	21 (53.8%)
Female	18 (46.2%)
Age	
Mean (SD)	49.7 (13.0) years
Median (range)	53 (20–69) years
Occupation	
Student	1 (2.6%)
Full time employment	16 (41.0%)
Part time employment	5 (12.8%)
Unemployed	0
Retired	11 (28.2%)
Other	1 (2.6%)
Unknown	5 (12.8%)
Marital status	
Married	27 (69.2%)
Single	8 (20.5%)
Unknown	4 (10.3%)
Socioeconomic deprivation	
High	7 (17.9%, 95% confidence interval (CI) 7.5–33.5%)
Mid	15 (38.5%, 95% CI 23.4–55.4%)
Low	17 (43.6%, 95% CI 27.8–60.4%)

<sup>a</sup> Except age, as indicated.

**Table 4 – Utilities for ovarian cancer states and global QoL scores**

Cluster	Mean	SD	Median	Min	Max	Global QoL domain score
1	0.977	0.044	0.995	0.775	1	78.12
2	0.930	0.071	0.96	0.675	0.990	67.10
3	0.886	0.139	0.955	0.325	0.990	56.53
4	0.817	0.175	0.875	0.225	0.985	49.43
5	0.788	0.189	0.875	0.125	0.980	46.10
6	0.694	0.221	0.775	0.125	0.970	30.31

global QoL domain scores and utilities for each cluster show a very close correspondence. Not only is the rank order identical, but also the decrements in utility/QoL shown between successively worse states, i.e. moving from cluster 1 to cluster 6, are of a similar magnitude.

Twelve unambiguous logically ordered pairings of health state descriptions were identified, giving 468 values to consider in the analysis of logical consistency. Only 41% (8.8%) of responses were logically inconsistent, of which 31 (76%) were tied. Not surprisingly, inconsistent responses were more common between states closer in terms of severity (e.g. 23% of responses to clusters 1 and 2 were tied compared to no inconsistent responses in the pairing of cluster 1 and cluster 6). Over all inconsistent responses, the mean size of the discrepancy in utility was 0.007. The difference in mean values with and without inconsistent responses ranged from -0.007 (cluster 1) to 0.012 (cluster 6).

#### 4. Discussion

Using an individual patient set of EORTC QLQ-C30 and clinical data, we have identified clinically and statistically coherent clusters, which describe quality of life in advanced ovarian cancer. The population, though small, is likely to be representative of patients undergoing chemotherapy. Using a panel of members of the public, we have estimated the utility associated with these different patterns of quality of life impact as between 0.977 and 0.694. As might be expected, as the complexity and severity of quality of life impairment increases, the preferences of respondents show more dispersion. Using members of the public means values conform to the requirements of international guidelines<sup>3,4</sup> and the data could be used in future syntheses of research (i.e. decision analytic modelling studies) on new treatments for advanced ovarian cancer.

The utility values obtained here are similar to those mentioned in previous studies, although somewhat higher. For example, Tengs et al., in a very wide review of utilities, report a range of 0.37–0.84 for ovarian cancer.<sup>13</sup> Comparison between studies is complicated by a number of methodological factors. In previous studies, the time trade-off method for utility measurement has been used, which is likely to result in lower estimates than the standard gamble.<sup>31</sup> Patient values, as used in some studies,<sup>9,10</sup> may be higher than those from non-sufferers due to adaptation. Furthermore, reporting of methods for health state development are limited in previous studies and do not always meet suggested best practice.<sup>32</sup> Finally, the specific methods of health state valuation used in previous studies were sometimes limited, e.g. very short time horizon for time trade-off.<sup>10</sup>

This is the first application of data clustering methods to enable utility estimation in oncology. This data-driven approach identifies 'prototypical' QoL experiences and allows a more complex picture of impact to emerge. The utilities are based on a validated cancer outcome measure and so reflect the particular experiences of women with the condition more specifically than would be expected

with a generic measure such as the EQ5D which, for example, does not include fatigue, a particularly important symptom in this condition. When combined with valuation by members of the general public, this approach allows the requirements of utility assessment for policy making to be based on a more appropriate measure of patient experience.

The clusters, which are defined using the entire dataset, show that the preferences of the general public on quality of life impact correspond, in terms of rank, to the experience of patients, demonstrating that this method preserves the ordinal measurement properties of the EORTC instrument in patients with ovarian cancer.

Our study has some limitations. The sample was small and followed up for a relatively short period. Because patients were being considered for chemotherapy, performance status was relatively good, e.g. there were no women with PS = 4. This may further explain the limited impairment in clusters 1 and 2 and consequent high utility values.

Although the health state descriptions are based on a validated instrument, and have, we believe, *prima facie* advantages over generic instruments in terms of richness of description, this may come at a cost of cognitive challenge to respondents in the preference study. However, validation of the utility data was reassuring, suggesting that the respondents were able to understand the states and express preferences accordingly.

The members of the public who provided utility estimates were not representative of the UK general population in terms of socio-economic status and representation of ethnic minorities. Although demographic characteristics may act as determinants of preferences,<sup>16,33</sup> other factors such as risk or time preference may also be important. Further methodological research into these areas is warranted, as is enquiry into the impact of different approaches to the development of health states. However, we believe that our findings will provide a valuable starting-point to clinicians, policy makers and health service researchers in the development of policy in advanced ovarian cancer.

#### Conflict of interest statement

None declared.

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## Appendix. Health State Descriptions

### CLUSTER 1

- Usually you have no physical problems. Rarely you have a little difficulty carrying out physical activities.
- Usually you feel a little tired but sometimes you feel no tiredness at all.
- Usually you have no problems in sleeping, but sometimes you have a little difficulty in sleeping.
- Usually you have no pain. Rarely you experience a little pain.
- Usually you have no shortness of breath. Rarely you feel a little breathless.
- Usually you have no difficulty with carrying out work, daily activities or leisure pursuits. Sometimes you have a little difficulty with these sorts of activities.
- Usually you have no limitations in family or social life. Sometimes you have a little limitation in these aspects of life.
- Usually you have no problems with worry, tenseness, irritability or a feeling of depression. Sometimes you have these sorts of problems a little.
- Usually you have no problems with memory or concentration. Rarely you experience these sorts of problems a little.
- Usually you have no problems with appetite or constipation. Rarely you would describe having 'a little' difficulty in these areas.
- You have no problems with nausea, vomiting or diarrhoea.

### CLUSTER 2

- Usually you have no physical problems. Sometimes you experience a little limitation and rarely you are limited quite a bit.
- Usually you feel a little tired. Rarely you have no tiredness.
- Usually you have no problems in sleeping. Sometimes you have a little difficulty.
- Usually you have no pain. Sometimes you have a little pain.
- Usually you have no shortness of breath, but sometimes you feel a little breathless.
- Usually you have a little difficulty with carrying out work, daily activities or leisure pursuits. Rarely you have quite a bit of limitation in these areas.
- Usually you have a little limitation in family or social life, but sometimes you have no problems in these areas.
- Usually you have no worry, tenseness, irritability or depression, but sometimes you have these sorts of problems a little.
- Usually you have no problems with memory or concentration. Sometimes you have these sorts of problems a little.
- Usually you have no problems with appetite or constipation. Rarely you would describe having 'a little' difficulty in these areas.
- Rarely you have a little nausea, vomiting or diarrhoea.

### CLUSTER 3

- Usually you have no physical problems. Sometimes you experience a little limitation and rarely you are limited quite a bit.
- Usually you feel a little tired. Sometimes you are tired quite a bit
- Sometimes you have no difficulty in sleeping, but usually you have a little difficulty. Rarely you have quite a bit of problems in sleeping.
- You have pain more often than not. Usually this is only a little pain, rarely it may be quite a bit.
- Usually you feel a little short of breath but sometimes you have no breathlessness.
- Usually you have have a little difficulty in working or carrying out daily or leisure activities, but this is variable. Rarely you have no limitations, or quite a bit of limitation in these areas of life.
- Usually you have a little limitation in family or social life. Sometimes you have no problems in these areas and rarely you are limited quite a bit.
- Usually you feel a little worried, tense, irritable or depressed. Rarely these feelings affect you quite a bit and rarely you have no feelings like these.
- Usually you have a little difficulty with memory or concentration, but sometimes you have no problems in these areas.
- Usually you have no problems with appetite or constipation, but sometimes you have a little difficulty. Rarely these problems affect you quite a bit.
- Usually you have no nausea, vomiting or diarrhoea. Rarely these problems affect you a little.

### CLUSTER 4

- Usually you have quite a bit of limitation in physical function. But this varies, from having no problems to being affected very much.
- Usually you feel quite a bit of tiredness. Sometimes you are only affected a little, and rarely you experience this problem very much.
- Usually your sleep is not impaired, but sometimes you have a little, or quite a lot of problems in sleeping.
- Usually you have no pain, but sometimes you have a little, and rarely you have quite a bit.
- Usually you feel a little short of breath. Sometimes you have no breathlessness and rarely you have quite a bit.
- Usually your ability to work or carry out daily or leisure activities is limited very much. Sometimes it is limited only quite a bit, but rarely only a little.
- Usually your family and social life are limited quite a bit. Sometimes they are restricted very much and rarely only a little.
- Usually you feel a little worried, tense, irritable or depressed. Sometimes you have no feelings like these, but rarely they may affect you quite a bit.
- Usually you have no problems with memory or concentration but sometimes you are affected a little, and rarely quite a bit.

- Usually you have no difficulties with appetite or constipation. Sometimes these problems affect you a little and rarely quite a bit.
- Usually you have no problems with nausea, vomiting or diarrhoea. Rarely you have a little difficulty in these areas.

## CLUSTER 5

- Your physical ability varies. Mostly you have no problems but sometimes you have a little, or quite a bit of difficulty with physical function.
- Usually you feel quite a bit tired. Rarely you feel only a little fatigue.
- Usually your sleep is affected very much. Sometimes it is only affected a little and rarely quite a bit.
- Usually you have a little pain. Rarely you have none. Sometimes you have quite a bit of pain.
- Usually you feel a little breathless. Sometimes you have no shortness of breath and rarely you have quite a bit.
- Usually your ability to work or carry out daily or leisure activities is limited quite a bit, but sometimes only a little.
- Usually your family and social life are limited quite a bit but sometimes they are affected only a little.
- Usually you feel quite a bit worried, tense, irritable or depressed. Sometimes these feelings affect you only a little, but rarely you feel them very much.
- Usually you have a little difficulty with memory or concentration. Sometimes you have quite a bit of problems in these areas but rarely you have none.
- Usually you have a little difficulty with appetite or constipation. Rarely these problems affect you quite a bit or very much.
- Usually you have no problems with nausea, vomiting or diarrhoea. Sometimes you have a little difficulty in these areas.

## CLUSTER 6

- Usually your physical abilities are very much limited.
- Usually you feel tired: either quite a bit or very much.
- It is rare for you to have no problems in sleeping. Usually your sleep is affected quite a bit; sometimes it is only affected a little and rarely quite a bit.
- Usually you have a little pain. Rarely you have none. Sometimes the pain affects you quite a bit or very much.
- Usually you feel breathless, which ranges from a little to very much.
- Usually your ability to work or carry out daily or leisure activities is limited very much, but sometimes only quite a bit.
- Usually your family and social life are limited quite a bit, but sometimes they are affected very much. Rarely they are only affected a little.
- Usually you feel a little worried, tense, irritable or depressed. Sometimes these feelings affect you quite a bit.
- Usually you have a little difficulty with memory or concentration. Sometimes you have no problems in these areas but rarely you have quite a bit.

- Usually you have a little difficulty with appetite or constipation.
- Usually you have no problems with nausea, vomiting or diarrhoea. Sometimes you have a little difficulty in these areas and rarely you are affected quite a bit.

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