University College London Hospitals NHS Foundation Trust

Full Title
Evaluating Patient Preferences for the Treatment of Localized Prostate Cancer
A Discrete Choice Experiment

Acronym and Short Title
COMPARe study: **COM**paring treatment options for **P**rost**A**te cance**R**

Trial registration
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UCH/UCL Joint Biomedical Unit Protocol code
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Signatures

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

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Abbreviations

PSA - Prostate Specific Antigen
DCE – Discrete Choice Experiment
MRI – Magnetic Resonance Imaging
CT – Computed Tomography
HIFU – High Intensity Focused Ultrasound

1 Study Summary

Acronym and Short Title	**COMPAR**e study: **COM**paring treatment options for **P**rost**A**te cance**R**
Objective	To evaluate the importance of prostate cancer treatment characteristics to men with localised prostate cancer
Design	Multicentre, prospective, cohort, discrete choice experiment
Population	Men between 45-80 years of age with organ-confined, histologically proven adenocarcinoma of the prostate
Sample Size	Initial n=5 in pilot stage, main stage n=432
Planned Clinical Start	2Q 2012
Planned Clinical End	3Q 2013
Sponsor	University College London
Study Intervention	Initial Stage: written questionnaire and semi-structured interview (one centre) Second Stage: written questionnaire
Primary Outcomes	Men's preferences for, and trade-offs between, the attributes of sexual function; urinary function; return to normal activities; aim of treatment; retreatment rate; and mortality rate
Secondary Outcomes	To determine the correlation between attributes that are important to men and baseline demographics, functional status and disease risk characteristics To determine whether men will accept randomisation between standard of practice treatment options and novel minimally-invasive therapies

2 Background

Traditionally the extent of patients' involvement in medical decision-making has been minimal. This has been true at both the micro-level of the patient consultation with a doctor and the macro-level of health economics and service planning. Ascertaining patients' views allows such information to be used for health planning and priority setting as it reflects real-life decisions that men face once diagnosed. This is essential, particularly in light of the myriad of treatment options and research avenues available for men with prostate cancer and the requirement for healthcare systems to limit the availability of some treatments. Discrete choice experiments represent a validated method for obtaining information about what is important for patients and health service users, in this case men in prostate cancer treatments, and may prove useful for bodies such as the National Institute of Clinical and Health Excellence (NICE) which issue guidelines for clinicians and funding bodies on what should and should not have priority in funding. Equally, the data from discrete choice experiments can aid clinicians and researchers in constructing new research questions that have relevance to priorities for men.

2.1 Prostate Cancer

The current options: Men with localised prostate cancer have to choose between active surveillance or radical therapy. Radical therapy involves a variety of treatment options that range from radiotherapy (external beam, brachytherapy) to surgery (laparoscopic, robotic, open) as well as minimally-invasive interventions (cryosurgery, high intensity focused ultrasound). The participation of men in decision-making is key since the differences between surveillance and radical therapies in terms of cancer control is small.

Active Surveillance: Active surveilllance involves monitoring the disease with clinical examination, prostate specific antigen (PSA) blood tests and yearly biopsies to determine whether the cancer is changing or progressing. If progression occurs, men are offered radical therapy, which happens in one-third of men who are offered active surveillance. A Randomised Controlled Trial comparing surgery and watchful waiting showed the absolute difference in preventing cancer mortality within 14 years was 5% [1,2]. This is probably smaller in men diagnosed in the modern era due to screening practices which detect lower risk disease in younger men. Indeed, the absolute risk reduction of surgery or radiotherapy in preventing prostate cancer mortality for the PSA screened population compared to active surveillance within 10-15 years is unknown and subject to long-term randomised controlled trials. The recent European screening study demonstrated a reduction in prostate cancer specific mortality from PSA screening and treatment. Commentators have called for caution in implementing these findings as the harms associated with a screening strategy are over-diagnosis, over-treatment and treatment-related harms. Currently, of 1,410 men screened, 48 need to be diagnosed and treated so that one cancer-related death is avoided over a 9 year period [3, 4].

Radical Therapy: The harm from radical therapy can be significant. These side-effects occur as a result of the treatment causing damage to structures adjacent to the prostate because the whole gland is treated irrespective of the volume or location of cancer. These structure include the bladder neck, external urinary sphincter, neurovascular bundles and rectum. Radiotherapy causes moderate rectal side-effects (diarrhoea, bleeding, pain) and urinary incontinence in 5-20% of men. Surgery causes long term urinary symptoms in one third. Both modalities cause

impotence in 30-90% of men who had erections beforehand [5, 6]. Greater specification of radiotherapy (e.g., intensity modulated radiotherapy, robotic/laparoscopic radical prostatectomy) have not lead to significant improvements in long-term genitourinary toxicity [7, 8]. A number of minimally-invasive therapies have also emerged in the treatment of localised prostate cancer such as high intensity focused ultrasound, cryotherapy and photodynamic therapy. When used in the setting of ablating the whole gland there has been variable benefit in terms of reducing side-effects, again with little overall improvement in the rate of long-term side-effect [9].

Focal therapy: More recently, the concept of focal therapy has been proposed as a way of managing localised prostate cancer. Focal therapy involves treating only the areas of cancer and leaving normal tissue or insignificant cancers untreated. Focal therapy in prostate cancer mirrors the change from mastectomy to lumpectomy seen in breast cancer. In other words, by avoiding the bladder-neck, rectum, external sphincter and at least one neurovascular bundle, side-effects could be reduced [10, 11]. Cancer control would also need to be at acceptable levels. Focal therapy using cryosurgery has early results. These demonstrate impotence rates of approximately 5-15% [12, 13, 14]. However, these early studies have important weaknesses that make their acceptability into normal practice limited. These weaknesses are that the studies were not clinical trials approved by ethical committees and therefore not monitored closely. In addition, other weaknesses include poor definition of the population of men treated, poor reporting of how patients were selected and inconsistent reporting of side-effect data. For this reason, a number of ethics committee approved clinical trials in focal therapy of prostate cancer to investigate early side-effect rates are near completion in London (National Cancer Research Network approved). Results from the first trial show that 90-95% of men treated in a focal manner have return of normal urinary and erectile function within 3-6 months of treatment [15].

Long term data are not yet available on cancer control although the short to medium term PSA kinetics and post-treatment biopsy rates in these series show no evidence of disease in 80-90%. However, it may be argued that the efficacy of focal therapy may be less than radical therapy because untreated tissue is left, which may demonstrate progression of small foci of cancer initially missed or new cancers emerging as a result of field change. Such a presumed lower efficacy may be acceptable to men if, 1) the treatment carries significantly fewer side-effects, 2) the difference in efficacy between focal therapy and radical therapy is small, and 3) any recurrence of disease can be treated without significant loss in cancer control or additional harm. There has been very little research to determine to what extent men will choose the strengths and weaknesses of one treatment over a different set of strengths and weaknesses of another treatment when making a choice between them. Such an analysis can be made using a discrete choice experiment.

Randomised Controllled Trial Feasibility: Randomised trials in prostate cancer which began over a decade ago, such as PIVOT [16], ProTect and the Scandinavian SPCG-4 trial have been successful in recruitment but have required a large infrastructure and much expense to conduct and complete. Indeed, Pivot required 52 centres that screened over 13,000 men, of which 5,000 met entry criteria and 731 were eventually randomized. In the case of ProTect, dedicated nursing staff to counsel patients regarding randomization were needed [17,18,19]. However, more recently randomized trial designs in prostate cancer have had problems in recruitment

(Sabre, ProStart, Canadian randomized trial comparing external beam radiotherapy with cryosurgery, SPIRIT) [20,21]. Randomized controlled trials in which surgery is compared to conservative measures can be difficult to recruit [22]. In addition, many have argued that as currently conducted, RCTs are inefficient, complex, time-consuming and expensive and report outcomes that have little relevance at the time of reporting [23]. The need for trials to be efficient, cost-effective and future-proof by capitalizing on existing resource and having a pragmatic and adaptive approach to design is key to delivering answers to healthcare services on comparative effectiveness of novel interventions in a timely fashion. Necessary attributes comprise broad entry criteria that are representative of routine practice and a pragmatic design that mimics real life practice as much as is possible. One of the main barriers to recruitment is that the equipoise of the patients considering enrollment and clinicians advising them does not mirror the equipoise in those who designed the study [24,25,26]. Pragmatic trials that have an adaptive approach overcome some of the issues related to external validity and equipoise by attempting to reflect decisions, treatment options, follow-up and outcome measures that fall within standard clinical practice and mirror the choices men might make when faced with a randomized controlled trial.

2.2 Discrete Choice Experiments

Individuals' preferences for alternative treatments for prostate cancer need to be considered based on the different characteristics of the available treatments (surveillance, radical and focal therapies). Discrete choice experiments (DCEs) are an approach to preference elicitation that is widely applied in health care applications [27]. This approach identifies the key characteristics of alternative treatments and selects a series of levels for each. The method is gaining wide-spread use in healthcare and has been applied successfully in several areas, including eliciting patients' and the community's preferences in the delivery of health services; determining optimal treatments for patients; evaluating alternatives within randomized controlled trials; and establishing patients' preferences in the doctor-patient relationship.

In the case of prostate cancer treatments key characteristics are based on genitourinary side-effects, surveillance burden and cancer control. These can be described by X number of levels (X1, X2, X3) representing percentages or rates of a certain event or frequency of a certain test. The key characteristics are combined with different levels to form treatment profiles. Individuals are asked to choose between two or more treatment profiles. Individuals may be asked to make a series of such choices (up to 16 choices). The relative importance of characteristics to individuals and the risk-benefit trade-offs that individuals make between the characteristics are calculated based on these choices.

One DCE has been conducted using men who are faced with choices in advanced prostate cancer (conducted at University College London) [28]. This evaluated the following characteristics, based on androgen deprivation hormone treatment and radiotherapy, in men with locally advanced non-metastatic prostate cancer: diarrhoea, hot flushes, ability to maintain an erection, breast swelling or tenderness, physical energy, sex drive, life expectancy, and out of pocket expenses. These treatments are generally deferred for high-risk patients, especially in the case of hormonal ablation. The study showed that on average, they were most willing to give up life expectancy to avoid limitations in physical energy (mean three months) and least willing to trade life expectancy to avoid hot flushes (that result from hormone treatment).

Minimally-invasive and focal therapies are likely to be applied to low and intermediate risk groups where the therapeutic dilemma between surveillance and radical therapy is particularly polarized. The aforementioned study was not able to answer questions about the trade-offs men make when faced with the potential characteristics of these minimally-invasive therapies and standard of care. Nonetheless, it demonstrates that men are willing to contemplate trade-offs between life expectancy and the burden of side effects, such as limitations in physical energy. Our group has also carried out a DCE evaluating men's preferences in the medical treatment of benign prostatic hyperplasia (which causes obstructive urinary flow) demonstrating that men were willing to wait longer for therapeutic benefit if a particular drug gives rise to better symptom relief in the long term [29].

3. Objectives

3.1 Primary

Men's preferences for, and trade-offs between, the attributes of a) pre-treatment evaluation; b) sexual function; c) urinary function; d) return to normal activities; e) post-treatment frequency of biopsies; f) aim of therapy; g) retreatment rate; and h) mortality rate

3.2 Secondary

To determine the correlation between attributes that are important to men and baseline demographics, functional status and disease risk characteristics

To determine whether men will accept randomisation between standard of practice treatment options and novel minimally-invasive therapies

4. Study Design

This will be a cross-sectional questionnaire study. It will be divided into two stages, the initial pilot stage and then the main stage. Each stage will have specific consent form, patient information sheet and a questionnaire.

4.1 Initial Pilot Stage

This stage will include 5 men who will undergo interviews after they have had a chance to read the patient information sheet, look at the attributes and the questionnaire in its initial design. This will occur in only one centre, University College Hospital. A semi-structured interview will be used. Patients will be asked to look at a model questionnaire and make comments on the following:

1. Questionnaire prose to ensure clarity and precision
2. Questionnaire structure to ensure understanding and clarity of what is being asked
3. Whether the choices make sense and identify any specific attribute that is commonly not of importance to men
3. Acceptability of burden of questionnaire
4. Acceptability of asking about randomisation

5. Acceptability of asking patients to fill in functional status questionnaires and question on whether men would accept randomisation between each option

Interviews with patients will be recorded in writing in summary format. Common themes will be extracted. The responses and suggestions from this group will be used to develop the questionnaire in order to ensure that 1) any characteristics or levels that do not seem appropriate are removed or modified; 2) any additional characteristics or levels that are not in the questionnaire are included; 3) the questionnaire is understandable; and 4) any complex treatment information is explained in a simplified manner. **A second version of the questionnaire will be written for the main phase which will be subject to a submission to the ethics committee for approval as a substantial amendment. Versions of the PIS and Consent form will also be amended for the main stage and resubmitted for research ethics committee approval as a substantial amendment.**

4.2 Main Stage

Men will be recruited in this stage across a number of centres. They will be asked to fill in the finalised version of the questionnaire.

5. Study Group

Patients who have histologically confirmed prostate cancer which has not been treated and meeting the entry criteria will be approached for the study **at least 1 week after the diagnosis of prostate cancer is given to them**. They will be given as much time as they need to consider whether or not they wish to participate (minimum 24 hours). In the initial pilot stage, patients who wish to participate after reading the patient information sheet will be given a date for the interview (face-to-face or via telephone). In the main stage, patients who meet the eligibility criteria and are willing to participate will be given the questionnaire to fill in their own time either in the hospital clinic or in their own home. Informed consent will be signed before implementation of any study-related procedure.

6. Eligibility

6.1 Inclusion Criteria

- Men with a histological diagnosis of prostate cancer on trans-rectal or transperineal template prostate biopsies
- Gleason score ≤7
- Clinical stage ≤T2cNoMo (radiological T3a allowed)
- Serum PSA ≤15ng/ml
- Local staging imaging as per guidelines to demonstrate localised disease (this may include MRI, CT and/or bonescan)
- Signed informed consent by patient

6.2 Exclusion Criteria

- Men who have had previous radiation therapy
- Men who have had androgen suppression/hormone treatment within the previous 12 months for treating prostate cancer

- Men who have prostate surgery for cancer control e.g., radical prostatectomy, HIFU, cryosurgery, photodynamic therapy.

7. Discrete Choice Questionnaire Design

We have selected a number of attributes that apply to radical therapies and new minimally-invasive therapies. These attributes were selected by the investigators as clinically important within the literature, as well as a pre-pilot phase in which stake-holder groups (see response to REC, 10/02/2012) were approached for their detailed views and feedback. Further, all characteristics will be subject to an initial pilot stage in which a 5 men will be interviewed to determine whether such characteristics and their levels are appropriate and relevant to men with localised prostate cancer. This method of staged design has been described and accepted as good practice in DCEs [30,31,32,33].

7.1 Sexual health

This will include the ability to maintain an erection sufficient for intercourse. The definition of erectile function is variable and controversial. There are a number of elements to it. The literature on potency outcome refers to the percentage of men who have return of erectile function sufficient for intercourse at 12 months and is only relevant to those men who have good baseline function. Those who do not have return of function at this stage may have partial erections or no erections whatsoever, with the former having some degree of sexual satisfaction. Equally, it is known that prior to 12 months follow-up, the degree of impotence is much greater after radical therapy with most men impotent within the first 6 months. Early results from focal therapy show return of erections to normal levels in two-thirds of men within two weeks, and over 90% having erections sufficient for intercourse at 3-6 months. Further, ejaculatory function is affected in most men who have radical therapy with lack of semen production. With preservation of tissue in focal therapy, a significant proportion of men have wet ejaculations. Whether this is an important element of sexual function that will influence a man's preference for treatment is not known. These additional characteristics of this attribute will be explored in the pilot stage.

Levels to be used in active treatment options:

- Proportion of men able to maintain an erection sufficient for intercourse at 12 months (%)
  a. 50
  b. 65
  c. 80
  d. 90

7.2 Urinary function

Again, in the early post-radical therapy follow-up stage most men leak urine and require a number of pads every day with slow improvement over time after which leakage will require surgical correction. Continence outcome is again defined at 12 months and pad usage is the

most common characteristic evaluated. However, some men after radical surgery may wear one pad overnight or during the day, deemed the security pad, 'in case' they leak urine. These men are not counted within the literature as part of the incontinent group [34,35].

Levels to be used in active treatment options:

- Proportion of men who are incontinent and requiring at least 1 pad per day at 12 months (who were continent prior to treatment) (%)

a. 5
b. 10
c. 15
d. 20

7.3 Return to normal activities (e.g., work, gardening, sports, shopping)

This is a difficult characteristic to define precisely. Each treatment may or may not require anaesthetic; surgery will require incisions to the abdomen and may require admission to hospital for a number of days, whilst radiotherapy requires attendance to hospital every weekday over 5-7 weeks to give the full radiotherapy dose. Ablative therapy used for whole-gland treatment or focal therapy can be done as a day-case setting with shorter anaesthetic time. There will also be less trauma to the tissues due to the use of minimally-invasive techniques and therefore may allow return to normal activities sooner. However, normal activity will be problematic to define and this characteristic will be influenced by the genito-urinary side-effects described above (interaction). The initial phase of the study will need to carefully evaluate whether this characteristic can be truly differentiated from the others in a DCE.

Levels to be used in active treatment options:

- Average time until physically able to return to day-to-day activities (e.g. return to work, gardening, go to supermarket...)

a. 1 week
b. 1 month
c. 3 months
d. 6 months

7.4 Aim of Treatment

In patients undergoing radical prostatectomy, the proportion of patients with unifocal disease (just one cancer area in the prostate) varies from 13-38% with variations largely dependent on patient selection [36,37]. Wise et al [38] analysed radical prostatectomy specimens over a 4 year period in 3mm step-sections and found that in those with multi-focal lesions progression free-survival was associated with the index (largest lesion) cancer volume, but not with secondary tumours. Arora et al [39] reported that in 97% of cases who had undergone radical prostatectomies for multifocal disease the primary Gleason grade of the index tumour was the same as the overall primary Gleason grade with Ohori et al [40] reporting that 80% of tumour volume arose from the index tumour. Extracapsular extension was present in 28% of patients,

of which 92% arose from the largest index lesion. Other studies have provided further support for the thinking that disease progression is related to the main or index lesion and not the secondary lesions [41,42,43,44]. These studies provide the rationale for targeting the index lesion alone thereby potentially decreasing total tumour volume and eliminating the most likely source of extracapsular extension [45]. Focal ablation of the index lesion proposes that not all the disease is treated since most men are likely to have multifocal prostate cancer which if treated with whole-gland treatment is likely to severely curtail quality of life. The objective of focal index lesion ablation is to delay disease progression by ablation of the index tumour that is likely responsible for disease progression, so that further treatments (such as androgen deprivation, surgery, radiotherapy) could be delayed.

Levels to be used in active treatment options:

- The aim of treatment will be for

a. all cancer areas treated with all normal tissue
b. all cancer areas treated but not normal areas of tissue
c. all large high risk areas of cancer treated, but small low risk areas are left behind for surveillance
d. all large high risk areas of cancer are treated, but small medium risk areas of cancer are put on surveillance.

7.5 Cancer Control

Cancer outcomes in prostate cancer are difficult to define because the natural history of the disease is long and deaths from prostate cancer are only seen after 10-15 years in the majority of those diagnosed in the current era. Clinicians tend to use surrogate markers of long-term outcome such as PSA levels after treatment, but these are not robust enough to be used on their own. Further, these will be difficult to evaluate in a DCE because definitions of what constitutes a good PSA outcome differ in radiotherapy and surgery. In focal therapy, PSA outcome will be problematic because normal tissue (which releases PSA) is left behind and there is a natural tendency for this tissue to grow with age and release PSA into the blood. The common cancer outcomes that can be applied to all treatments are need for further treatment (due to disease progression or initial failure of treatment), metastases and death from cancer. After radiotherapy, 20-30% of men may require salvage treatment (using surgery to remove the prostate or minimally-invasive treatments such as HIFU or cryosurgery to ablate the gland). After surgery, 20-30% of men may require adjuvant radiotherapy because of positive margins in the tissue removed. Both treatments may fail in the long-term and require hormonal treatment or chemotherapy. Additional therapies usually carry greater side-effects and healthcare burden and may be an important characteristic that men consider when choosing treatments. Ablative treatments that carry out whole-gland or focal therapy may require any form of salvage treatment or it may be possible to carry out further focal therapy, if a new cancer forms in untreated tissue which is involves a small area.

Levels to be used in active treatment options:

- Chance of needing more treatment within the next 10 years (%)

a. 10
b. 20
c. 30

d. 40

- Chance of cancer-related death within 10-15 years (%)

a. 5
b. 10
c. 15
d. 20

7.8 Selection of Characteristics

The key characteristics are combined with different levels to form treatment profiles. The combination of 6 attributes with their levels as described below will lead to 96 choices in total. Individuals will be asked to choose between two treatment profiles with up to 8 choices in total per respondent, so that respondents are not overburdened with the choices they make. The exact burden per respondent will be determined in the pilot stage. The relative importance of characteristics to individuals and the risk-benefit trade-offs that individuals make between the characteristics are calculated based on individuals' choices. These attributes were selected by the investigators as clinically important within the literature, and subject to a pre-pilot phase with discussions with stakeholder groups and individuals. All characteristics will be validated in an initial stage during which 5 men will participate in interviews to determine the treatment characteristics important to them. This stage of the study will also pre-test the survey instrument and modify the design if necessary. The initial pilot phase will include 5 men. This phase will also allow the survey instrument to be pretested in order to optimise questionnaire design. In the final stage, 432 respondents will be required with recruitment occurring in the collaborating centres. The final number of respondents will be determined by the questionnaire attributes and levels since the power to determine the importance of attributes depends on the number of attributes we include in the final design and the levels for each.

7.11 Patient Choice Questionnaire

An example of a patient choice that will be used in the questionnaire is shown in appendix 2. In addition, baseline demographics such as age, working/retired/unemployed/household income, prostate cancer characteristics (PSA level, Gleason grade, stage) and baseline functional status (genitourinary function using patient-reported outcomes) and final treatment choice will also be collected in order to ascertain whether there is any relationship and association between patient preferences for treatment and these baseline demographics. Men will also be asked whether they would consider a randomisation between a particular set of options, as this will help guide the need and feasibility of future clinical trials in this area. This questionnaire will be subject to changes as a result of any suggestions from the initial pilot stage.

8. Recruitment of Patients

All men with localised prostate cancer diagnosis made at the hospital or referred to the hospital will be identified prior to the man having made a treatment decision but at least one week after the initial clinic appointment in which the diagnosis was given. Each hospital's researcher will identify patients through the multidisciplinary team meeting and the coordinator for this.

Patients will also be identified in clinic if they have been referred from outside of the hospital. This will be carried out by doctors and nurses who will then give the PIS to men if they are interested to fill in at home or in clinic (in the main stage). There will be no payment for patients.

9. Data collection

Data on age, ethnic group, blood results (PSA), histology outcomes (burden of cancer, Gleason grade), and stage of disease on imaging/clinical examination as well as data on co-morbidities and medication will be collected. All data points from the questionnaires will also be collected on the case report forms. Only one time point will be used to collect data.

10. Data Handling and Record Keeping

Data will be held according to the Data Protection Act 1998 and anonymised as necessary. Each participant will be given a study number and this will be used on all their study records. The code for this number will be known to Professor Mark Emberton, Mr Hashim U Ahmed and Dr Verity Watson. All clinical information will be kept in study records and analysed at the end of the study. The records will be kept in a secure manner in the research offices with access available to named individuals from the study group only. The data will be retained for a minimum of 10 years after the end of the study. Any information which leaves the hospital/surgery will be anonymised. The Investigator is ready to receive and cooperate with any auditor designated by the Sponsor to ascertain the performance of the study according to Research Governance. Archiving will be carried out at the clinical sites in an appropriate room designed for record retention. This room is locked around the clock, and includes fire-detection monitoring. The Investigator will retain originals of the approved project protocol, patients' participation agreements, relevant source documents (patient questionnaires and protocol files, protocol documents) and all other supporting documentation related to the project. He will make these files available for inspection by an authorized representative of the Sponsor or the regulatory authorities upon reasonable request. All study-related records, including source documents, case report forms, and regulatory documents, will be retained for at least 20 years after the end of the study. These documents should be retained for a longer period if demanded by regulatory requirements or by an agreement with the Sponsor. All electronic hardware and records will be heavily encrypted.

11. Statistics

11.1 Sample Size Calculation

The DCE data will be analysed using regression methods, thus the appropriate sample size must be calculated. It is desirable that the sample size permits choice probabilities to be modelled with a given level of accuracy. Following Louviere et al (2000) [46], p is defined as the population proportion of respondents selecting an alternative, q is $(1-p)$, and r is the number of questions (choice sets) per individual. The minimum sample required to estimate p within a percent of the true value with a probability of a or greater is given by:

$$n \geq \frac{q}{rpa^2}\Phi^{-1}\left(\frac{1+\alpha}{2}\right)$$

Where Φ^{-1} is the inverse of the cumulative normal distribution function.

To be conservative we calculate the sample size on the assumption that p=0.1, in most cases more than 10% of respondents will prefer one alternative in the DCE over the other. Each respondent will be presented with a minimum of 8 choices. Thus, to estimate *p* within 10% of the true value with a probability of 95%, the sample size should be 432 or greater.

11.2 Planned analysis

From the results of the DCE it is possible to estimate the relative importance of attributes, the trade-offs that individuals are willing to make between attributes of an intervention or treatment, that is how much of one attribute respondents are willing to give up for improvements in another. Responses from the DCE will be analyzed using multinomial logit regression techniques. An equation was estimated to estimate treatment utility characterized by any combination of attributes and levels will be developed. The coefficients preceding each attribute in the equation will indicate the relative importance of each attribute when respondents were choosing between treatments. The sign of the coefficients will indicate whether the attribute had a positive or negative effect on respondent utility. Trade-offs that respondents make between treatments attributes when making choices are represented by the ratio of the coefficients. Subgroup analysis will be carried out to investigate the influence of baseline co-morbidity scores (using ASA grade and the commonly used Charlson score of comorbidity index), functional scores as well as demographics, on their preferences. Multinomial logit regressions will be run using responses from men categorised into a range of ages and functional score groups with. Results across subgroups will be compared using the likelihood ratio test.

12. Research Governance

12.1 Compliance

We anticipate a high compliance rate once the consent form has been signed, as patients will be encouraged to fill in the questionnaire at the same time. Those patients who sign the consent form and then do not fill in the questionnaire will be withdrawn from the study and additional patients will be recruited in order to ensure that the required number of patients is recruited. A 'withdrawal from study' form will be filled in and filed in the case report form and the patient's medical records.

12.2 Ethics

The study will be conducted in accordance with the principles of the Declaration of Helsinki, the Research Governance Framework (version 2) and local laws. This Protocol, its associated Patient Information Sheet and Informed Consent form and any advertising must be reviewed and approved by the appropriate Research Ethics Committee (REC). All protocol amendments must be approved by the REC prior to their implementation. A copy of the letter signed by the Chairman of the REC to the Chief Investigator indicating REC approval of the protocol must be

received by the sponsor and maintained in the study file prior to study initiation. The trial will be monitored according to a monitoring plan agreed by the sponsor. MHRA approval is not required. Approval from each NHS Trust and other hospitals' delegated committees will be required.

12.3 Adverse Event Reporting

Although this study is very low risk for adverse events related to administration of the questionnaire, a mechanism for reporting adverse events which occur between signing consent and the interview, or filling in the questionnaire, will be in place. All Serious Adverse Events will be reported in writing to the ethics committee and UCH/UCL Joint Biomedical Unit, the sponsor.

13. Liabilities and Insurance

UCL will provide insurance against claims for compensation for injury caused by participation in this study (i.e. non-negligent compensation). Patients wishing to make a claim should address their complaint to the Chief Investigator in the first instance. In the event of negligent harm occurring, no special compensation arrangements exist. However, if a patient is harmed due to someone's negligence, they may have grounds for a legal action but may have to pay for it. Regardless of this, if patients wish to complain, or have any concerns about any aspect of the way they have been approached or treated during the course of the study, the normal National Health Service complaint mechanisms are available to them.

14. Reporting and dissemination of results

The data will be analysed and any results may be published in medical journals and submitted for conference presentations. If the data is to be used in any other way in future studies then approval will be sought from the local Research Ethics Committee. All publications arising from this work will require the agreement of the principal investigators.

15. References

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