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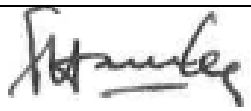
Prostate Testing for Cancer and Treatment (ProtecT) Study

Statistical Analysis Plan – **15 years**

Version 1.0 19th November 2020)

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Chris Metcalfe	Author		19.11.2020
Tim Peters	Statistical Reviewer		19.11.2020
Freddie Hamdy	Chief Investigator		19.11.2020

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1. INTRODUCTION & PURPOSE

*This document details the statistical analysis proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the median **15-year** results from the **Prostate Testing for Cancer and Treatment (ProtecT) Study**. As far as possible this plan will follow the approaches in the main ProtecT statistical analysis plan written for the primary analysis of median 10-year follow-up, which is available at*: https://njl-admin.nihr.ac.uk/document/download/2021093

The purpose of the plan is to:

1. Make explicit the details of the planned analysis, as agreed with the Trial Steering Committee.

2. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of *a priori* and post-hoc analyses is appropriate.

3. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence, or to replicate the analyses

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

IMPORTANT: *This synopsis is purely to provide background information for those reading the statistical analysis plan. It does not replace the study protocol; the current version of which must be consulted for all other purposes.*

2.1. Trial objectives and aims

The ProtecT trial was designed in the late 1990s and early 2000s to compare the major conventional treatments for patients with clinically localised prostate cancer detected through population-based PSA testing. The three treatments were radical prostatectomy, external beam three-dimensional (3D) conformal radiotherapy, and active monitoring.

2.1.1. Primary objective

In men with localised prostate cancer detected through population-based PSA testing, to compare definite or probable prostate cancer specific mortality (including definite or probable intervention related mortality) at a median of 10 years following random allocation to radical prostatectomy, external beam three dimensional (3D) conformal radiotherapy, and active monitoring.

2.1.2. Secondary objectives

To make the same comparison on a number of secondary outcome measures, including overall survival, clinical disease progression, treatment complications, lower urinary tract symptoms, quality of life, and sexual function. To estimate the resource use and costs of case-finding, treatment and follow-up, and to compare costs and outcomes of treatment in terms of survival and health related quality of life.

2.2. Trial design and configuration

A three parallel groups randomised controlled trial.

2.3. Trial centres

Recruitment to the trial took place at general practices in and around nine study centres across the UK: Newcastle, Sheffield, Bristol, Cardiff, Edinburgh, Birmingham, Leicester, Cambridge, and Leeds.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

- Men
- Age 50-69 years on the date of preparation at the general practice of the list of potential participants
- Able to give written informed consent to participate
- Fit for any of the three treatments and with a life expectancy of at least 10 years
- Registration with the participating general practice on the date of the PCC
- For randomisation: clinically localized prostate cancer (confirmed by isotope bone scan in men with PSA of 10ng/L or more) diagnosed by 10-core biopsy following a PSA level of 3ng/L or more.

2.4.2. Exclusion criteria

- Concomitant or past malignancies (other than a small treated skin cancer)
- Prior treatment for prostate malignancy
- Serious cardiac or respiratory problems in the previous 12 months of the PCC, e.g. stroke, MI, heart failure, COPD
- Kidney dialyses or transplantation
- Bilateral hip replacement
- Previous entry to the ProtecT study at a prior general practice
- PSA 20ng/L or more at diagnosis

2.5. Description of interventions

The **Active Monitoring Protocol** aimed to avoid immediate radical treatment whilst assessing the disease over time, with a review and the opportunity for radical treatment if there was evidence of disease progression. PSA levels were measured and reviewed every three months in the first year and twice yearly thereafter. Changes in PSA levels were assessed, and a rise of at least 50% over the previous 12 months triggered repeat testing within six to nine weeks. If the PSA levels were persistently raised, or th e patient had other concerns, a review appointment was made to consider treatment options.

The **Radiotherapy Protocol** began with neoadjuvant androgen suppression, given for three to six months before and concomitantly with 3D-conformal radiation therapy delivered at 74 Gy in 37 fractions.

Surgery was a radical retropubic prostatectomy procedure. The surgical approach was left to the discretion of the surgeon, and was most commonly open, but laparoscopic, or robot-assisted approaches were permitted from 2003.

2.6. Randomisation procedures

Randomisation was stratified by centre with stochastic minimization by age at invitation, Gleason score (primary and secondary grades), and mean of baseline and first biopsy PSA results. Men who declined randomisation were offered identical follow-up and formed an observational patient preference cohort.

2.7. Blinding

The process used to assess cause of death was adapted from the PLCO algorithm and ERSPC process. The medical records of deceased participants were summarised by trained researchers, anonymised and reviewed by an independent endpoint committee. Table 1 presents the classification of deaths by study arm.

2.8. Trial committees

For the current period of follow-up, ProtecT has a Trial Steering Committee, chaired by Professor Deborah Ashby (Imperial College).

2.9. Outcome measures

2.9.1. Primary outcome

The primary outcome is definite or probable prostate cancer mortality, including intervention-related deaths, at a median 10 years' follow-up.

We will repeat the analysis of definite or probable prostate cancer mortality, including intervention-related deaths, at 10 years (with all participating men having more than 10 years' follow-up) and at the median 15 years' follow-up.

As previously the plan is for the primary outcome measure to be determined by the independent cause of death committee. If this proves not possible, we will rely on certified underlying cause of death where necessary.

2.9.2. Secondary outcomes

Secondary clinical and patient-reported outcomes to be presented in the 15-year results papers are:

- *overall mortality*

- *metastatic disease*
- *clinical disease progression*
- *initiation of long-term hormone therapy*
- *patient reported outcomes (PROMs)*

Metastatic disease is defined as positive imaging showing bony, visceral and/or lymph node metastases, or PSA above 100; or bone marrow infiltration with associated systemic symptoms.

Clinical disease progression will be measured as person-years free of the consequences of disease progression. Signs of disease progression will include evidence of metastatic disease; the initiation of long-term hormone therapy; diagnosis of clinical T3 or T4 disease; or ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment. There will be a review of cases where disease progression or metastatic disease are uncertain.

As the ascertainment of clinical disease progression may differ between the three study arms, we will also present the initiation of long-term hormone therapy, to indicate those men whose disease is no longer curable.

The reporting of metastatic disease, clinical disease progression, and initiation of long-term hormone therapy is conditional on securing the data.

The patient-reported outcomes which have been measured are listed in the Appendix. These measures are derived from validated questionnaires and have been completed at recruitment, at first biopsy, six months after randomisation, and yearly thereafter. These measures will be reported in a separate companion paper, to be submitted for publication at the same time as the primary outcomes paper.

2.10. Interim analysis

There have been no analyses of the outcome data that have accumulated since publication of the findings at median ten-years follow-up.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. Analysis populations

The primary analysis data set is all men **randomly allocated** to one of the three management options being compared in the ProtecT trial.

3.2. Procedures for missing data

Where a man has omitted responding to a small number of items on a patient reported outcome measure, these will be imputed as per the guidance for that measure.

Where the patient has not responded to any or most of the items on a measure, the main analysis of patient-reported outcomes will NOT be based on data with those missing scale scores imputed. However, the amount of missing data, by allocation arm, will be presented. All men providing at least one post-randomisation patient-reported measure will be included in the relevant analysis.

3.3 Definitions of treatment received

Men were considered to have received each of the treatments according to the following definitions; men who did not fulfil these were excluded.

1. Active Monitoring (AM) if there were ≥ two PSA tests and no radical treatment in the 12 months following diagnosis.
2. Surgery (RP) if RP carried out within 12 months following diagnosis.
3. Radiotherapy (RT) if treatment protocol was started within 12 and completed within 15 months.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Disposition

Details of the recruitment of the ProtecT randomised trial cohort, up to the point of randomisation, were presented in the *Baseline Paper* (Lane et al, 2014). Details of how many men were excluded and for what reasons are presented. The subsequent flow of patients through the trial will be summarised in a CONSORT diagram that will include the numbers randomised to the three treatment groups, losses to follow-up and the numbers analysed. *This extends the diagram in Hamdy et al (2016) to make clear losses to follow-up since the median ten-year follow-up (Figure 1).*

5. ANALYSIS OF EFFECTIVENESS

5.1. Summary of outcomes to report at median 15 years follow-up

The following summaries of the outcome events will be presented for each treatment allocation group:

- Number of deaths due to prostate cancer.
- Prostate cancer mortality at 15 years, with 95% confidence interval.
- Prostate cancer mortality per 1,000 person years of follow-up, with 95% confidence interval.
- Kaplan-Meier survival of death from prostate cancer as a function over time.

The following summaries will be presented for the clinical secondary outcome events:

- Number of events.
- Events per 1000 person years of follow-up, with 95% confidence interval.
- Kaplan-Meier overall survival and survival free of disease progression as functions over time

In addition, if the data can be obtained, the Kaplan-Meier cumulative incidence of the uptake of radical treatment will be presented for the three treatment groups as a function over time.

5.2. Prostate cancer mortality at median 15 years follow-up

This analysis will be conducted on an intention-to-treat basis comparing allocated groups. Deaths occurring until a median of 15-year follow-up has accumulated (23:59 on Monday 23rd November 2020) will be included in the locked database. We will allow up to 30th June 2021 to be notified of deaths (we may revise this deadline for notification if the COVID-19 outbreak causes delays).

Prostate cancer (definite, probable, or intervention-related) mortality will be compared between the three treatment groups using Cox's proportional hazards regression adjusted for study centre (all nine centres distinguished using dummy variables), age at baseline (continuous measure in years), Gleason score (2-6, 7, 8-10), and PSA at baseline (continuous measure in ng/ml, log-transformed to accommodate positive skewed distribution):

$$h(t) = h_0(t)\exp\{\beta_{1j}x_{1i} + \beta_{2k}x_{2i} + \beta_3 x_{3i} + \beta_{4m}x_{4i} + \beta_5 ln.\, x_{5i}\}$$

β_{1j} is the log hazard ratio comparing two of the treatment arms, with two of the three pairwise comparisons being available from a single iteration of the analysis (i.e. j=1,2 the estimated comparisons depending on the choice of comparator treatment). x_{1i} is the treatment allocation (0,1,2) for participant i. β_{2k} (k=1 to 8) captures differences in the hazard of the primary outcome event between study centres, x_{2i} being the study centre for participant i. β_3 is the linear effect of age, with x_{3i} being the age in years for participant i. β_{4m} (m=1,2) accommodates the effect of Gleason score category with x_{4i} being the Gleason score category for participant i. Finally β_5 is the linear effect of log-transformed PSA level, x_{5i} being the PSA level at diagnosis for participant i.

Plots and tests based upon Schoenfeld residuals will be investigated to determine whether the proportional hazards assumption is reasonable; if not the model will be elaborated to allow for a changing magnitude of treatment effect with time.

The hazard ratio and 95% confidence interval for the treatment effect estimated in each pairwise comparison of allocated treatments will be presented, but pairwise significance tests will only be conducted if a test of an equal 15-year disease specific mortality risk across all three arms yields a p-value of less than 0.05 (Table 3). This conditional approach keeps the overall false positive rate at 5% and has been found to maintain power in simulation studies (Bauer 1991).

The competing risk of all-cause death is not anticipated to influence the estimation of the treatment effect on the risk of prostate cancer mortality. Age is the only strongly influential risk factor shared by all-cause and prostate cancer mortality, and age is included as a covariate in all models.

5.3. Other analyses at median 15-years follow-up

The approach to the primary analysis will be adapted to the analysis of secondary outcome events, i.e. definite, probable or possible prostate cancer mortality; all-cause mortality; and metastatic cancer.

For patient reported outcomes (see Section 2.9.2) summary statistics by allocated group will be presented graphically for the baseline, 6-month, 12-month and subsequent assessment points up to 12 years (we will accept questionnaires returned by September 30th 2021, by which time all men will have this duration of follow-up). This approach will also be taken for those questionnaires dropped from the battery in November 2018, with the consequent loss of responses for later assessment points being made clear. All graphical presentations will present the full 12 years follow-up but will focus on the novel data for the period from 73 to 132 months.

Analyses will employ multi-level models for repeated measures to estimate average treatment effects. These analyses will be adjusted for the stratification (centre) and minimisation (baseline age, Gleason score, PSA level) variables as described in the previous section. Consistent with the focus of the current analysis, the null

hypothesis of no difference in the population means of an outcome measure between allocated treatment groups, for the period from 73 to 144 months, will be tested.

5.4. Subgroup analyses

Following peer-reviewed criteria for the credibility of subgroup analyses (Sun et al, 2010), we have pre-specified a small number of subgroup analyses investigating whether treatment effectiveness in reducing prostate cancer specific mortality is modified by the following factors measured at diagnosis:

- Age (above versus below 65 years)
- Grade Group (Group 1 versus Group 2; Group 2 versus Group 3+)
- PSA (PSA < 10ng/ml versus 10 and above)
- Clinical stage (T1 versus T2)
- Aggregate tumour length in biopsy cores (<4mm versus 4mm+)
- Maximum tumour length in a single biopsy core (<2mm versus 2mm+)
- D'Amico low risk versus moderate / high risk.
- CAPRA low risk (score 0-1) versus moderate / high risk (>1)

Age, clinical stage, grade group, tumour burden and PSA are commonly used factors in the prediction of risk of disease progression. We anticipate that men at the lowest risk of disease progression have least to gain from radical treatment in comparison to their outcome with active monitoring. Wilt et al (2020) obtained results consistent with this hypothesis.

The D'Amico risk categories (D'Amico, 1998) are **low** (Gleason score is 6 or less, and PSA is 10ng/ml or less, and clinical stage is T1c/T2a); **high** (Gleason score is 8 or more, or PSA more than 20ng/ml, or stage is T2c); and **intermediate** (Gleason score is 7, or PSA is higher than 10ng/ml but no more than 20ng/ml, or stage is T2b).

To facilitate comparison of our results to those of Wilt et al (2020) we have adopted the CAPRA score of disease risk (Cooperberg et al, 2006) and will repeat this set of subgroup analyses with all-cause mortality as the outcome measure.

The statistical models used in the primary analysis will be extended to incorporate interaction terms, to test null hypotheses of no variation in treatment effect across subgroups. For sub-group analyses based on age, PSA, and tumour length measures, the interaction test will be based on the continuous measure, and departures from the assumption of a linear relationship will be investigated (and accommodated if necessary) by introducing polynomial terms. Significance testing will be conducted with the principles of the primary analysis being followed as closely as possible.

We will also investigate whether the relative impact of intervention on key PROMs (pad use, nocturia, erectile dysfunction , and bloody stools) is modified by age and the risk of disease progression at baseline, as incorporated for the clinical measures.

5.5. Sensitivity analyses

The analysis of prostate cancer mortality will be repeated, but with the outcome defined as death definitely, probably **and possibly** due to prostate cancer.

6. 15-YEAR PUBLICATION PLAN

6.1. Planned papers and timelines

The intention is to present the clinical and patient-reported outcomes in a pair of papers, to be submitted to a high impact medical journal by late 2021. With a census date of **23rd November 2020** for clinical outcomes contributing to this analysis, this will allow those routine data available by 30th June 2021 to be incorporated.

7. FINAL REPORT TABLES AND FIGURES

Figure 1. CONSORT flowchart, illustrating the flow of participants through each of the three arms of the trial, from the point of randomisation.

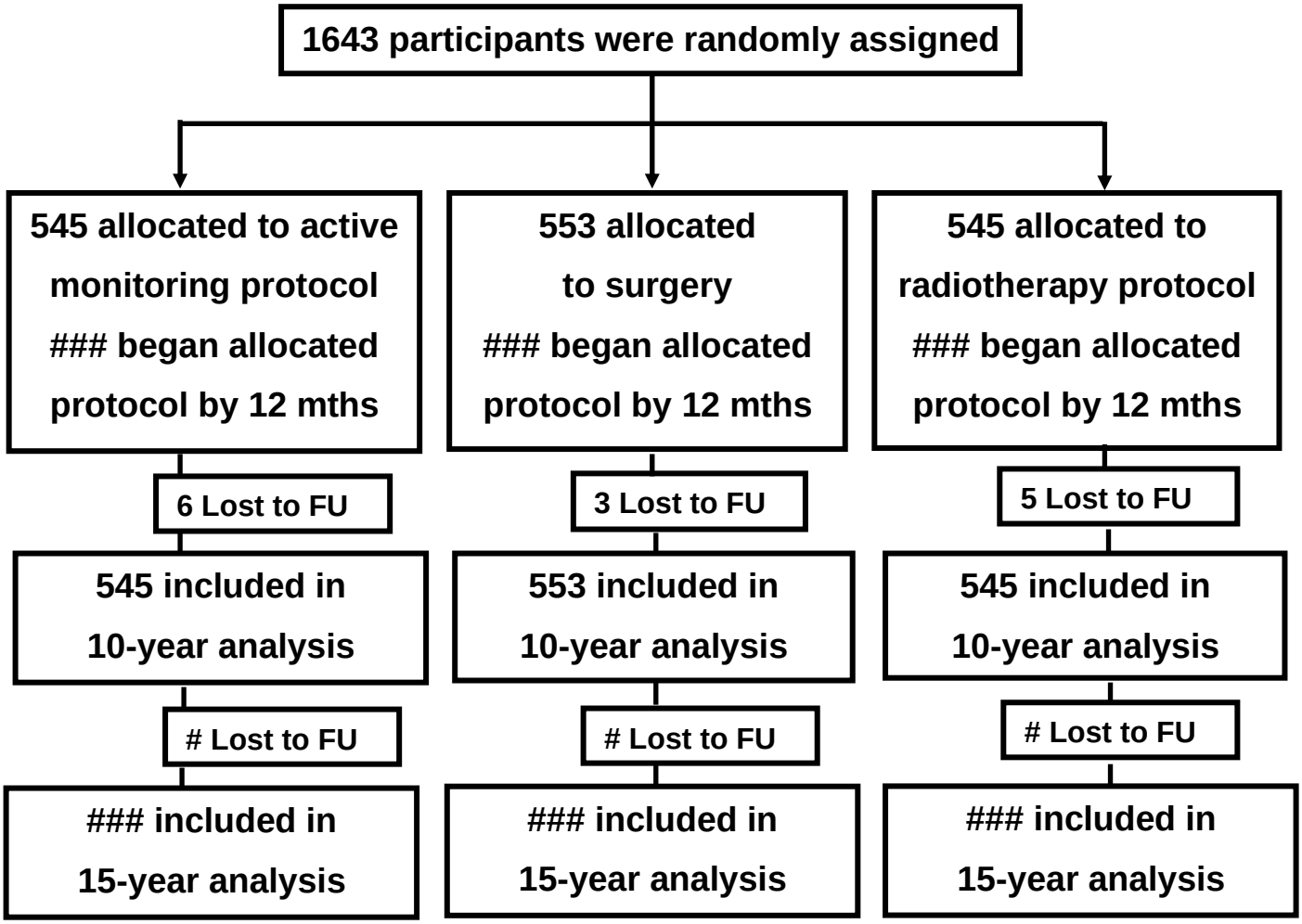

Figure 2. Kaplan-Meier estimates of the cumulative probability of undergoing radical interventions during the follow-up period, according to treatment group.

Radical intervention was defined as a radical prostatectomy, per-protocol radiotherapy, non-protocol radiotherapy (including brachytherapy), or high-intensity focussed ultrasound therapy.

Figure 3. Kaplan-Meier estimates of prostate cancer-specific survival and freedom from disease progression, according to treatment group: active monitoring (solid line), surgery (long dash line) and radiotherapy (short dash line) treatment groups

Panel A shows the rate of prostate cancer-specific survival. Prostate cancer-specific deaths were those that were definitely or probably due to prostate cancer as determined by an independent cause-of-death evaluation committee whose members were unaware of treatment assignments.

Panel B shows the rate of overall survival.

Panel C shows the rate of freedom from disease progression. Clinical progression of prostate cancer included metastases and death due to prostate cancer or its treatment.

Table 1. Prostate cancer mortality, Clinical progression, metastatic disease and all-cause mortality, by randomised group

	Active monitoring protocol (N=545)	Surgery (N=553)	Radiotherapy protocol (N=545)	p-value[1]
Total person years in follow-up				
Number of deaths due to prostate cancer[2]				
% prostate cancer mortality at median 10 years (95% CI)				
% prostate cancer mortality at median 15 years (95% CI)				
Prostate cancer deaths[1] per 1000 person years (95% CI)				
Number of deaths due to any cause				
All-cause deaths per 1000 person years (95% CI)				
Person years of follow-up free of hormone treatment				
Number of men treated with hormones for advanced disease				
Starting hormone treatment per 1000 person years (95% CI)				
Person years of follow-up free of clinical progression[3]				
Number of men with clinical progression				
Clinical progression per 1000 person years (95% CI)				
Person years of follow-up free of metastatic disease				
Number of men with metastatic disease				
Metastatic disease per 1000 person years (95% CI)				

[1] Likelihood ratio test of the null hypothesis “no difference in prostate cancer mortality between the three treatment arms”, adjusted for study centre, age, mean PSA at prostate check clinic and biopsy, and Gleason score at baseline. [2]Death probably or definitely due to prostate cancer or its treatment as judged by an independent committee. [3]Disease progression includes evidence of metastatic disease; the initiation of hormone therapy; diagnosis of clinical T3 or T4 disease; or ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

Table 2. Prostate cancer deaths by randomised group and subgroup

	Rate prostate cancer mortality[1] per 1000 person years (number of deaths)			
	Active monitoring protocol (N=545)	Surgery (N=553)	Radiotherapy protocol (N=545)	p-value[2]
Age at randomization				
< 65 years				
65 years+				
Grade group at diagnosis				
Group 1				
Group 2				
Group 3+				
Aggregate tumour length in biopsy cores				
<4mm				
4mm+				
Maximum tumour length in any single biopsy core				
<2mm				
2mm+				
PSA level at diagnosis				
< 10 ng/ml				
10 ng/ml+				
Clinical stage at diagnosis				
T1c				
T2				
CAPRA risk score				
Low risk (score 0-1)				
Medium / high risk (score >1)				
D'Amico risk group				
Low				
Intermediate / high				

[1]Death probably or definitely due to prostate cancer or its treatment as judged by an independent committee.[2]Likelihood ratio test of the null hypothesis "equal relative treatment effects across the subgroups", adjusted for study centre, age, mean PSA at prostate check clinic and biopsy, and Gleason score at baseline.

8. APPENDIX

The following standard assessment tools have been completed by men participating in the ProtecT study:

- Expanded Prostate Index Composite
- International Consultation on Incontinence Questionnaire (ICIQ)
- International Continence Society urinary function (ICS*male*SF)
- EORTC QLQ-C30 cancer-specific impacts
- Hospital Anxiety and Depression Scale (Until November 2018)
- Short Form 12 (SF-12) mental and physical subscales (Until November 2018)
- EuroQoL-5D (EQ-5D) generic quality of life

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