ECTU WPD Identifier	ECTU HE W1
Version No	1.1
Effective Date	TBC

CARDIAC CARE

Health Economic Analysis Plan (HEAP)

Version No	1.0
Date Finalised	10 June 2022
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Document Control		
Version No	Date	Summary of Revisions
1.0	05.04.2022	Initial Creation by author Marek Atter
1.1	05.05.2022	Response to comments by Peter Hall and Andy Stoddart

Supporting Internal Documents	Version No
Cardiac CARE Protocol	11.0
Cardiac CARE Statistical Analysis Plan	1.0
Rapid Literature Review of Cost-Utility Model Structures in Test-guided Interventions in Breast Cancer and Lymphoma	1.0

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List of Abbreviations

Abbreviation	Full Name
ARB	Angiotensin Receptor Blockers
CCF	Congestive Cardiac Failure
CEAC	Cost-Effectiveness Acceptability Curve
CEP	Cost-Effectiveness Plane
CI	Chief Investigator
CRF/eCRF	Case Report Form / electronic CRF
DFS	Disease-Free Survival
DR	Distant Recurrence
ECG	Electrocardiogram
ECTU	Edinburgh Clinical Trials Unit
EME	Efficacy and Mechanism Evaluation
HEAP	Health Economics Analysis Plan
hs cTnI	High Sensitivity Cardiac Troponin I
ICER	Incremental Cost-Effectiveness Ratio
INMB	Incremental Net Monetary Benefit
LOS	Length of Stay
LVEF	Left Ventricular Ejection Fracture
MRI	Magnetic Resonance Imaging
MUGA	Multigated Acquisition Scan
NHS	National Health Service (UK)
NICE	National Institute for Healthcare Excellence
NIHR	National Institute for Health and Care Research
OOP	Out of Pocket
OWSA	One-Way Sensitivity Analysis
PRO	Patient-Reported Outcome
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-adjusted Life Year
RFS	Recurrence-Free Survival
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Standard Operating Procedure
VOI	Value of Information
WTP	Willingness to Pay

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1. Purpose of Document and Responsibilities of Authors and Signatories

This document details the criteria to be used for the definition of the analysis, populations, and health economic methods for analysis for the Cardiac CARE study (trial registration number: ISRCTN24439460). The study is funded by NIHR EME (reference number: 15_48_20). This document has been written based on information contained in the trial protocol (version 3.0, 27/07/2021), and Statistical Analysis Plan (SAP, version 1.0, 17/03/2022). The HEAP is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan and it should be read in conjunction with them.

1.1. Responsibilities of Authors and Signatories

The HEAP will be written by the author. Supervision and quality checking will be undertaken collaboratively with the sub-investigator/co-applicant responsible for health economics (Dr Peter Hall, p.s.hall@ed.ac.uk) (see protocol). Ultimate responsibility for analysis authorisation lies with the chief investigator.

2. Study Details

2.1.Background

The study background of the Cardiac Care study is summarised in the protocol:

> *Breast cancer is common. The lifetime risk of women developing breast cancer in the UK is 1 in 8. Survival continues to improve. This improved survival is in part down to chemotherapy drugs called anthracyclines. This medication can cause the unwanted side effect of heart muscle injury. Breast cancer survivors have increased rates of heart problems including heart muscle failure.*
>
> *[…] We aim to test whether tablet medications called angiotensin receptor blockers (ARB) and B-blockers can prevent heart muscle injury related to chemotherapy. These medications are well established treatments for improving symptoms and survival in patients with heart failure. We will examine a blood test called cardiac troponin I which can detect very slight heart muscle injury. In the trial only patients with increased levels of this marker will be treated with ARB and B-blocker.*

2.2.Study Hypothesis

The study hypothesis posits that carvedilol and candesartan will prevent development of cardiac dysfunction in at-risk patients identified by elevated plasma cTnI concentrations.

2.3.Primary Health Economic Objectives

Based on the protocol, the research question of the Cardiac Care health economic analysis is:

- What are the "important drivers of differences in costs and QALYs between standard care and hs cTnI guided cardioprotection"?

To answer the research question, two deliverables will be produced:

1. A within-trial analysis of total costs and quality-adjusted life years (QALYs, see section 3) and measure healthcare utilisation associated with each trial arm (cardioprotection vs standard care for breast cancer and lymphoma patients with elevated cTnI) within the study 6-month time horizon;

2. A decision analytic model that measures the cost-effectiveness within a broader time horizon (see Section 3.3) of hs cTnI-guided cardioprotection compared to universal anthracycline treatment in breast cancer and lymphoma patients.

As specified by the protocol, the analysis will be contingent upon "confirm[ing] the feasibility of data capture" and "assess[ing] the quality of data obtainable in this patient population."

2.4.Secondary Health Economic Objectives

The secondary research question of interest is:

- Is the benefit of further research into the drivers of uncertainty in costs and QALYs between hs cTnI-guided cardioprotection and universal anthracycline treatment likely to be greater than the costs of undertaking it?

The secondary objective of the health economics analysis will therefore be to conduct a value of information (VOI) analysis (see Section 6.8) to estimate the benefits of future research in this area. However, this is subject to data quality and time resource constraints.

2.5.Study Population and Sample Size

The study population will consist of adult patients with histological diagnosis of invasive non-HER2+ breast cancer or non-Hodgkin lymphoma who are due to start anthracycline therapy.

The total enrolled will be at least 168. The protocol estimates that a third of enrolled participants will develop a plasma cTnI concentration above the defined threshold for randomisation, and they will be randomised 1:1 into treatment arm or standard of care (SOC). The estimated 112 participants enrolled who do not develop a plasma cTnI concentration above the defined threshold for each cycle will not be randomised and will continue with standard care. Recruitment is expected to occur over a 2-year period.

2.6.Study Centres

The Cardiac Care study includes nine sites from three countries within the UK (four from England, three from Scotland and two from Wales).

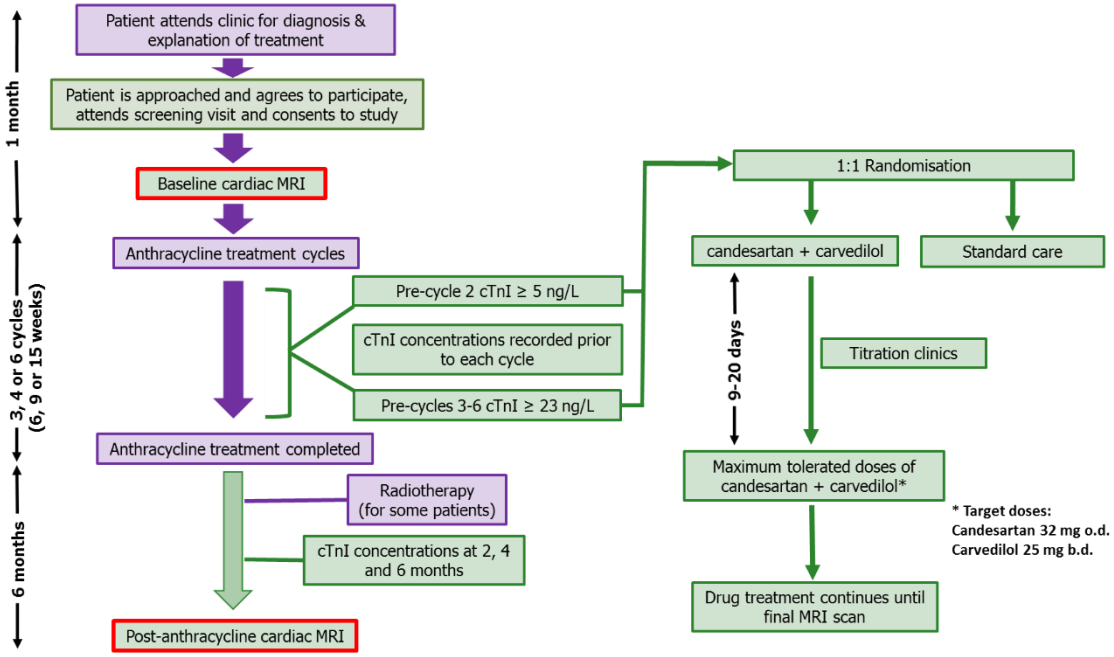
- Edinburgh Western General Hospital (WGH) and St John's Livingston (Scotland, UK)
- Glasgow Beatson West of Scotland Cancer Centre & Queen Elizabeth University Hospital (Scotland, UK)
- Velindre Cancer Centre (Wales, UK)
- University Hospital of Wales (Wales, UK)
- The Christie (England, UK)
- Mount Vernon Cancer Centre (England, UK)
- Oxford University Hospitals (England, UK)
- Milton Keynes University Hospital* (England, UK)
- Glasgow New Victoria Hospital* (Scotland, UK)

Two sites did not recruit patients (marked with a '*').

2.7.Treatment groups

The Cardiac Care study treatment pathways are illustrated in Figure 1. All patients in the study begin by undergoing a baseline cardiac MRI scan, followed by anthracycline treatment cycles. Then, cTnI concentrations are measured; patients with elevated cTnI scores (≥5ng/L for pre-cycles 2 and ≥23ng/L for pre-cycles 3-6) are randomised 1:1 into SOC and intervention arms while the remaining patients stay on standard care treatment. Anthracycline treatment consists of 3, 4 or 6 cycles, lasting 6, 9 or 15 weeks. Once anthracycline treatment is completed, some patients undergo radiotherapy. Finally, patients undergo further cTnI tests and post-anthracycline cardiac MRI.

Figure 1: Cardiac Care treatment pathways (from protocol)



2.7.1. Intervention Group

In the intervention arm, receive candesartan and carvedilol, after which they continue anthracycline chemotherapy. Participants receiving the study drugs will undergo a maximum of 4 dose up-titration clinic attendances for 9-20 days.

2.7.2. Comparator Group

Patients in the comparator group do not receive candesartan and carvedilol, but undergo otherwise identical anthracycline chemotherapy. The comparator trial population includes the non-randomised patients and those randomised to standard care.

3. Economic Principles

3.1.Overview and Aims of the Economic Evaluation

The aim of the economic analysis is ultimately to help UK decision makers in incorporating Cardiac CARE study results into clinical practice and improving resource allocation efficiency in order to maximise the benefits provided by the NHS. There is a possibility that this analysis will show cTnI-guided treatment for heart failure in breast cancer to be potentially cost-saving or cost-effective, which would help the NHS allocate the right resources to provide improved treatment in this disease area.

3.2.Perspective

The analysis will be conducted from both the healthcare payer (NHS) and societal perspective. Analysis from the NHS perspective will only take into account direct costs. The societal perspective factors in both direct and indirect costs. Direct costs include costs of hospitalisation (short- and long-term), outpatient follow-up, residential and day care, drugs, laboratory testing, and benefit payments, while indirect costs include lost productivity and the cost that the care-givers bear by contributing their time and in-kind services.[1]

3.3.Time Horizon

A rapid literature review conducted as part of the preliminary background research for the economic analysis identified 15 cost-utility analyses of test-guided drug-based therapies for breast cancer and/or lymphoma patients, of which a majority (11) used the lifetime horizon (i.e. costs and outcomes are tracked/projected from treatment initiation until death); this will be the baseline assumption in Cardiac CARE economic analysis. Other studies identified in the review restricted the time horizon to 20, 10 and 5 years; these options will be explored in sensitivity (scenario) analyses.

3.4.Discount Rates

Base-case discount rates will be set to 3.5% for both costs and outcomes, following the NICE reference case,[2] as this is the most appropriate option in the UK context. Indeed, all UK based studies identified

in the rapid literature review followed the same approach. However, non-UK based studies identified by the review used discount rates ranging between 1.5% and 5%; these values will be tested in the one-way sensitivity analysis (OWSA, see Section 6.6.1) to measure the impact of discounting on results and to provide insight into cost-effectiveness in non-UK contexts.

3.5.Cost Effectiveness Threshold(s)

The intervention will be considered cost-effective if its incremental cost-effectiveness ratio (ICER) is below the willingness-to-pay (WTP) threshold of £30,000/QALY. This is the figure used by the UK-based studies identified in the rapid literature review and is consistent with NICE methodological recommendations.[3]

4. Data Management

Data management procedures are specified in the study protocol and SAP. The Trial Manager is responsible for data management, including checking the case report forms (CRFs) for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

4.1.Data Entry Methods

As described by Section 8 of the study protocol, research staff at each site will enter data onto an electronic CRF (eCRF) via a secure, web-based portal. Furthermore, the Section 7.2.7 describes the how health utility and cost/resource use data will be collected using questionnaires based on EuroQoL EQ-5D-5L and the UK Cancer Costs Questionnaire,[4] respectively.

4.2.Data Validation and Cleaning

Section 8.1 of the protocol specifies that designated staff at ECTU will follow ECTU SOPs to obtain missing data and resolve queries with site staff and to ensure data quality and completeness of data across sites. Furthermore, where necessary, the health economic analysis will follow the SAP in removing observations with missing outcome variable data from analysis.

4.3.Data Archiving

Data archiving procedures are set out by ECTU standard operating procedure (SOP) ECTU_TM_W2.

4.4.Analysis Software

The primary software used for analysis will be the R programming language.[5] Supplementary software may consist of Microsoft Excel where necessary.

5. Data Collection, Processing & Analysis

5.1.Health Economic Analysis Population

The health economics analysis will follow the protocol in conducting an intention-to-treat complete case analysis. From the SAP:

> *The intention-to-treat (ITT) population will include all patients who have been randomised into the Cardiac CARE trial, and who did not withdraw consent for their data to be stored in the trial database, according to the Change of Status form. Patients will be analysed in the intervention group to which they were allocated, regardless of the intervention they actually received.*

The patient population will follow the definitions and stratifications defined in the SAP.

5.2.Summary of Data Collection & Follow up Timing

As discussed in Section 4.1, health economics data is collected from patients via self-reported PRO forms (see Appendix) and entered into the database by on-site researchers. Table 1 provides a list of items collected as part of the health economics analysis, as well as collection time points and properties. The follow-up time points consist of:

1. 3-week post anthracycline visit (for participants on 3 cycles only)
2. Chemotherapy cycle 4 visit (if applicable)
3. Chemotherapy cycle 6 visit (if applicable)
4. 2 months after chemotherapy
5. 4 months after chemotherapy
6. 6 months after chemotherapy

Table 1: Summary of Health Economic Data Collection based on baseline and follow-up Cardiac CARE PRO forms

Item	**Timepoint**						
	Baseline	**Follow-up** (see above list)					
	0	**1**	**2**	**3**	**4**	**5**	**6**
EQ-5D-5L							
Visual Analogue Scale (VAS)							
Productivity*							
Hospital services							
Scans/screenings used (e.g. x-ray)							
Community care							

Item	Timepoint						
	Baseline	**Follow-up** (see above list)					
	0	**1**	**2**	**3**	**4**	**5**	**6**
Travel costs							
Out of pocket (OOP) costs							

5.3.Resource Use

5.3.1. Identification of Resources and Other Base Units of Cost Inputs

As discussed in Section 3.2, the analysis will be conducted from both the NHS (healthcare payer) and societal perspectives, which include direct and all (direct + indirect) costs, respectively. In this analysis, resources used to calculate direct costs will include the costs of items recorded in the PRO forms (see Appendix).

5.3.2. Unit costs

Given the UK study setting, all costs will be sourced from UK-based data (e.g. NHS reference costs, Public Health Scotland) and converted to a common base year using the NHS cost Inflation Index (NHSCII).[6–9] Resources included in the analysis, along with valuation methods and unit costs, are summarised in Table 2.

Table 2: Illustrative summary of unit costs in 2022 GBP

Item	Unit cost	Source, Dates and Notes
cTnI test	£5.53	CA$10 (2016)[10] converted to 2016 £4.89 using xe currency conversion tables from 01.01.2016 and adjusted by the health-specific CPIs for January 2022 and 2016 (annual): 115.4/102.1.[6,7]
Candesartan 1mg	£0.072	Derived from the drug tariff price of £1.01 for 7 candesartan cilexetil 2mg tablets (2022)[11]
Carvedilol 1mg	£0.01	Derived from the drug tariff price of £0.9 for 28 carvedilol 3.125mg tablets (2022)[12]
Anthracycline	£537.03	Obtained by adjusting the chemotherapy cost of £524 (2020) by the health-specific 2015-based CPIs for 2020 (annual) and January 2022: 112.6/115.4.[7,13]
Radiotherapy	£169.1	£165 from 2020 adjusted by the health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Cardiac MRI scan	£184.38	£173 (2020)[13]

Item	Unit cost	Source, Dates and Notes
Inpatient stay (per case)	£3,606.51	Obtained by adjusting £3,519 from 2020 by the health-specific 2015-based CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Inpatient stay (per diem)	£704.05	Derived from average inpatient week cost in Scotland of £4,702 from 2019 adjusted by the health-specific CPIs for January 2022 and 2019 (annual): 115.4/110.1[7,9]
Hospital doctor visit	£197.8	Based on medical oncology outpatient attendance unit cost of £193 in 2020, inflated by 2015-based CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Surgeon visit	£143.48	Based on general surgery unit cost of £140 (2020) inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Hospital nurse visit	£101.46	Based on the specialist cancer-related face-to-face nursing unit cost of £99, inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Hospital nurse phone call	£32.8	Based on the specialist cancer-related non-face-to-face nursing unit cost of £32 (2020) inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Breast cancer nurse visit	£101.46	Based on the specialist adult cancer-related face-to-face nursing unit cost of £99 (2020) inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Breast cancer nurse phone call	£32.8	Based on the specialist adult cancer-related non-face-to-face nursing unit cost of £32 (2020) inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
CT-Scan	£216.25	Based on cardiac CT scan unit cost of £211 (2020) inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Ultrasound	£76.87	£75 (2020)[13] inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
Bone Scan	£272.61	2-3 phases, ≥19: £266 (2020) inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
ECG	£162.95	£159 (2020) inflated by 2015-based health-specific CPIs for January 2022 and 2020 (annual): 115.4/112.6.[7,13]
X-ray	£29.41	£25 (2014) adjusted by the health-specific CPIs for January 2022 and 2014 (annual): 115.4/98.1.
Unscheduled hospital assessment	£197.8	Assumed to be equal to outpatient visit costs (see above)
Hospital doctor phone call		*To be identified*

Item	Unit cost	Source, Dates and Notes
Physiotherapist visit	£115.3	£114 (2021), one-to-one session adjusted by the health-specific CPIs for January 2022 and 2021 (annual): 115.4/114.1.[7,8]
Physiotherapist phone calls		*To be identified*
Cancer treatment helpline call		*To be identified*
NHS direct call		*To be identified*

5.3.3. Cost Calculation

Total costs will be calculated by multiplying total units used in each arm by the relevant unit cost. If a resource recorded in the data does not have a corresponding unit cost in Table 2, for example because it was entered into, NHS reference costs will be searched to identify the unit costs.

It is important to note that, since cost-effectiveness analysis primarily aims to identify incremental differences, costs that are assumed to be equal in both treatment arms can be removed from analysis. As shown by the treatment pathways in Figure 1, MRI, anthracycline and radiotherapy costs are not determined by the treatment arm and can be cancelled out – the analysis will there for consist of scenarios with and without cost cancellation for result comparisons.

5.4.Outcomes

5.4.1. Identification of Outcomes

The primary outcomes of the health economic analysis will quality adjusted life years (QALYs), derived from health-related quality of life (HRQoL) measured by the EuroQoL EQ-5D-5L questionnaire. The protocol specifies that:

> *Health utility (preference based quality of life) will be measured using the EuroQoL EQ-5D-5L questionnaire administered at chemotherapy cycle 1 by a research nurse then approximately every 9 weeks by post or in clinic until study completion (5 times).*

Conversion of patient-level EQ-5D-5L data into time-point-specific health utility values will follow NICE guidance in using 5L-to-3L crosswalk mapping.[14]

5.4.2. Outcome calculation

QALYs will be calculated from time-point-specific health utility values using an area-under-the-curve technique and regression-adjusted to account for baseline utilities.[15]

5.5.Missing Data

The approach to missing data will follow that outlined by the SAP:

> *Where there is missing data for an outcome variable, in the first instance, those records will be removed from any formal statistical analysis relating to that outcome variable (complete case analysis), unless otherwise specified. In tabulations, numbers of missing observations will be provided, but percentages will not include them.*

Furthermore, since the health economics data relies heavily on PRO questionnaire data, missing values are likely to be a bias concern. The numbers and rates of missing data will be reported for each variable, which will be an important part of the data quality review. If sufficient data is missing (>10% across all data), mean imputation and/or multiple imputation by chained equations will be considered subject to feasibility.

5.6.Timing of Analyses

Primary analysis will be undertaken after the data lock. Preliminary analysis and rapid literature reviews will be undertaken before the data lock to inform model structure and parametrising the standard care arm.

6. Modelling

Modelling will be undertaken in addition to within-trial analysis in order to report estimates of long-term cost-effectiveness of the intervention as well as to increase the understanding of results uncertainty.

6.1.Cost Effectiveness Analysis

The primary objective of the cost effectiveness analysis will be to estimate the ICER of cTnI-guided cardioprotection relative to standard care. The ICER is derived from the following formula, where C denotes total costs, E denotes effects (total QALYs), I denotes the intervention arm and S denotes standard care:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_I - C_S}{E_I - E_S}$$

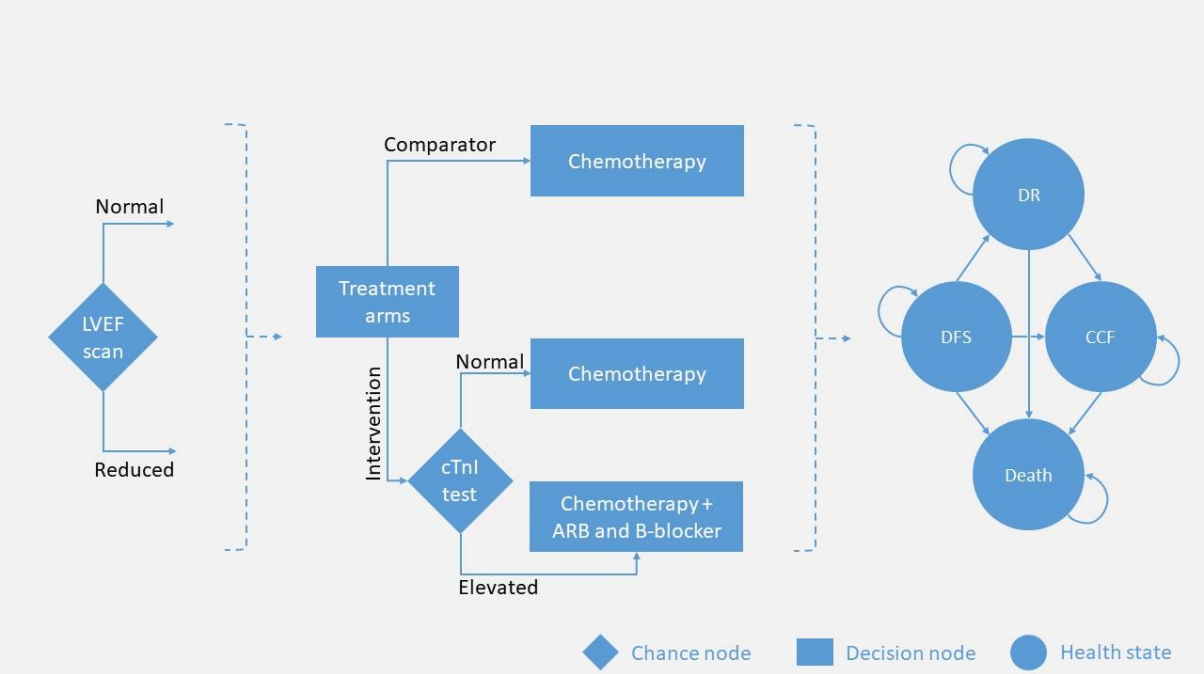
Since utility-based QALYs will be used to measure effectiveness, the type of cost-effectiveness analysis being undertaken is cost-utility modelling.

6.2.Model Structure

A rapid literature review of cost-utility breast cancer models for test-driven drug-based therapies was conducted to inform the model development. Following the review, a derived decision analytic (decision tree + Markov chain) based on identified published model structures was identified as the optimal approach.

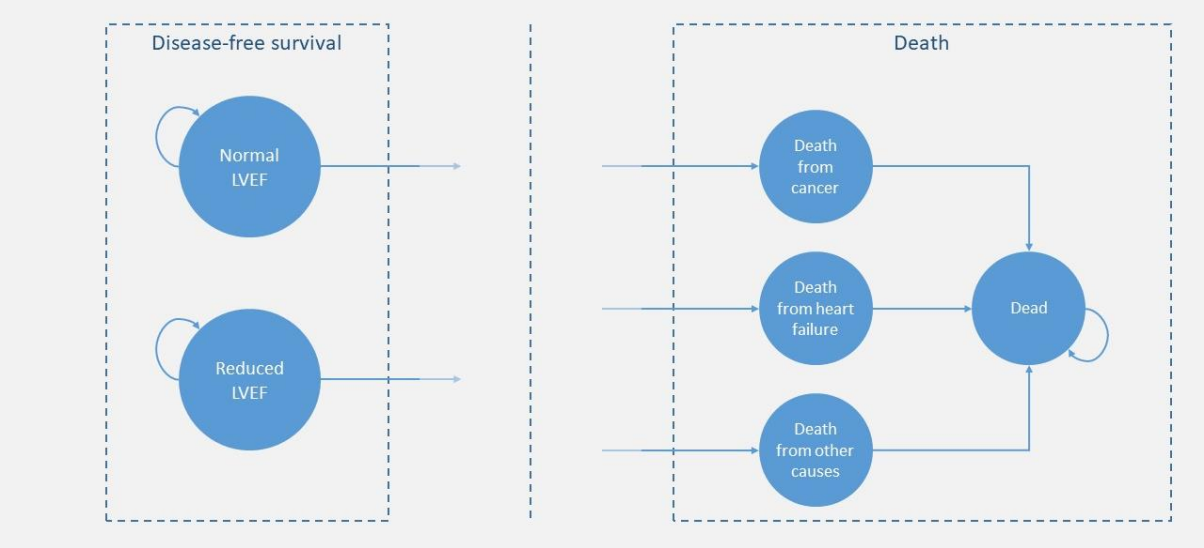
The model will be designed to process a patient cohort through a decision tree (Figure 2) and a Markov model. The decision tree begins with a LVEF measurement either through an ECG or a multigated acquisition scan (MUGA). Then, patients in the comparator arm are assigned to standard care (chemotherapy), while those in the intervention arm receive a cTnI test which determines cardioprotection assignment in addition to standard care. The decision tree outcomes will then populate each outcome group into mutually exclusive health states, which include disease-free survival (DFS), distant recurrence (DR), congestive cardiac failure (CCF) and death.

Figure 2: Proposed Cardiac Care decision tree and Markov model



Furthermore, subject to sufficient data and/or literature sources, sub-state and tunnel state stratifications may be added to the model. This may include separating the DFS and DR states based on LVEF measurement and adding three single-cycle death event states stratified by cause of death (see Figure 3). Additionally, a combined DR-CCF state may also be required to prevent the underestimation of death from cancer amongst metastatic patients who develop congestive heart failure.

Figure 3: Sub-states and tunnel states



6.2.1. Cycle lengths

The rapid literature review identified breast cancer cost-utility Markov models with a range of model cycle lengths, including 1 month, 3 months, 6 months and 1 year. All cycle lengths can be tested. However, using 1-month and 3-month cycles could also allow the model to include transition probabilities calculated from the trial data using Kaplan-Meier estimation.

6.3.Model Assumptions

The model will assume that patients cannot move from DR to DFS or from CCF to DR or DFS. Furthermore, if tunnel states are applied, the model will assume that all movement from CCF to 'Dead' must first go through 'Death from heart failure' and cannot die from any other causes.

6.4.Discount Rate Application

Discount rates (outlined in Section 3.4 for future costs and outcomes will be applied according to the following formula, where t denotes the time period (measured in years since the start of treatment), $V_{d,t}$ denotes the discounted value (of costs or QALYs) in year t, V_t denotes the undiscounted value in year t and r denotes the discount rate:

$$V_{d,t} = \frac{V_t}{(1+r)^t}$$

6.5.Cost Effectiveness Thresholds

The choice of cost-effectiveness willingness-to-pay threshold is discussed in Section 3.5. The WTP will primarily be used in the model to estimate the likelihood of cost-effectiveness by comparing the proportion of probabilistic model iterations (see Section 6.6) with ICER results below the WTP.

6.6.Addressing Uncertainty and Sensitivity Analyses

Sensitivity analysis relies on running the model multiple times with different parameter values determined by or sampled from appropriate distributions using the method of moments. Where appropriate, the gamma distribution will be prioritised for cost variables, while the beta distribution will be used for HSUVs. Joint probabilities (e.g. transitions) will be tested using the dirichlet or beta distributions. Other distributions (e.g. normal, truncated, etc.) will be considered depending on data limitations and availability. Some assumption-based parameters may have manually set ranges (e.g. a range of 1.5%-5% may be applied to the base-case discount rate of 3%, because that is the range of values used in the literature).

Two types of sensitivity analysis will be conducted: one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA).

6.6.1. One-way Sensitivity Analysis

OWSA is a type of deterministic sensitivity analysis which aims to identify the parameters to which the ICER is most sensitive to or which generate the most uncertainty in the model. An OWSA requires two model iterations for each model parameter, selecting the upper and lower bounds from the confidence interval or range of each variable, holding all other factors constant. The output of this analysis will be a tornado diagram.

6.6.2. Probabilistic Sensitivity Analysis

The PSA is a type of Monte Carlo simulation that relies on running multiple iterations of the model using bootstrapping using the method of moments (sampling parameters from their corresponding distribution) to report the mean and variability of results.

6.7.Methods for Identifying and Estimating Parameters

Model parameters for the standard care arm will be sourced from the rapid literature review and supplemented by a further literature search. In the intervention arm, some monthly or quarterly transition probabilities can be estimated from the trial (see Section 6.2.1).

6.8.Value of Information Analysis

Subject to sufficient data quality and project time constraints, a value of information (VOI) analysis will be conducted to report the incremental net monetary benefit (INMB) of adopting the intervention, along with the expected value of perfect information, following published methodological guidance.[16] The purpose of this exercise will be to assess the cost associated with choosing the less cost-effective treatment option as well as estimating the potential monetary value of future research aimed at reducing the uncertainty of model parameters. The VOI analysis will be conducted using the results of the PSA (see Section 6.6.2).

7. Presentation of Results

7.1. Reporting Standards

The process for preparing results for reporting and publication results will be guided by methodology outlined in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[17]

7.2. Deviations from Previous HEAPs

This is the first draft of the Cardiac Care HEAP; no deviations from previous HEAPS have occurred. In future versions, substantial changes and corrections implemented will be detailed in a change log recorded in this section. Minor corrections have been implemented since v 1.0.

7.3. Blank tables

Table 3 will collect every variable of interest in the health economic analysis, including all PRO data (see Appendix), where 'n' denotes the number of observations recorded for each variable, σ denotes the standard deviation. In the 'Missing (%)' column, the total number of missing entries will be entered as plain text, along with the percentage of total observations missing in brackets.

Table 3: Tabulation table (empty)

Variable	n	Mean	σ	Min	Max	Missing (%)
EQ-5D-5L: Mobility						
EQ-5D-5L: Self-care						
…						
Other expenses (total cost)						

8. References

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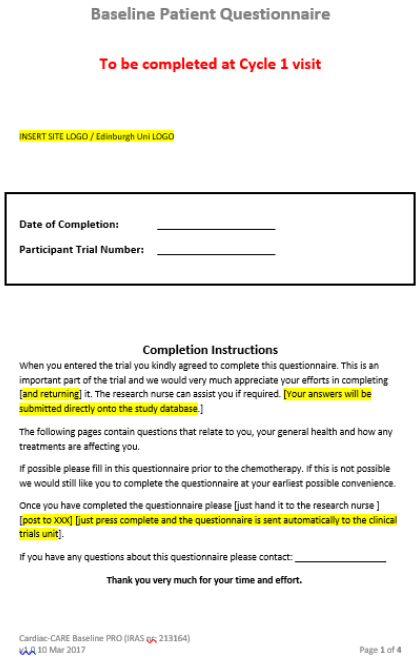
9. Appendix

9.1.Baseline PRO questionnaire v1



Baseline Patient Questionnaire

To be completed at Cycle 1 visit

INSERT SITE LOGO / Edinburgh Uni LOGO

Date of Completion: _____

Participant Trial Number: _____

Completion Instructions

When you entered the trial you kindly agreed to complete this questionnaire. This is an important part of the trial and we would very much appreciate your efforts in completing [and returning] it. The research nurse can assist you if required. [Your answers will be submitted directly onto the study database.]

The following pages contain questions that relate to you, your general health and how any treatments are affecting you.

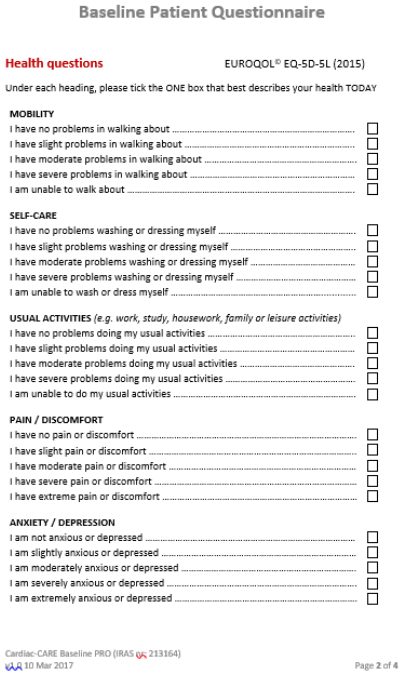
If possible please fill in this questionnaire prior to the chemotherapy. If this is not possible we would still like you to complete the questionnaire at your earliest possible convenience.

Once you have completed the questionnaire please [just hand it to the research nurse] [post to XXX] [just press complete and the questionnaire is sent automatically to the clinical trials unit].

If you have any questions about this questionnaire please contact: _____

Thank you very much for your time and effort.

Cardiac-CARE Baseline PRO (IRAS ~~0~~ 213164)
VAR 10 Mar 2017 Page 1 of 4



Baseline Patient Questionnaire

Health questions EUROQOL® EQ-5D-5L (2015)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY
I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

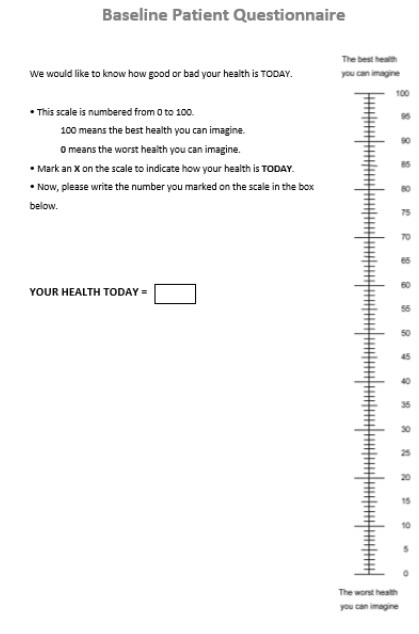
SELF-CARE
I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

Cardiac-CARE Baseline PRO (IRAS ~~0~~ 213164)
VAR 10 Mar 2017 Page 2 of 4



Baseline Patient Questionnaire

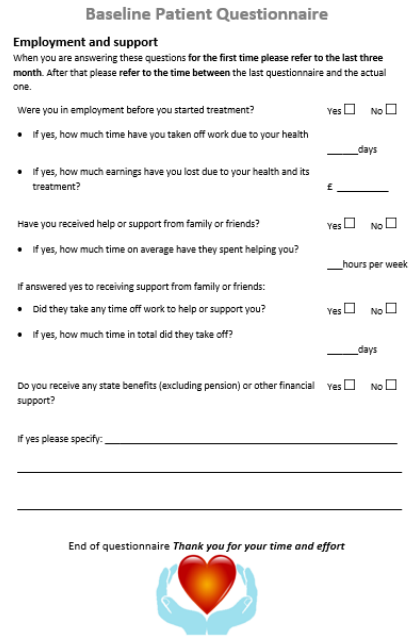
We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
  100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

The best health you can imagine
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
The worst health you can imagine

Cardiac-CARE Baseline PRO (IRAS ~~0~~ 213164)
VAR 10 Mar 2017 Page 3 of 4



Baseline Patient Questionnaire

Employment and support

When you are answering these questions **for the first time please refer to the last three month**. After that please **refer to the time between** the last questionnaire and the actual one.

Were you in employment before you started treatment? Yes ☐ No ☐

- If yes, how much time have you taken off work due to your health _____days
- If yes, how much earnings have you lost due to your health and its treatment? £ _____

Have you received help or support from family or friends? Yes ☐ No ☐

- If yes, how much time on average have they spent helping you? ___hours per week

If answered yes to receiving support from family or friends:

- Did they take any time off work to help or support you? Yes ☐ No ☐
- If yes, how much time in total did they take off? _____days

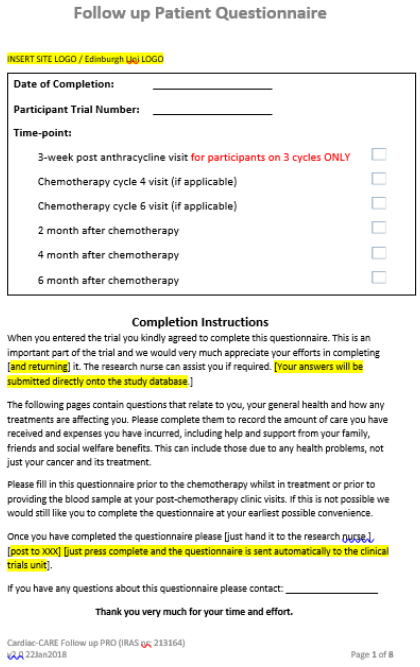
Do you receive any state benefits (excluding pension) or other financial support? Yes ☐ No ☐

If yes please specify: _____

End of questionnaire ***Thank you for your time and effort***

Cardiac-CARE Baseline PRO (IRAS ~~0~~ 213164)
VAR 10 Mar 2017 Page 4 of 4

9.2.Follow up PRO questionnaire v2.0



Follow up Patient Questionnaire

INSERT SITE LOGO / Edinburgh Uoj LOGO

Date of Completion: _____

Participant Trial Number: _____

Time-point:

- 3-week post anthracycline visit for participants on 3 cycles ONLY ☐
- Chemotherapy cycle 4 visit (if applicable) ☐
- Chemotherapy cycle 6 visit (if applicable) ☐
- 2 month after chemotherapy ☐
- 4 month after chemotherapy ☐
- 6 month after chemotherapy ☐

Completion Instructions

When you entered the trial you kindly agreed to complete this questionnaire. This is an important part of the trial and we would very much appreciate your efforts in completing [and returning] it. The research nurse can assist you if required. [Your answers will be submitted directly onto the study database.]

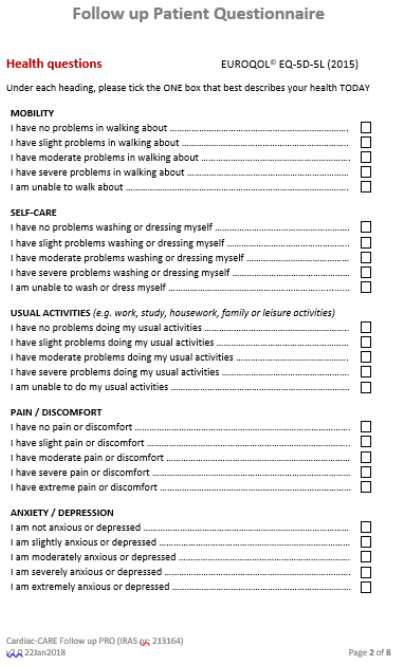
The following pages contain questions that relate to you, your general health and how any treatments are affecting you. Please complete them to record the amount of care you have received and expenses you have incurred, including help and support from your family, friends and social welfare benefits. This can include those due to any health problems, not just your cancer and its treatment.

Please fill in this questionnaire prior to the chemotherapy whilst in treatment or prior to providing the blood sample at your post-chemotherapy clinic visits. If this is not possible we would still like you to complete the questionnaire at your earliest possible convenience.

Once you have completed the questionnaire please [just hand it to the research nurse.], [post to XXX] [just press complete and the questionnaire is sent automatically to the clinical trials unit].

If you have any questions about this questionnaire please contact: _____

Thank you very much for your time and effort.



Follow up Patient Questionnaire

Health questions EUROQOL© EQ-5D-5L (2015)

Under each heading, please tick the ONE box that best describes your health TODAY

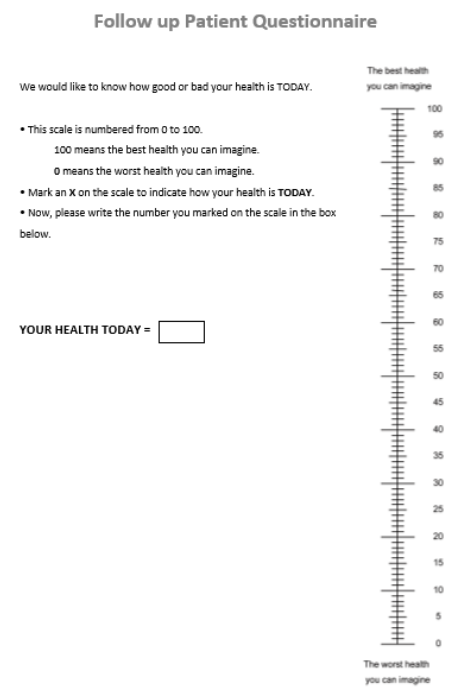
MOBILITY
- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE
- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐



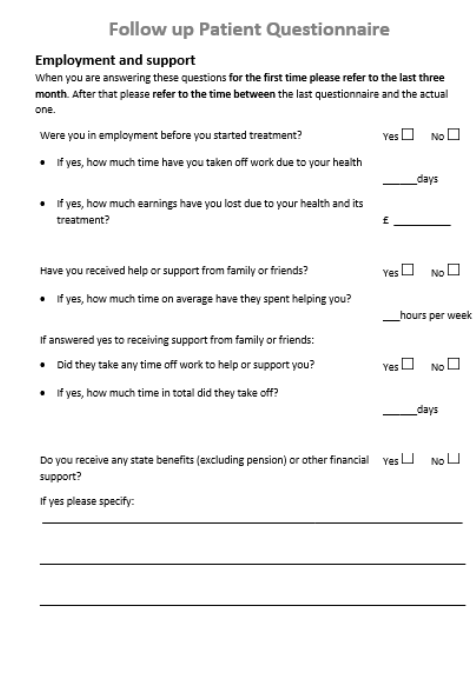
Follow up Patient Questionnaire

We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
  - 100 means the best health you can imagine.
  - 0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

The best health you can imagine
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
The worst health you can imagine



Follow up Patient Questionnaire

Employment and support

When you are answering these questions **for the first time please refer to the last three month**. After that please **refer to the time between** the last questionnaire and the actual one.

Were you in employment before you started treatment? Yes ☐ No ☐

- If yes, how much time have you taken off work due to your health _____days
- If yes, how much earnings have you lost due to your health and its treatment? £ _____

Have you received help or support from family or friends? Yes ☐ No ☐

- If yes, how much time on average have they spent helping you? ___hours per week

If answered yes to receiving support from family or friends:

- Did they take any time off work to help or support you? Yes ☐ No ☐
- If yes, how much time in total did they take off? _____days

Do you receive any state benefits (excluding pension) or other financial support? Yes ☐ No ☐

If yes please specify:

_____

_____

_____

Follow up Patient Questionnaire

Healthcare

Please record the **number** of services you have used **since the last questionnaire** including those due to any health problems, not just those referring to cancer and its treatment when filling in this questionnaire.

Hospital
This refers to any contacts you make with the hospital. This includes overnight stays in hospital, outpatient visits, telephone calls to hospital-based health professionals and physiotherapy for example.

Type of service	Have you used the service in the past 3 months? *(tick if yes)*	Total number of days
Hospital inpatient stay (>24 hours, or with an overnight stay)	☐	_____
Unscheduled hospital assessment (<24hrs without an overnight stay)	☐	< 1

Please specify all outpatient services that you have used **since the last questionnaire**.

Type of Outpatient service	Have you used the service in the past 3 months? *(tick if yes)*	Total number of visits	Total number of contacts by telephone
Hospital doctor	☐		
Surgeon	☐		
Hospital nurse	☐		
Breast cancer nurse	☐		
Physiotherapist	☐		
Cancer treatment helpline	☐		
NHS direct	☐		
Other:			

Follow up Patient Questionnaire

Please specify any tests or scans performed in the hospital (e.g. x-ray, CT-scan) **since the last questionnaire**.

Description	Number
Mammogram	
X-ray	
CT-Scan	
Ultrasound	
MRI Scan	
Bone Scan	
ECG	
Other:	

Follow up Patient Questionnaire

Community
This refers to all health care and social care that is **not** based in the hospital. This includes your GP, practice or community nurse, social worker, home help, physiotherapist etc.

Type of service	Have you used the service in the past 3 months? *(tick if yes)*	Total number of clinic visits	Total number of home visits	Total number of contacts by telephone
GP, surgery	☐			
Nurse	☐			
Psychiatrist or Psychologist or Psychotherapist	☐ ☐ ☐			
Physiotherapist	☐			
Other:				

Charity *(e.g. MacMillan, Maggie's, Breast Cancer Care, others please specify)*

Type/name of Charity	Reason/Treatment	Number of visits

Follow up Patient Questionnaire

Travel

This section refers to how much you spent on travel to attend hospital or other health and social care appointments, including any unplanned visits. When you are answering these questions **please refer to the time since the last questionnaire.**

How many miles have you travelled by car? _____ miles

How much have you spent on health-care related parking? £ _____

How much have you spent on fares for public transport, taxis, etc.? £ _____

Other expenses

Do you pay for your prescriptions? Yes ☐ No ☐

Have you personally incurred any other expenses due to your health or treatment?
(e.g. home adaptations, extra laundry, cleaning services)
Please fill in **all costs of the last three month or since the last questionnaire**.

Description	Total cost (£)

End of questionnaire ***Thank you for your time and effort***

ECTU HEAP CardiacCARE v1.1

Final Audit Report 2022-06-12

Created:	2022-06-10
By:	Morag Maclean (mmaclea2@exseed.ed.ac.uk)
Status:	Signed
Transaction ID:	CBJCHBCAABAADa0rKkHIChwfX_TPySbj9vQkpP1DbNji

"ECTU HEAP CardiacCARE v1.1" History

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