Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease (ALL-HEART)

Health Economic Analysis Plan

Study Title:	Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease
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1. Introduction

1.1 Study Background

Allopurinol has several potentially positive effects on the cardiovascular system, is inexpensive and is already widely used in patients with gout. Ischaemic heart disease (angina or heart attack) is a common cause of death in people in the UK and treatment of patients with ischaemic heart disease (IHD) costs the NHS billions of pounds each year. The aim of this study is to improve the treatment of patients with IHD and determine whether adding allopurinol up to 600mg daily to these patients' usual medications will reduce their risk of having a stroke, heart attack or of dying due to cardiovascular disease and is cost-effective.

1.2 Study Objectives

The objective of this Health Economic Analysis Plan is to compare the decision to begin treatment with allopurinol or to continue usual care in patients with IHD in terms of cost-effectiveness..

1.3 Study Design

The study is a multi-centre, controlled, prospective randomised open-label blinded endpoint (PROBE) trial of allopurinol up to 600mg daily vs. no treatment added to usual therapy in patients 60 years and over with ischaemic heart disease (IHD). Full details of the study design, including inclusion and exclusion criteria, can be found in the study protocol.

2. Health Economic Analysis Plan (HEAP)

2.1 HEAP Objectives

The objective of this HEAP is to describe the analyses to be carried out to assess cost-effectiveness in the ALL-HEART Study.

2.2 General Principles

If the trial does not show statistically significant superiority of allopurinol treatment over no treatment on top of usual care with respect to both the primary endpoint and all-cause mortality, the economic evaluation will be restricted to a within-trial assessment of the incremental cost effectiveness ratio (ICER). This is defined to be the ratio of the mean between treatment group difference in costs divided by the mean difference in quality adjusted life years (derived from EQ-5D-5L questionnaire responses). Because of censoring, these quantities will be estimated using inverse probability of censoring weighting (IPCW). The accuracy of the ICER will be assessed using the bootstrap. Results will be displayed graphically in the incremental cost-effectiveness plane. We do not intend to apply time preference discounting to costs or benefits for the within-trial analysis.

If the trial does show statistically significant superiority of allopurinol treatment over no treatment on top of usual care with respect to the primary endpoint or all-cause mortality, the economic

evaluation will be based on a lifetime approach with future costs and benefits based on a Markov Model. Future costs and benefits will be discounted at a rate of 3.5% per annum.

Multiple imputations will be carried out using SAS procedure PROC MI.

For the purpose of the health economic analysis, follow-up will be censored at five years.

2.3 Current Protocol

The current study protocol at the time or writing is version 5, dated 15/02/2019. Future amendments to the protocol will be reviewed for their impact on this HEAP, which will be updated only if necessary. If changes are required to this HEAP following future amendments to the study protocol, this will be documented as part of the Robertson Centre for Biostatistics Change Impact Assessment processes.

2.4 Deviations and Additions To The Analyses Specified In The Study Protocol

The details of the analyses specified in the protocol have been modified. This is based on advice about the type of analysis that HTA might expect in the context of a neutral or negative study and also on the availability of data in the trial. In particular, HRG codes were not available.

2.5 Software

Data will be analysed using R version 4.1.2 for Windows or SAS version 9.3 for Windows, or higher.

2.6 Within-trial Analysis

2.6.1 Study Population

The health economics Full Analysis Population (FAP) will consist of all patients who are randomised and provide EQ-5D-5L health utility data at baseline.

2.6.2 Analyses

2.6.2.1 *Costs*

Costs will be calculated and analysed on a 6-monthly basis from the perspective of the NHS and social services. Costs included in the analysis will be the costs associated with allopurinol treatment, the costs of hospital admissions associated with the components of the primary endpoint (myocardial infarction, stroke and cardiovascular death) and the cost associated with health service usage. Incomplete health service usage data will be imputed and data for intermediate periods prior to follow-up assessments interpolated. Differences between treatment groups in mean costs over the period of follow-up will be calculated using the method of IPCW.

2.6.2.2 *Quality-Adjusted Life Years (QALYs)*

Health utility will be assessed using the EQ-5D-5L questionnaire. EQ-5D-5L utilities will be calculated on a 6-monthly basis. Incomplete data will be imputed and data for intermediate periods

prior to follow-up assessments interpolated. Differences between treatment groups in mean costs over the period of follow-up will be calculated using the method of IPCW.

2.6.2.3 *Incremental Cost Effectiveness Ratio (ICER)*

Patients are asked about their use of resources such as GPs, practice nurses and community nursing at 1 year and the end of the trial. This will cover the preceding 12 months. At interim years 2 3, 4, etc we contacted a randomly selected 25% sample of patients for the same information. In the population with expected data at year 1 and end of trial, missing data will be imputed and results for intermediate time points interpolated for existing data. A similar process will be repeated for the 25% samples.

1000 bootstrap replicates with replacement will be obtained within each treatment group. Single imputations will be repeated within each bootstrap sample. 95% confidence intervals for mean differences in costs, mean differences in QALYs and their ratio (the ICER) will be estimated from the bootstrap samples. The mean differences in costs and QALYs will be plotted on the incremental cost effectiveness plane

2.7 Lifetime projection analysis

If the study does show statistically significant evidence of benefit of allopurinol treatment for the primary endpoint or all-cause mortality, lifetime costs and benefits of treatment with allopurinol will be assessed using a Markov modelling approach. The states in the model will be: no event, events of different types (e.g. alive after stroke, alive after MI), and death (cardiovascular disease and other death). We will estimate transition probabilities from the trial data using a cycle length of 6 months and use this to make projections over the lifetime of the patients. As it is expected that compliance to allopurinol medication will decrease over time, we will project future compliance to allopurinol treatment from within trial data. Likewise, as ALL-HEART is a very large trial of representative ICHD patients with a wide range of ages, we will estimate the decrement in QALYs after a myocardial infarction or stroke and the impact of agingIn addition we will estimate, from within trial data, the hazards of death from cardiovascular or non-cardiovascular causes and the hazards of non-fatal stroke or myocardial infarction. Treatment differences in mean costs and mean quality-adjusted survival time will be calculated in 1000 bootstrap replicates. These will be used to calculate 95% confidence intervals for differences in mean costs, differences in mean quality adjusted survival time and for the ICER.

2.7.1 Cost Effectiveness Acceptability Curve

If neither treatment strategy is clearly dominant (defined as having more QALYs and less cost than the alternative), cost effectiveness acceptability curves will be produced, to indicate the weight of evidence in favour of each treatment strategy being the most cost-effective across a range of values of willingness to pay, between £0 and £50,000 per QALY. The percentage of bootstrap estimates for which each strategy is cost-effective will be reported for willingness to pay values from £0 to £50,000 per QALY in £5,000 increments.

2.7.2 Sub-group analyses

Subgroup analyses will be carried out to assess whether the relative cost-effectiveness of the two treatment strategies might vary between subgroups of the study population. Cost-effectiveness

graphs will be produced for each subgroup, along with ICER estimates and 95% CIs if appropriate. Cost effectiveness acceptability curves will be presented for each subgroup, where appropriate. Subgroups will be defined by the adjustment variables included in the main analyses; continuous variables will be divided at the median to define subgroups. Pre-specified subgroup analyses will include uric acid at baseline split into thirds of its distribution, baseline eGFR 30-59 mL/min/1.73m^2 vs baseline eGFR ≥ 60 mL/min/1.73m^2 and patients aged <70 years vs those aged ≥70 years.

2.7.3 Sensitivity Analyses
Univariate sensitivity analyses will be carried out to test the sensitivity of the overall results to modifications in the estimated unit costs for selected cost components and uncertainty about projected impact on QALYs. Results will be summarised, and presented graphically as tornado plots of the incremental cost effectiveness ratio and/or the cost effectiveness acceptability estimate at willingness to pay values of £20,000 and £30,000 per QALY.

2.8 Costs used in the analyses

Item	Cost (£)	Source
Allopurinol 100mg	0.86 per 28 tablets	BNF (2021)
Allopurinol 300mg	1.20 per 28 tablets	BNF (2021)
GP consultation	39	PSSRU (2021) page 111 https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/
Practice nurse consultation	14	PSSRU page 109 (20 minutes) https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/
Community nurse contact	22	PSSRU page 108 (30 minutes) https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/
Outpatient doctor clinic	140	NICE HTA papers , TA773 https://www.nice.org.uk/guidance/ta773/evidence/committee-papers-pdf-11004994333
Physiotherapy visit	56.00	https://beta.isdscotland.org/topics/finance/file-listings-fy-2019-to-2020/ and Excel file R046
Acute stroke hospitalisation	8767	Jowett S et. al. Cost-Effectiveness of Antihypertensive Deprescribing in Primary Care: a Markov Modelling Study Using Data From the OPTiMISE Trial. Hypertension (2022) 79, 1122–1131
Acute myocardial infarction hospitalisation	5415	Jowett S et. al. Cost-Effectiveness of Antihypertensive Deprescribing in Primary Care: a Markov Modelling Study Using Data From the OPTiMISE Trial. Hypertension (2022) 79, 1122–1131
Cardiovascular death not occurring during a	3126	McEwan P et. al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. European Journal of Heart Failure (2020) 22, 2147–2156

hospitalisation for stroke or myocardial infarction		
Cost per day for a cardiovascular hospitalisation	919	https://beta.isdscotland.org/topics/finance/file-listings-fy-2019-to-2020/ and Excel file R040