The PANDA Study:

Severity and duration of depressive symptoms associated with response to sertraline versus placebo

Version 0.92, January 2018.			
The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents:			
Name	**Role**	**Signature**	**Date**
Padraig Dixon William Hollingworth	Health Economist Co-applicant		
	Chair of DMC		
Glyn Lewis	Chief Investigator		

Change log		
Change	**Date**	**Comments**
Initial version of HEAP drafted	June 2017	
Draft version (v0.9) agreed between health economists – circulated to PI and study manager	20 July 2017	
Revised draft version (v0.91) circulated to PI and trial statistician	23 July 2017	
Revised draft version (v0.92) accepted by PI	02 January 2018	

Contents

1. Health Economics Analysis Plan

1.1 Purpose of plan

The purpose of this health economics analysis plan is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken in the PANDA RCT. The analysis plan is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan (SAP), and it should be read in conjunction with them.

The plan also describes the circumstances under which amendments to planned analysis are permitted and the documentation of such changes; any deviations from this plan will be justified in the final report. The analysis plan is designed as a working document that will evolve throughout data collection, data cleaning and preliminary descriptive analysis. The analysis plan will be finalised before any unblinded comparison between trial arms, with the exception of the section on post-hoc analyses.

1.2 Economic analysis background

Aim

A full description of the study context, setting, patients and interventions is provided in the study protocol. Briefly, the PANDA RCT aims to inform primary care prescribing practice by investigating the severity and duration of depressive symptoms that are associated with a clinically significant response to sertraline compared to placebo, in people presenting to primary care with depression. Participants who consented to participate in the trial will be randomised to receive either sertraline or matching placebo, starting at 50 mg daily for 1 week, increasing to 100 mg daily for up to 11 weeks and then for a 2-week tapering period. Participants, their GPs and the research team will be blind to treatment allocation.

The aim of the economic analysis was to estimate the cost-effectiveness of sertraline in comparison to placebo at the end of 12 weeks follow-up in relation to the baseline severity and duration of depressive symptoms. Secondary analysis will estimate the cost-effectiveness of sertraline in comparison to placebo.

Perspective

The primary economic analysis will be from the NHS and personal social services (PSS) perspective. A secondary analysis will be undertaken from the perspective of individual patients, accounting for

costs such as expenditure on private health care. We will also consider the cost to society of work absences.

Time horizon

The time horizon for the economic analysis will be up to 12 weeks to reflect the duration of follow-up in the trial. As the follow-up period does not extend beyond one year, discounting of costs and benefits will not be applied.

1.3 Economic measurements

Identification of outcomes

The primary economic outcome measure will be Quality Adjusted Life Years (QALYs) derived from utility scores, obtained using the EQ-5D-5L quality of life instrument[1].

Measurement of outcomes

Measurements will be recorded prior to randomisation (baseline), 2 weeks, 6 weeks and 12 weeks post-randomisation. Baseline and research follow-up assessments will take place at the participant's home, general practice, or at university premises.

Valuation of outcomes

Utility scores will be derived from responses to the EQ-5D-5L using valuations obtained from an English population [2]. These will be used to form Quality Adjusted Life Years (QALYs) over the 12-week period, adjusting for any imbalances in baseline EQ-5D-5L scores [3].

Identification of relevant resource use

The process of analyzing resource use in the two arms of the trial involves:

– Identifying the category of resource items used;
– Measuring the quantum of resources used in each category;
– Valuing these quanta of resource use using unit costs.

The analysis will identify which resources are used, calculate a unit cost, and then value overall resource use in each arm of the trial by multiplying unit costs for every item by the associated number of units used.

For the NHS and PSS perspective, data will be collected on use of health services in primary and secondary care including primary care appointments, prescribed medication, hospital admission and outpatient attendance, and community-based care.

For the analysis including the patient perspective, we will additionally collect data on travel costs and expenditure on over-the-counter medication, and private therapies and treatments. The value of productivity losses will be estimated using data on time off work by patients.

Measurement of resource use

Health and social care resource use

Primary care appointments with GPs, practice nurses or healthcare assistants GP will be captured through electronic downloads of GP records; manual data capture may be used as a back-up if GP records do not support automatic downloads.

NHS secondary care, community care, care from social services and patient personal resource use during trial follow-up will be captured using patient-reported questionnaires at 2, 6 and 12 weeks. Examples of the resource use questionnaire are provided in Appendix 1. Our base case analysis will include costs associated with all primary care, community based care and secondary care.

Sensitivity analysis will examine the impact of excluding secondary care and prescriptions extracted from medical records that are judged to be not directly related to the treatment of depression. This will involve a blinded assessment by clinically-qualified co-investigators of all medications (excluding drug classes used for depression) and of secondary care episodes. A simple tripartite classification will be used of "probably directly related", "probably not directly related", and "unsure". We will also conduct a further sensitivity analysis removing all secondary care from cost analyses. This will assess whether recall bias, misclassification, or infrequent but expensive events differed between arms.

Productivity

Time off work by patients will be captured in the patient-reported questionnaires (see appendix).

Personal expenditure on healthcare

Expenditure on over-the-counter medication, and private use of treatments and therapies will be captured in the patient-reported questionnaires at 2, 6 and 12 weeks.

Valuation of resource use

The cost of each resource item will be calculated by multiplying the number of resource units used by the unit cost. The total cost for each individual patient will then be estimated as the sum of the cost of resource-use items consumed. The level of detail employed in each step of this analysis will depend on the likelihood that there will be an economically important incremental difference in

resource use between arms. Drummond et al [1] note that judgment must be formed on how precise cost estimates need to be in a particular study, stating that 'It is not worth investing a great deal of time and effort considering costs that, because they are small, are unlikely to make a difference to the study result…It is still worthwhile identifying such cost categories in any event, although the estimation of them might not be pursued in any great detail'

The costs of medications will be estimated from the British National Formulary. We will assign a zero value to the cost of the placebo therapy used in the control arm. Community and primary care costs will be based on national estimates [4]. Codes for Healthcare Resource Groups (groups of events that have been judged to consume similar levels of resources) will be assigned to secondary care contacts and will be costed based on the most recently published national reference costs where available (*e.g.* DOH [5]). Productivity costs will be estimated based on national average weekly earnings stratified by sex (*e.g.* ONS [6]). Resource use will be combined with unit costs to estimate the incremental cost of the PANDA intervention.

All costs will be reported for the most recent cost year available in pounds sterling, adjusted for inflation if necessary.

1.4 Economic analyses

A cost-effectiveness analysis will be conducted using intention-to-treat principles, comparing the two groups as randomised and including all patients in the analysis. This analysis will estimate how net monetary benefit (see below) varies with baseline severity and with symptom duration. A separate descriptive, non-inferential cost-consequence analysis [7] will compare NHS, PSS and personal costs to response against the primary trial outcome of depressive symptoms measured by the PHQ-9 at 6 weeks post-randomization.

Data cleaning and missing costs and outcomes

We will undertake exploratory analysis to ensure ranges and distributions of variables used in the economic analysis are appropriate. We will also present by arm descriptive statistics of data, such as means, medians, and frequencies.

We will liaise with trial statisticians and project manager in identifying issues with data such as mis-codings. Data cleaning and imputation will be undertaken prior to unblinding by the economic researcher. Data cleaning will include correction of obvious 'free text' response errors (*e.g.* misspelt drug names), group coding of similar resource items (*e.g.* 'orthopaedics' and 'trauma &

orthopaedics' clinics) to enable unit costing, and simple imputation of data missing minor details (*e.g.* missing drug dose) based on reasonable assumptions, provided that this simple imputation can be undertaken conservatively. Any remaining areas of uncertainty will be discussed between two health economists and, where necessary, referred for adjudication by a clinical expert.

The primary analysis will include all participants using multiple imputation to predict missing costs and outcomes [8, 9]. If possible the same imputation models will be used for the primary effectiveness analysis and the economic evaluation. The approach taken to missing data and any imputation will be clearly justified in terms of best practice[9] and the characteristics of the data. The exact specification of an imputation model will depend on the level of missingness of each variable but it will be stratified by arm, and will include available cost measurements, trial arm as a covariate, age, sex, and available EQ-5D-5L scores. There will be a clear discussion of the equations used in any multiple imputation, in line with best practice recommendations [2]. The software package and software version used for multiple imputation will be reported. We will follow the CONSORT recommendation in stating the number of patients included in each analysis.

Analysis of outcomes

We will report the incremental mean difference in QALYs between the two arms of the trial and 95% confidence intervals using linear regression.

Analysis of costs

Overall mean costs and measures of their variance, stratified by NHS & PSS, patient and productivity costs for both arms of the trial will be calculated. We will estimate the incremental mean difference in total costs between the two arms of the trial and 95% confidence intervals using linear regression.

Analysis of cost-effectiveness

Cost and QALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic [10] from the NHS and PSS perspective.

$$NMB_i = \lambda E_i - C_i$$

For each individual *i*, the NMB statistic is given as the cost-effectiveness threshold, λ, multiplied by the patient outcome E_i (*i.e.* QALYs), from which the total cost C_i is subtracted. In the primary analysis we will estimate whether the PANDA intervention is cost-effective at a NICE threshold value of £30,000 per QALY. The purpose of the primary analysis will be to determine how estimates of NMB vary with baseline severity and with symptom duration. We will identify the threshold level of

severity and duration, if any, at which sertraline becomes cost-effective in comparison to placebo, as measured by NMB. We will do this by calculating NMB regressions [11, 12] using interactions between the treatment indicator and baseline severity, and in a separate model between the treatment indicator and symptom duration. Uncertainty in the point estimate of cost per QALY will be quantified using regression methods to calculate confidence intervals around the NMB. We will calculate cost-effectiveness acceptability curves (CEACs) to indicate how the cost-effectiveness of sertraline changes with respect to the cost-effectiveness threshold, while accounting for interactions between severity and depression.

We will conduct a subgroup analysis estimating NMB according to higher and lower baseline severity, and according to longer and shorter symptom duration. We will also undertake a secondary analysis estimating the cost-effectiveness of sertraline to placebo, irrespective of baseline severity and symptom duration. All regression models will adjust for study centre as random effects or other similar methods to reflect site-specific variation.

1.5 Further economic analyses

Further sensitivity analyses

The following sensitivity analyses, not already described above, will be conducted

- Complete case analysis
- An imbalance between arms in the number of deaths is not anticipated. However, such an imbalance, were it to be observed in the trial, could have a material impact on the between-arm comparison. If such an imbalance is observed, a sensitivity analysis excluding people who have died will also be conducted.

Subgroup analysis

As noted, we will undertake a subgroup analysis of net benefit by baseline severity and by net benefit. Any other subgroup analyses developed after unblinding will be described as post hoc analysis.

1.6 Updating the economic analysis plan

Changes to existing analyses

Dated changes to the analysis plan will be documented (see page 2) in this section. We will update the version number reported on the front page and in the footer of the document. Circumstances under which changes will be permitted are as follows.

- Development of statistical methods that are deemed more appropriate for this analysis.
- Clarification of currently debated issues.
- Preliminary data cleaning or analysis (conducted prior to unblinding) suggesting that planned analyses may require amendment.

Post hoc analyses

Any suitable analyses that are identified after unblinding or during the refereeing process will be listed in this section, described as "changes to existing analyses", dated and the source of proposed changes will be identified. Such analyses will be identified clearly as *post hoc* analyses in trial reports.

References

1. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research. 2011;20(10):1727-36.
2. Devlin N, Shah K, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. 2016.
3. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health economics. 2005;14(5):487-96.
4. Curtis L, Burns A. Unit Costs of Health & Social Care. Published annually; Available from: http://www.pssru.ac.uk/project-pages/unit-costs/
5. DOH. NHS Reference costs. Published annually; Available from: https://www.gov.uk/government/collections/nhs-reference-costs
6. Office for National Statistics. Annual Survey of Hours and Earnings Pension Tables Statistical bulletins. Published annually; Available from: http://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/workplacepensions/bulletins/annualsurveyofhoursandearningspensiontables/previousReleases
7. Coast J. Is economic evaluation in touch with society's health values? BMJ. 2004;329.
8. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338:b2393.
9. Faria R, Gomes M, Epstein D, White I. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. Pharmacoeconomics. 2014 2014/12/01;32(12):1157-70.
10. Löthgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health economics. 2000;9(7):623-30.
11. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ. 2002 Jul;11(5):415-30.

12. Hoch JS, Dewa CS. Advantages of the net benefit regression framework for economic evaluations of interventions in the workplace: a case study of the cost-effectiveness of a collaborative mental health care program for people receiving short-term disability benefits for psychiatric disorders. J Occup Environ Med. 2014 Apr;56(4):441-5.

Appendix 1. Examples of resource use data collected

Hospital care – Hospital stay

1. Since your last trial appointment (*date* .....) or in the last *XX* weeks, have you been admitted to hospital for an overnight stay **for any reason?**	**Yes** ☐$_1$ Please give more details below	**No** ☐$_0$ Please go to **A&E**
2. How many separate stays in hospital have you had?	..... stays	

For each separate stay in hospital, how many nights did you stay, what was the main reason for your stay and what treatment did you receive?

Stay	3. Number of nights	4. Reason for stay (*e.g.* psychotic episode, hysterectomy)	5. Did you have surgery?	6. Name of hospital
1				
2				

Hospital Care – A&E

1. Since your last trial appointment (*date* .....) or in the last *XX* weeks, have you been to A&E (Casualty) **for any reason?**	**Yes** ☐$_1$ Please give more details below	**No** ☐$_0$ Please go to **Outpatient Clinic**
2. How many separate visits to A&E have you made?	..... visits	

For each separate visit, what was the main reason you attended A&E?	
Visit	3. **Reason attended A&E** (*e.g.* broken limb)
1	
2	

Hospital Care – Outpatient clinic

1. Since your last trial appointment (*date* .....) or in the last *XX* weeks, have you attended an NHS hospital outpatient clinic **for any reason?**	**Yes** ☐1 Please give more details below	**No** ☐0 Please go to **Community-based NHS care**
2. How many different clinics have you been to?	..... **clinics**	

For each separate location you attended, what was the name of the clinic, how many visits did you make, and what was the reason for attending?

Clinic	3. **Name of clinic** (*e.g.* Psychiatry, Dermatology)	4. **Number of visits**	5. **Reason attended clinic** (*e.g.* diabetes, depression)
1			
2			

Community-based NHS care (i.e. care given outside of a hospital or GP surgery)

1. Since your last trial appointment (*date*.....) or in the last *XX* weeks, have you seen a health care worker face to face or had contact by telephone, provided free by the NHS or charities **because of your mental health?**		Yes ☐$_1$ Please give more details below	No ☐$_0$ Please go to **Home Visits**
		Number of sessions, visits or calls	**Where were these sessions held?** (*e.g.* Brislington, home)
2. Counselling (or talking therapy)	Yes ☐$_1$ No ☐$_0$		
5. Face to face cognitive behavioural therapy (CBT)	Yes ☐$_1$ No ☐$_0$		
8. Computer-based cognitive behavioural therapy (CBT)	Yes ☐$_1$ No ☐$_0$		
11. Mental health clinic	Yes ☐$_1$ No ☐$_0$		
14. Exercise or physical activity scheme or "Exercise on prescription"	Yes ☐$_1$ No ☐$_0$		
17. NHS Direct or "Call 111"	Yes ☐$_1$ No ☐$_0$		
20. NHS walk-in centres	Yes ☐$_1$ No ☐$_0$		
23. Ambulance or hospital transport	Yes ☐$_1$ No ☐$_0$		
26. Other (please specify)	Yes ☐$_1$ No ☐$_0$		

Home visits

1. Since your last trial appointment (*date*.....) or in the last *XX* weeks, have you had any home visits from any of the following healthcare workers **because of your mental health?**	**Yes** ☐1 Please give more details below	**No** ☐0 Please go to **Additional help**
Type of home visit		**Number of visits**
2. a community support worker?	**Yes** ☐1 **No** ☐0	
4. a mental health nurse (CPN)?	**Yes** ☐1 **No** ☐0	
6. an occupational therapist?	**Yes** ☐1 **No** ☐0	
8. a social worker?	**Yes** ☐1 **No** ☐0	
10. a GP?	**Yes** ☐1 **No** ☐0	
12. any other health care professionals?	**Yes** ☐1 **No** ☐0	
14. Other (please specify)	**Yes** ☐ **No** ☐0	

Additional Help

17. Since your last trial appointment (*date*.....) or in the last *XX* weeks, have you received additional help from a home help/ home care worker or attended any groups **because of your mental health?**	**Yes** ☐$_1$ Please give more details below	**No** ☐$_0$ Please go to **Employment and Benefits**

Type of additional help		**Approximately how much have you spent on using this help?**
18. Have you received additional help from a home help/home care worker?	**Yes** ☐$_1$ **No** ☐$_0$	£ : [zero if nothing]
20. Have you been to a day centre/drop-in/social club?	**Yes** ☐$_1$ **No** ☐$_0$	£ : [zero if nothing]
22. Have you been to a self-help group?	**Yes** ☐$_1$ **No** ☐$_0$	£ : [zero if nothing]

Employment and Benefits

24. Are you in paid employment?	Yes ☐ 1 Please answer all the questions below	No ☐ 0 Please go to question 31.

25. Has your ability to work been affected by your mental health or emotional problems (including depression)?

No	0 ☐	If No go to question 31.
Yes, I have had to take sick leave	1 ☐	
Yes, I have reduced my hours	2 ☐	
Yes, my activities at work have been restricted or changed	3 ☐	

26. Approximately how much time have you lost from work since your last appointment (date.....) or in the last xx weeks due to your mental health or emotional problems (including depression)?	..... Working days

27. What was the main way your employer dealt with your absence from work?

Work was done by colleagues in addition to their own work	0	☐
Someone was employed temporarily to cover	1	☐
I had to catch up by doing extra hours when I returned to work	2	☐
The work was not done or it was put off until a further date	3	☐
Other, please specify	4	☐

.....

.....

.....

29. Have you lost any income as a result of this time off work since your last appointment or in the last xx weeks?	**Yes** ☐$_1$ Please answer all the questions below	**No** ☐$_0$ Please go to question 31.

30. In total, approximately how much income have you lost since your last appointment (date……) or in the last xx weeks?	£ …… If unsure please estimate

Other care

31. Since your last trial appointment (*date*……) or in the last *XX* weeks, apart from the care described above and your regular trips to the GP, have you received any other care provided by NHS, social services, or arranged privately?	**Yes** ☐$_1$ Please give more details below	**No** ☐$_0$

32. If Yes, type of care, from whom, how many hours, total cost to date etc….

Comments:

……

……

……

……