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The Health Technology Assessment programme is managed by NETSCC, HTA as part of the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton.

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HTA no 10/30/01: Management of treatment resistant depression

FINAL PROTOCOL

June 2011

1. Title of the project:

Lithium or an atypical anti-psychotic in the management of treatment resistant depression: systematic review and economic evaluation

2. Name of TAR team and project 'lead'

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3. Plain English summary

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration.1

Depression can be categorised into two broad categories; unipolar depression and bipolar depression. People with unipolar depression suffer with only episodes of depression, whereas people with bipolar depression suffer with episodes of low mood, and abnormally elevated mood (also known as mania). The most common mood disorder is unipolar depression and

because the pharmacological treatment of unipolar and bipolar depression are somewhat different we will be focusing on the people with unipolar depression in this report.

Depression may be treated with medication known as antidepressants, various kinds of psychological treatments or self-help measures.

There are lots of different antidepressant medications available and so if someone does not get better with their first treatment a different one may be tried.

This report will focus on people who have unipolar depression and who have not responded to treatment with at least two previous antidepressant medications; we refer to these people as having treatment resistant unipolar depression.

In people with treatment resistant depression it is thought that the addition of another medication such as lithium or an atypical anti-psychotic drug could offer some benefit; however there is limited evidence directly comparing lithium and atypical antipsychotics in people with treatment resistant unipolar depression.[2]

The aim of this report is to identify how effective adding either lithium or an atypical anti-psychotic medication to an antidepressant is at managing people with treatment resistant unipolar depression.

We also aim to perform an economic analysis to see how cost-effective these medications are when used to treat depression.

4. Decision problem

Background

Depression is a common mental disorder affecting about 121 million people worldwide and is among the leading causes of disability.[1] People presenting with depression may complain of depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration.

Depression can be diagnosed clinically using different criteria, the most commonly used of which are the DSM IV criteria as published by the American Psychiatric Association and the ICD 10 criteria developed by the World Health Organisation.[3,4]

Up to two thirds of patients with major depression will either not respond to or will have a sub-optimal response to first line treatment with antidepressants (i.e. they may respond but not enter remission which is the relative absence of clinical symptomatology). There are several potential pharmacological treatment options for patients not achieving sufficient response with antidepressants, one of which is to augment the antidepressant with an agent not approved for use as monotherapy in major depressive disorder.5

Current NICE guidance2 for the sequencing of treatments in depression after an inadequate response to at least one antidepressant recommends that people who are informed about and prepared to tolerate the increased side-effect burden, should be considered for treatment with the combination or augmentation of an antidepressant with lithium or an antipsychotic such as aripiprazole, olanzapine, quetiapine or risperidone or another antidepressant such as mirtazapine or mianserin.

Objective

This report aims to determine the clinical and cost effectiveness of SSRI antidepressant therapy with either lithium or an atypical anti-psychotic in the management of people with treatment resistant unipolar depression.

For this review, treatment resistant depression will be defined as failure to respond to at least two previous antidepressant medications. We will not impose restrictions on the maximum number of previous antidepressant drugs allowed so as not to reduce the amount of data available for analysis as we aware that there will be limited relevant SSRI RCT data available. This assumes that there is a consistent relative treatment effect independent of line of therapy; i.e. addition of an atypical or lithium has the same relative benefit whether given with third line SSRI or fourth line SSRI, etc. However, a sensitivity analysis will be conducted to assess the impact of this assumption.

PICO criteria

The planned PICO is as follows:

- **Population:** Adults with treatment resistant unipolar depression defined as failure to respond to at least two previous antidepressants in the current episode of depression only.
- **Intervention:**
    - An **SSRI (selective serotonin reuptake inhibitor)** (defined as either Citalopram (Cipramil), Escitalopram (Cipralex), Fluoxetine (Prozac, Felicium,

Prozep, Prozit), Fluvoxamine (Faverin), Paroxetine (Seroxat) or Sertraline (Lustral))

PLUS

- **An atypical anti-psychotic drug** (defined as either Amisulpride (Solian), Aripiprazole (Abilify), Clozapine (Clozaril, Denzapine, Zaponex), Olanzapine (Zyprexa, Zypadhera), Paliperidone (Invega), Quetiapine (Seroquel), Risperidone (Risperdal) or Ziprasidone (Geodon))

- **Comparator:**
  - **An SSRI** (defined as either Citalopram (Cipramil), Escitalopram (Cipralex), Fluoxetine (Prozac, Felicium, Prozep, Prozit), Fluvoxamine (Faverin), Paroxetine (Seroxat) or Sertraline (Lustral))

    PLUS
  - **Lithium** (Lithium carbonate (Camcolit, Liskonum, Priadel) or Lithium citrate (Li-Liquid, Priadel) or Lithium (Litarex, Lithonate, Phasal))
- **Outcomes:**
  - Disease severity
  - Quality of life
  - Adverse effects
  - Withdrawals (all cause) as a surrogate outcome for adherence to medication
  - Relapse rate
  - Mortality
  - Cost effectiveness

Subgroup analyses

The planned subgroup analyses are as follows:

- Different durations of depression (i.e. time since first onset of current episode of depression)
- Class's of previous antidepressants (e.g. SSRI or tricyclic antidepressant)
- Genders (i.e. males and females)
- Age (i.e. those <75 years and those ≥75 years old)
- People with different severity's of depression (i.e. based on trial entry Hamilton Depression Rating Scale rating)

Objectives

The key areas that we plan to address in this report are:

- To identify and review the existing evidence relating to the clinical outcomes as pre-specified above
- To report the cost effectiveness of these treatments
- To identify what the potential areas for future research might be

5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the PRISMA statement (formerly the QUOROM statement).6

Search strategy

The search strategy will comprise the following main elements:

1. Searching of electronic bibliographic databases
2. Contact with clinical experts in the field
3. Review of the reference lists of retrieved papers

1. The electronic databases that will be searched are EMBASE, MEDLINE, PsycINFO and the Cochrane Controlled Trials Register.

   We will also search the clinicaltrials.gov website to identify relevant ongoing clinical trials that when completed may have an impact on the results of this review, to assist us in drawing up our final recommendations.

2. We will contact clinical experts in the relevant therapy areas to request details of trials (published and unpublished) of which they may be aware. We will allow the experts 1 calendar month to provide an initial response, with any additional time allowed being dependent on whether we have reached the data analysis stage of the review..

3. The references from any relevant review papers or randomised controlled trials (RCTs) uncovered in the search will also be examined for additional references potentially relevant to the review.

Abstract appraisal

Titles and abstracts of studies identified by the search process will be assessed independently by two reviewers (VH and SB) for inclusion. In cases where the reviewers are unable to reach

a consensus as to whether the full text should be obtained for further appraisal, the full text will be obtained.

When potentially relevant data are available in only an abstract format then we will attempt to contact the corresponding author in order to obtain the full publication; however, there will be a pre-specified deadline of 1 calendar month by which they will need to have contacted us, but we may allow additional time for them to supply the data requested depending on where we are in the review process. Any information supplied after the deadline will be included in only the discussion section of the review report.

Inclusion criteria

- For the review of clinical effectiveness, only RCTs will be included
- Adults ≥18 years
- People with unipolar depression only
- Treatment resistant depression defined as failure to respond to at least two previous antidepressants in the current episode of depression only
- SSRI (selective serotonin reuptake inhibitor) given as baseline treatment and patient randomised to either lithium or an atypical anti-psychotic
- Minimum duration of 4 weeks treatment with study medication for the current episode of depression
- Studies reporting on one or more of the following outcomes:
    - Disease severity
    - Quality of life
    - Adverse effects
    - Adherence to medication or withdrawals (all cause)
    - Relapse rate
    - Mortality
    - Cost effectiveness

Exclusion criteria

- Non-randomised studies
- Narrative reviews, editorials, opinions
- Studies performed in animals
- Studies not focusing on the treatment of the acute phase of depression (i.e. those only focusing solely on maintenance therapy)
- Bipolar depression or bipolar disorder diagnosis prior to study entry

- Underlying medical condition or another substantial co-morbid psychiatric condition
- Trials reporting only post-crossover results

Study inclusion assessment

Two reviewers (VH and SB) will independently assess for inclusion the full text of the trials identified during the abstract assessment stage and any differences in opinion will be arbitrated by a third reviewer (SJE).

Data extraction strategy

Data will be extracted by one reviewer (VH) using a standardised data extraction form (for draft copy of data collection form, please see appendix 10.2) and validated by second reviewer (SB).

A pragmatic decision for data validation will be made depending on the number of trials identified due to the time constraints for completing this review. If a large number of trials are identified then all data will be validated (checked) by a second reviewer, with a sample being fully independently data extracted. This sample will be 25% or a minimum of 5 papers (whichever is larger).

The Data Extraction Form will be pilot tested on a sample of three papers by the reviewers and a final version agreed.

Discrepancies in the data extracted by the two reviewers will be resolved through discussion, with involvement of a third reviewer (SJE) if necessary.

Data from intention-to-treat (ITT) analyses will be extracted (per protocol (PP) data will also be extracted for use in a sensitivity analysis). Should a trial not report ITT data, we will treat missing data as treatment failures to allow our analysis to conform to an ITT analysis. For the purpose of this review, ITT will be defined as patients being analysed in the treatment group they were allocated to at randomisation regardless of whether they received the wrong intervention, withdrew or were lost to follow-up.

Study authors will be contacted to supply any additional information not included in published sources (including pre-crossover results in those trials reporting only post-crossover results) and there will be a pre-specified deadline by which we would require a response. The deadline will be 1 calendar month from the date of sending the request by which time they

must have contacted us with at least an initial response acknowledging their intent to supply some of the information required. We may allow additional time for them to supply the data requested depending on where we are in the review process, however any information received after the deadline will be included in only the discussion section of the review.

Quality assessment strategy

Outcomes from the studies that meet the inclusion criteria will be assessed using the updated risk of bias tool developed by the Cochrane Collaboration (March 2011).[7]

These criteria assess the following areas:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcomes assessment
5. Incomplete outcome data
6. Selective reporting
7. 'Other bias'

Based on these criteria, an assessment for each outcome reported in the trial will be allocated based on the identified risk of bias. The three bias assessment categories used will be: low risk, high risk and unclear risk. Unclear risk is likely to be assigned due to poor reporting of how the trial was conducted rather than a poorly conducted trial.[8] Trials that are deemed to be at low or unclear risk of bias will be included in the main analysis; however, the trials rated high risk will be included in a sensitivity analysis.

Two reviewers (VH and SB) will independently rate the trial outcomes for inclusion and any differences in opinion will be arbitrated by a third reviewer (SJE). An outcome from an RCT will be considered appropriate for inclusion unless the trial demonstrates some feature that necessitates the exclusion of that outcome.

Methods of analysis/synthesis

Data will be tabulated and, where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on ITT analyses (with a sensitivity analysis based on per protocol data).

We will not be assuming there is a class effect for any of the drugs included and so each individual drug will be considered separately in the review, i.e. each SSRI and atypical antipsychotic or lithium combination will form separate analyses.

Standard pair-wise meta-analysis will be conducted when more than one trial is identified for inclusion for any pair of treatments under investigation. This will be carried out using a fixed effects model with the Mantel-Haenszel method.[9] Sensitivity analysis will be conducted using a random effects model with the DerSimonian & Laird method.[10]

It is anticipated that a mixed treatment comparison (MTC; also called a multiple treatment meta-analysis and network meta-analysis) will need to be conducted to estimate the effects of the different treatments included in the research. An MTC can be seen as an extension of traditional pair-wise meta-analysis.[11,12,13] It has advantages over standard pair-wise meta-analysis as it is based on a network of connected trials where a new trial may enter the network if it is in a clinically comparable patient population, has a similar design to other trials incorporated in the network and contains at least one treatment that already exists within the network. It has been argued that this underlying assumption of exchangeability of data is no different from the practice within standard pair-wise meta-analysis of combining similar trials.

The MTC will be conducted based on a fixed effects and a random effects model with the most appropriate model identified as the one with the lowest deviance information criterion (DIC).[14] DIC measures the fit of the model while penalising for the number of effective parameters.[12,15] For the chosen model, consistency of the evidence will be assessed using the posterior mean residual deviance, which should approximate the number of unconstrained data points in a good-fitting model.

For dichotomous outcomes we will use odds ratio as the summary statistic, and for continuous outcomes we will use the weighted mean difference as the summary statistic.

- Primary analysis will be:
    - Disease severity (measured by a reduction of at least 50% on Hamilton Depression Rating Scale (HDRS)[16] or Montgomery-Åsberg Depression Rating Scale (MADRS)[17]. Where a study reports both we will use only the HDRS data).

- Secondary analyses will be:
    - Quality of life (QoL) as reported using a validated QoL rating scale[18], e.g. EQ-5D, SF-36, HUI.
    - Adverse effects (data will be collected on those adverse effects most burdensome to patients such as agitation, akathisia, anxiety, cognitive dulling, constipation, diarrhoea, dry mouth, dyspepsia, extrapyramidal symptoms, kidney and thyroid dysfunction, lipid disturbance, gastrointestinal bleeding, (orthostatic) headache, hyperglycaemia, hypotension, nausea, polyuria, restlessness, sedation, sexual dysfunction, sleep disturbance, thirst, tremor, visual problems, and weight gain).
    - Withdrawals (all cause) as a surrogate outcome for adherence to medication
    - Relapse rate
    - Mortality (all cause)
- 8-week outcome data will be collected where reported. If 8-week data are not available, we will use outcome data reported from the nearest available time point
- Subgroup analyses will be performed in the following populations on only the primary outcome (disease severity), subject to the availability of data:-
    - Different durations of depression (i.e. time since first onset of current episode of depression, short term <6 months, long term >6 months)
    - Class's of previous antidepressants (e.g. SSRI or tricyclic antidepressant)
    - Genders (i.e. males and females)
    - Age (i.e. those≥75 years and those <75 years old)
    - People with different severity's of depression, i.e. based on trial entry HDRS rating using the following categories: [16]
        - 0-7 = Normal
        - 8-13 = Mild Depression
        - 14-18 = Moderate Depression
        - 19-22 = Severe Depression
        - ≥ 23 = Very Severe Depression

In the absence of suitable data to perform a meta-analysis, the available data will be tabulated where possible and discussed in a narrative review.

Heterogeneity

In addition to the existing pre-specified subgroups, other potential sources of clinical heterogeneity could be a result of combining different preparations of drugs.

For pair-wise meta-analysis, heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic. Statistically significant heterogeneity will be defined as $p<0.10$. Levels of inconsistency will be assessed using $I^2$and will be defined as follows: I^2 of: 0%–25% = low level of inconsistency; 26%–50% = moderate level of inconsistency; and >50% = high level of inconsistency.19

If statistically significant heterogeneity is detected in any of the primary or secondary analyses, hypothesis-generating subgroup analysis will be conducted, but the results from such analyses will be treated with caution. Meta-regression will be attempted if significant statistical heterogeneity is identified among trials analysed and there are 10 or more trials in the review.

For the MTC, where a random effects model is deemed the best fit, the degree of heterogeneity will be investigated by evaluating the posterior mean tau-squared. Where possible, any closed loops formed by the network of trials will be assessed separately to determine if the results from the "direct" evidence is coherent with the "indirect" evidence when the wider network is introduced. Any incoherence identified will be investigated.

Sensitivity analysis

Sensitivity analyses are planned on the primary analysis and consist of:

- different number of prior antidepressants for the current episode of depression;
- assuming a "class" effect with SSRIs and atypical antipsychotics;
- changing the quality assessment to include the trial outcomes excluded on grounds of methodological quality; i.e. those categorised as of high risk of bias;
- changing the analysis from using ITT (intention to treat) data to per protocol data.

Publication bias

For each of the primary pair-wise meta-analyses, a funnel plot will be used to assess publication bias. A regression of normalized effect versus precision will also be calculated as a test for small study effects (using a $p<0.10$ as an indicator of a significant result).20

6. Report methods for synthesising evidence of cost-effectiveness

Identifying and systematically reviewing published cost-effectiveness studies

The following databases will be used to identify studies of the cost-effectiveness. MEDLINE, EMBASE, PsycINFO, CINAHL NHS Economic Evaluation Database, Health Technology Assessment Database and Office of Health Economics Health Economic evaluation database. We will apply a cost search filter to the comprehensive clinical search strategy described in section 5.

In order to express clinical outcomes in the form of QALYs, utility weights for health states relating to treatment resistant depression are required. Utility weights represent the health related quality of life (HRQOL) associated with specific health states; they are estimated based on people's preferences and perceptions of quality of life characterising the health states under consideration. We will undertake a systematic quality of life search where health economics and quality-of-life search filters will be used in MEDLINE, EMBASE, PsycINFO and CINAHL to identify relevant studies.

The inclusion and exclusion criteria for economic evaluations will be the same as those for the systematic review of clinical effectiveness and in addition the health economic evaluation will also include:

- non-randomised studies will be included (e.g. decision-model based analysis or analysis of person-level cost and effectiveness data alongside observational studies)
- full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequence analyses will be included
- stand-alone UK cost analysis will also be sought and appraised

Titles and abstracts returned by the search strategy will be assessed independently by two health economists (LN and NT) and screened for possible inclusion. Any disagreements will be resolved by a third health economist (SJE).

Evaluation of costs and cost effectiveness (may include development of a de novo economic model)

The methodological quality of economic evaluations will be assessed according to internationally accepted criteria such as the Consensus on Health Economic Criteria list questions developed by Evers *et al* (2005).21 Any studies based on decision models will be assessed using the checklist developed by Phillips *et al* (2004).18

In addition, a new economic evaluation will be carried out from the perspective of the UK NHS using a probabilistic decision analytic (Markov) modelling approach to estimate the costs and QALYs of SSRI with an atypical anti-psychotic compared with SSRI with lithium in the management of treatment resistant unipolar depression. An annual discount rate of 3.5% will be used for both costs and QALYs in accordance with NICE guidance.22 Model structure, data inputs and modelling assumptions will be determined in consultation with clinical experts to ensure they reflect the best current clinical practice and evidence. Uncertainty in the data used to populate the model will be characterised using appropriate methods, such as probabilistic sensitivity analysis. The time horizon of our analysis will preferably be a patient's lifetime in order to reflect the chronic nature of the disease. However time horizon may be dictated by the availability of data in which case shorter time horizons will be modelled.

Ideally, evidence on the impact of these therapies on HRQoL will be available directly from the trials included within the review. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources, such as related technology appraisals or clinical guidelines. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. We will also adjust utility for age using data from the Health Survey of England.23

Results will be presented as incremental cost-effectiveness ratios (ideally cost per quality adjusted life year) and cost-effectiveness acceptability curves, which quantify the degree of uncertainty.

7. Expertise in this TAR team

TAR Centre

The BMJ Evidence Centre comprises over 30 specialists with a wealth of experience in diverse health-related areas and includes clinicians, pharmacists, information specialists, health informatics specialists, project managers, systematic reviewers, clinical guideline developers and health economists.

The BMJ-TAG core team consists of 5 members. Together, we have an array of experience amongst us in producing focussed reports in a short timescale for policy customers such as NICE. Please see below for further details of each team member's experience.

- **Dr Steven J. Edwards DPhil MSc BSc (Hons), Head of Health Technology Assessment**

  Over the past 12 years, Steve has conducted over 40 systematic reviews and health economic evaluations in a range of therapeutic areas including cardiovascular, CNS, gastroenterology, infection, oncology and respiratory medicine. His interests are in the use of the best available evidence for decision making with an emphasis on the design and conduct of clinical trials, systematic reviews, meta-analyses, adjusted indirect comparisons and their subsequent use in economic evaluations. His postgraduate research in this area at the University of Oxford resulted in him being awarded the first doctorate of evidence based health care. In addition, Steve is an honorary senior lecturer in health economics at the London School of Hygiene & Tropical Medicine, a member of the Cochrane Statistical Methods Group, the Campbell & Cochrane Economics Methods Group, and an Editorial Board member of the *International Journal of Clinical Practice*.

- **Dr Samantha Barton PhD BSc (Hons), Health Technology Assessment Analyst**

  Sam has extensive experience in the critical appraisal of studies. During the past 4 years, she has contributed to the publication of over 50 systematic reviews on prevention and treatment of various clinical conditions. She has worked on reviews in the areas of mental health, sexual health, infectious diseases, cardiovascular disorders, respiratory disorders and oncology.

- **Dr Victoria Hamilton MBChB, Health Technology Assessment Analyst**

  Vicky has a clinical background with relevant experience in the fields of general surgery, general medicine, general practice, paediatrics and orthopaedic surgery. Vicky also has experience in the critical appraisal of clinical studies and over the last year has contributed to the publication of systematic reviews in a variety of clinical areas. She also has experience in the process and use of clinical audit to review current clinical practice within both primary and secondary care settings.

- **Mr Leo Nherera MSc BSc (Hons), Health Economist**

  Over the past 6 years, Leo has been working for the NICE clinical guideline programme and has successfully worked in eight published clinical guidelines and one Public Health guideline. His work involved appraising economic evaluations as well as doing original economic analysis for various guideline questions to assist in guideline recommendations. Leo was involved in organising and teaching the

Health Economics module at Queen Mary University of London. He has also peer-reviewed papers for the *International Journal of Clinical Practice*. His interests are in the use of the best available evidence for decision making with an emphasis on systematic reviews and meta-analyses and their subsequent use in economic evaluations.

- **Ms Nicola Trevor MSc BSc (Hons), Health Economist**
  Nicola has a strong mathematical background, with a Masters in analytical, numerical and statistical modelling techniques, which over the past 2 years she has applied in the field of health economics, conducting economic evaluations and statistical analysis for systematic review in disease areas such as multiple sclerosis, cardiovascular disease, Gaucher's disease and oncology. Her interests are in the use of the best available techniques for decision making with an emphasis on survival analysis, meta-analysis, modelling approaches and the use of Bayesian methods in economic evaluations.

Recent publications from the team members include:

- Halpin DMG, Gray J, Edwards SJ, et al. Budesonide/formoterol versus salmeterol/fluticasone in COPD: a systematic review and adjusted indirect comparison of pneumonia in randomized controlled trials. *International Journal of Clinical Practice* 2011; **65**: (in press).
- Nherera L, Marks D, Minhas R, et al. Probabilistic cost-effectiveness analysis of cascade screening for Familial Hypercholesterolaemia using alternative diagnostic and identification strategies. *Heart* 2011; **97**: (in press).
- National Collaborating Centre for Women's and Children Health. Multiple pregnancy: The management of twin and triplet pregnancy in the antenatal period London, Royal College of Obstetricians and Gynaecologists, 2011; (in press).
- Edwards SJ, Wordsworth S, Clarke MJ. Treating pneumonia in critical care in the UK following failure of initial antibiotic: a cost-effectiveness analysis comparing meropenem with piperacillin/tazobactam. *European Journal of Health Economics* 2011; **12**: (available online first at: www.springerlink.com/content/q044j5t32601vt4l/).
- Edwards SJ, Borrill J. Network meta-analysis: importance of appropriate trial selection. *Value in Health* 2010; **13**: 681-2.

- Edwards SJ, von Maltzahn R, Naya IP, et al. Budesonide/formoterol for maintenance and reliever therapy: a meta-analysis of randomised controlled trials. *International Journal of Clinical Practice* 2010; **64**: 619-27.
- Gray J, Edwards SJ, Lip GYH. Comparison of sequential rosuvastatin doses in hypercholesterolaemia: a meta-analysis of randomized controlled trials. *Current Medical Research and Opinion* 2010; **26**: 537-47.
- Trevor NC, Alnwick K. How can the use of predictive biomarkers lead to positive HTA recommendations? *Value in Health* 2010*;* **13**: A423-4.
- Trevor NC, Tang M, Samuels ER. Investigating the impact of R&D investment and policy on innovative performance in Europe. *Value in Health* 2010; **13**: A414.
- Edwards SJ, Gray J. Budesonide/formoterol plus tiotropium (BUD/FORM+TIO) vs salmeterol/fluticasone plus tiotropium (SALM/FLU+TIO): a systematic review and adjusted indirect comparison between two alternative triple treatments in chronic obstructive pulmonary disease (COPD). *Value in Health* 2010; **13**: A319.
- Edwards SJ, Welton NJ, Borrill J. Gefitinib compared with doublet chemotherapy for first-line treatment non-small-cell lung cancer (NSCLC) a systematic review and adjusted indirect comparison. *Value in Health* 2010; **13**: A252-3.
- Edwards SJ, Welton NJ, Borrill J. Tolerability of first-line treatments of locally advanced or metastatic non-small-cell lung cancer (NSCLC) a systematic review and adjusted indirect comparison. *Value in Health* 2010; **13**: A250.
- Nherera L, Calvert NW, DeMott K, et al. Cost effectiveness analysis of the use of a high intensity statin compared to a low intensity statin in the management of patients with familial hypercholesterolaemia. *Current Medical Research and Opinion* 2010; **26**: 529-36.
- Visintin C, Mugglestone MA, Almerie MQ, et al. on behalf of the Guideline Development Group. Management of hypertensive disorders during pregnancy: summary of NICE guidance. *British Medical Journal* 2010; **341**: c2207.
- National Collaborating Centre for Women's and Children Health. Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. London, Royal College of Obstetricians and Gynaecologists 2010.

External Clinical Expert Advisors

- **Professor Philip J. Cowen - MRC Clinical Scientist and Professor of Psychopharmacology; Specialist in Psychopharmacology of Mood Disorders.** Neurosciences Building,

Warneford Hospital,
Oxford OX3 7JX,
United Kingdom
phil.cowen@psych.ox.ac.uk

Recent publications include:

- McCabe C, Mishor Z, Cowen PJ, et al. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biological Psychiatry* 2010; **67**: 439-45.
- Harmer CJ, O'Sullivan U, Favaron E, et al. Effect of acute antidepressant administration on negative affective bias in depressed patients. *American Journal of Psychiatry* 2009; **166**: 1178-84.
- Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry* 2008; **195**: 102-8.
- Gelder M, Cowen P, Harrison P. Shorter Oxford Textbook of Psychiatry. Oxford University Press, Oxford, 1995, 2001, 2006.

- **Dr Luiz Dratcu - Consultant Psychiatrist and Specialist in Psychopharmacology, Treatment Resistant Mental Illness, Schizophrenia and Affective Disorders.**

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Recent publications include:

- Dratcu L. The quest for the pharmacological treatment of schizophrenia: from conventional neuroleptics to atypical anti-psychotics and beyond. *Vertex* 2010; **21**: 385-93.
- Dratcu L. The future of depression: a complex neuroendocrine, inflammatory and neurodegenerative systemic illness. *Vertex* 2009: **20**: 329-41.

- Dratcu L, Grandison A, McKay G, et al. Clozapine-resistant psychosis, smoking, and caffeine: managing the neglected effects of substances that our patients consume every day. *American Journal of Therapeutics* 2007; **14**: 314-8.
- Dratcu L, Olowu P, Hawramy M, et al. Aripiprazole in the acute treatment of male patients with schizophrenia: effectiveness, acceptability, and risks in the inner-city hospital setting. *Neuropsychiatric Disease and Treatment* 2006; **2**: 191-7.

8. Competing interests of authors

Steve Edwards has previously been an employee of AstraZeneca, which holds the marketing authorisation for Seroquel® (quetiapine). He has no ongoing financial connection nor owns significant shares with AstraZeneca.

Professor Philip J. Cowen has received consultancy fees from Servier, Lundbeck and Eli Lilly, and fees for speaking from AstraZeneca, Servier and Lundbeck. He has also provided advice to legal representatives of GSK.

Dr Luiz Dratcu has received consultancy fees, fees for speaking and hospitality from BMS/Otsuka and Merck. He has also received hospitality from Lilly.

9. Timetable/milestones

Finalise protocol – June 2011
Send progress report to NETSCC, HTA – February 2012
Submit assessment report to NETSCC, HTA – March 2012

The timetable is based on a 6-month working time-frame, commencing in mid-July assuming that the final approval of the protocol has been received by this time.

Timelines may be subject to change in the event of any additional urgent work commitments such as STA work for NICE; however we will endeavour to inform NETSCC of any commitments which may delay the completion of this project at the earliest possible date.

10. Appendices

10.1.1. Draft MEDLINE search strategy (Clinical)
10.1. 2. Draft MEDLINE search strategy (Health Economics and Quality of life)
10.2. Data extraction form

10.3 Team members' contributions

10.4 References

Appendix 10.1.1 Draft MEDLINE search strategy

<1948 to June Week 1 2011>

Search Strategy:

1 Randomized Controlled Trials as Topic/ (73451)

2 randomized controlled trial/ (308386)

3 Random Allocation/ (71692)

4 Double Blind Method/ (110600)

5 Single Blind Method/ (15044)

6 clinical trial/ (463236)

7 clinical trial, phase i.pt. (11244)

8 clinical trial, phase ii.pt. (17834)

9 clinical trial, phase iii.pt. (6176)

10 clinical trial, phase iv.pt. (614)

11 controlled clinical trial.pt. (82578)

12 randomized controlled trial.pt. (308386)

13 multicenter study.pt. (131287)

14 clinical trial.pt. (463236)

15 exp Clinical Trials as topic/ (242013)

16 or/1-15 (859148)

17 (clinical adj trial$).tw. (155138)

18 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (107934)

19 PLACEBOS/ (29733)

20 placebo$.tw. (129547)

21 randomly allocated.tw. (12594)

22 (allocated adj2 random$).tw. (14831)

23 or/17-22 (326697)

24 16 or 23 (954423)

25 case report.tw. (158367)

26 letter/ (716157)

27 historical article/ (275084)

28 or/25-27 (1139766)

29 24 not 28 (928335)

30 exp Depression/ or exp Depressive Disorder/ (127115)

31 (depress* or adjustment disorder* or mood disorder* or affective disorder* or affective symptom* or dysthymi* or dysphori*).mp. (344159)

32 30 or 31 (344159)

33 29 and 32 (39592)

34 Serotonin Uptake Inhibitors/ or Antidepressive Agents, Second-Generation/ or ssri*.mp. or exp Serotonin
Antagonists/ (59672)

35 citalopram.mp. or exp Citalopram/ (4058)

36 escitalopram.mp. (779)

37 fluoxetine.mp. or exp Fluoxetine/ (9218)

38 fluvoxamine.mp. or exp Fluvoxamine/ (2286)

39 paroxetine.mp. or exp Paroxetine/ (4469)

40 sertraline.mp. or exp Sertraline/ (2966)

41 36 or 37 or 38 or 39 or 40 (16313)

42 35 and 41 (1722)

43 35 or 37 or 38 or 39 or 40 (18583)

44 36 and 43 (713)

45 35 or 36 or 38 or 39 or 40 (11526)

46 37 and 45 (2095)

47 35 or 36 or 37 or 39 or 40 (17294)

48 38 and 47 (931)

49 35 or 36 or 37 or 38 or 40 (15845)

50 39 and 49 (1665)

51 35 or 36 or 37 or 38 or 39 (16994)

52 40 and 51 (1311)

53 42 or 44 or 46 or 48 or 50 or 52 (3310)

54 33 and 53 (799)

55 lithium.mp. or exp Lithium Carbonate/ or exp Lithium/ or exp Lithium Compounds/ or exp Lithium Chloride/ (29746)

56 (antipsychotic* or anti?psychotic* or anti-psychotic*).mp. (41739)

57 amisulpride.mp. (571)

58 aripiprazole.mp. (1454)

59 clozapine.mp. (8530)

60 olanzapine.mp. (5275)

61 paliperidone.mp. (153)

62 quetiapine.mp. (2428)

63 risperidone.mp. (5910)

64 or/34-40 (66927)

65 or/55-63 (72543)

66 33 and 64 and 65 (713)

67 54 or 66 (1455)

10.1. 2. Draft MEDLINE search strategy (Health Economics and Quality of life)

Economics search terms

1. exp economics/ (438053)
2. exp Costs and Cost Analysis/ (38816)
3. Cost Benefit Analysis/ (51007)
4. value of life/ (5162)
5. exp models economic/ (7945)
6. exp fees/and charges/ (7703)
7. exp budgets/ (10939)
8. (economic adj2 burden).tw. (2622)
9. (expenditure* not energy).tw. (14210)
10. budget*.tw. (14415)
11. (economic* or price* or pricing or financ*or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw. (128436)
12. (decision adj1 (tree* or analys* or model*)).tw. (6411)
13. Resource Allocation/ (6522)
14. (unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw. (16355)
15. ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw. (3225)
16. Markov Chains/ (7220)
17. exp Decision Support Techniques/ (48239)
18. (resource adj2 (use* or utili* or allocat*)).tw. (10801)
19. (cost adj2 (util* or effective* or efficac* or benefit* or consequence* or analys* or minimi* or allocation* or control* or illness* or affordable* or fee* or charge* or charges)).tw. (71017)
20. or/1–19 (627358)

*Combining condition, intervention, comparator and cost terms gets a total of **36** studies potential cost-effectiveness abstracts.*

Quality of life search terms

1. exp quality of life/ (90943)
2. quality of life.tw (100676)
3. life quality.tw (2525)
4. (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw (11072)
5. (euroqol or eq5d or eq 5d).tw (2147)
6. quality adjusted life$.tw (3963)
7. (QALY$ or lifeyear$ or life year$ or ((qualit$3 or value) adj3 (life or survival))).tw. (108136)
8. ((burden adj3 (disease or illness)) or (resource adj3 (allocation$ or utilit$)) or (value adj5 money)).tw. (12216)
9. (budget$ or cost$ or econom$ or expenditure$ or financ$ or fiscal$ or funding or pharmacoeconomic$ or price or prices or pricing).tw. (441366)
10. (Hamilton depression rating scale$).ab. (2004)
11. (Montgomery-Asberg depression rating scale$).ab. (1004)
12. or/1-11 (575570)

*Combining condition, intervention, comparator and quality of life terms gets a total of **136** potential quality of life abstracts.*

Appendix 10.2. Data extraction form

PART ONE: REVIEW, REVIEWER AND STUDY INFORMATION

Study ID:

Reviewer name:

Date of completion of this form:

Title of paper/abstract:

Source (journal, year, volume, pages):

Authors:

Language of publication:

Type of paper (e.g. full paper/abstract/poster):

PART TWO: VERIFICATION OF STUDY ELIGIBILITY

Type of clinical trial

1) Is the study randomised?	YES	UNCLEAR	NO

Population in the clinical trial

2) Is the population adults ≥18 years old?	YES	UNCLEAR	NO
3) Did the RCT include people with unipolar depression?	YES	UNCLEAR	NO
4) Did the RCT include people with treatment resistant depression (defined as failure to respond to ≥2 antidepressants)?	YES	UNCLEAR	NO

Interventions in the clinical trial

5) Does the trial compare SSRI + atypical antipsychotic or lithium or no treatment **with** SSRI + lithium or atypical antipsychotic or placebo or no treatment?	YES	UNCLEAR	NO
6) Did both groups experience the same care except for the two interventions under investigation?	YES	UNCLEAR	NO

Outcomes of the clinical trial

7) Does the study report on outcomes during the treatment of the acute phase of depression?	YES	UNCLEAR	NO

8) Did the clinical trial investigate at least one of the following: disease severity, quality of life, adverse events, withdrawals (all cause), relapse rate, mortality (all cause)? YES UNCLEAR NO

9) Are the outcomes measured after ≥4 weeks treatment with study medication? YES UNCLEAR NO

If you answered NO to any of the above questions do not proceed to Part 3.

PART THREE: INFORMATION ABOUT THE STUDY

Characteristics of the trial

Country(ies) where the clinical trial was conducted:

Sponsors of the clinical trial:

Any conflicts of interest reported for any of the researchers?

Date the clinical trial was conducted:

Type of clinical trial design (e.g. parallel, crossover, or cluster trial):

If the trial was of crossover design, are there pre-crossover results reported?

Was the trial multicentre? If so, how many centres were there?

Characteristics of the patients

Inclusion criteria: how and where were patients enrolled, were any patient risk factors used? What details of the antidepressant(s) patients had failed to respond to are provided?

Exclusion criteria: were specific groups of people excluded?

Total number of people randomised:
Information on the age of the patients:
Information on the sex of the patients (m/f):
Information on the ethnicity of the patients:
Information on patients' medical history (i.e. previous depression):

Type of intervention

Intervention 1: SSRI + XX *(where XX = atypical anti-psychotic or lithium or no treatment)*

SSRI name and brand:
SSRI dose and regimen used (e.g. 80mg OD):
Delivery of SSRI (e.g. PO tablet/dissolvable/enteric coated):
Number of doses of SSRI given per day (with SD/SE if given):
Duration of SSRI treatment in days (with SD/SE if given):

What was XX (name and brand)?
XX dose and regimen used (e.g. 80mg OD):
Delivery of XX (e.g. PO tablet/dissolvable/enteric coated):
Number of doses of XX given per day (with SD/SE if given):
Duration of XX treatment in days (with SD/SE if given):

Number of patients randomised:

Intervention 2: SSRI + YY *(where YY = lithium or atypical anti-psychotic or placebo or no treatment)*

SSRI name and brand:
SSRI dose and regimen used (e.g. 80mg OD):
Delivery of SSRI (e.g. PO tablet/dissolvable/enteric coated):
Number of doses of SSRI given per day (with SD/SE if given):
Duration of SSRI treatment in days (with SD/SE if given):

What was YY (name and brand)?

YY dose and regimen used (e.g. 80mg OD):

Delivery of YY (e.g. PO tablet/dissolvable/enteric coated):

Number of doses of YY given per day (with SD/SE if given):

Duration of YY treatment in days (with SD/SE if given):

Number of patients randomised:

Was the formulation and appearance of YY (e.g. lithium) matched to that of XX (e.g. atypical antipsychotic)?

Were any additional interventions given to either or both groups?

Types of outcome

Which of the following outcomes have been assessed in the clinical trial?

Disease severity? YES UNCLEAR NO

How was disease severity defined in the clinical trial?

Quality of life? YES UNCLEAR NO

How was quality of life defined in the clinical trial?

Adverse events? YES UNCLEAR NO

How were adverse events defined in the clinical trial? (e.g. investigator attributed?)

Withdrawal (all cause)? YES UNCLEAR NO

How was withdrawal defined in the clinical trial?

Relapse rate? YES UNCLEAR NO

How was relapse rate defined in the clinical trial?

All-cause mortality? YES UNCLEAR NO

How was all-cause mortality defined in the clinical trial?

Any other outcomes reported in trial (please list)?

ITT data collection table:

Outcomes		Timeframe (weeks)	SSRI +XX		SSRI + YY	
			n	N	n	N
Disease severity	50% reduction in HDRS					
	50% reduction in MADRS					

Quality of life	Trial scale:					
Withdrawals (all cause)						
Relapse rate						
All-cause mortality						
Adverse events (please specify)						

n = number of patients with the outcome; N = number of patients assessed

Per Protocol data collection table:

Outcomes		Timeframe (weeks)	SSRI +XX		SSRI + YY	
			n	N	n	N
Disease severity	50% reduction in HDRS					
	50% reduction in MADRS					
Quality of life	Trial scale:					
Withdrawals (all cause)						
Relapse rate						
All-cause mortality						
Adverse events (please specify)						

n = number of patients with the outcome; N = number of patients assessed

Did the RCT carry out any subgroup analyses of interest? (i.e. Different durations of depression, different classes of previous antidepressants, different genders, age, different severity's of depression or different number of prior antidepressants)
If yes, please give details here.

PART FOUR: CLINICAL TRIAL QUALITY

Please describe the method of randomisation and allocation concealment used in the clinical trial:

Please describe the method of blinding and who was blinded in the clinical trial:

Please describe the number of patients lost to follow up (the overall number and number by treatment group, give reasons for loss to follow up):

How would you describe the trials design to minimise bias for (please tick):

Outcome	Risk of Bias	Low risk	Unclear Risk	High risk	Comments
Disease severity	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants &personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Quality of life	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants &personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Withdrawals (all cause)	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants &personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Relapse rate	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants &personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				

	7) 'Other Bias'				
All-cause mortality	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants &personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Adverse events	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants &personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				

How would you rate the trials overall risk of bias?

Low risk **Unclear** **High risk**

Do you have any additional comments you would like to make about this clinical trial?

Ideally, would you like further information about the clinical trial from the authors (If so, please give details)?

Appendix 10.3 Team members' contributions

Steve Edwards, Head of HTA, will develop the protocol, act as the third reviewer for assessment of trials and cost-effectiveness studies, validate data extraction and any data analysis required, validate the economic model, contribute to writing/editing of the report, be overall director of the project and act as guarantor of the report.

Sam Barton, HTA Analyst, will act as co-reviewer for assessing trials for inclusion and data extraction, and contribute to the writing/editing of the report.

Vicky Hamilton, HTA Analyst, will provide overall project management, develop the protocol, write and run the search strategy, act as co-reviewer for assessing trials for inclusion and data extraction (and perform data analysis as required), and contribute to the writing/editing of the report.

Leo Nherera, Health Economist, will develop the protocol, act as co-reviewer of the cost-effectiveness studies, develop the economic model, and contribute to the writing/editing of the report.

Nicola Trevor, Health Economist, will act as co-reviewer of the cost-effectiveness studies, validate the economic model, and contribute to the writing/editing of the report.

Professor Cowen and Dr Dratcu, Clinical Expert Advisors, will provide clinical advice as required through out the protocol development and review processes.

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