PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Long term cost-effectiveness of collaborative care (versus usual care) for people with depression and comorbid diabetes or cardiovascular disease: a Markov model informed by the COINCIDE randomised controlled trial.
AUTHORS	Camacho , Elizabeth; Ntais, Dionysios; Coventry, Peter; Bower, Peter; Lovell, Karina; Chew-Graham, Caroline; Baguley, Clare; Gask, Linda; Dickens, Chris; Davies, Linda

VERSION 1 - REVIEW

REVIEWER	Nawaraj Bhattarai Health Economics Group, Institute of Health & Society (IHS), Newcastle University, United Kingdom
REVIEW RETURNED	20-May-2016

GENERAL COMMENTS	Overall well written and interesting piece of work. However, there are instances where it needs clarity. My comments are minor and are as follows: Minor comments: 1. Introduction section, second paragraph page 5: How does the usual care differ from the collaborative care? Could you please state clearly? 2. Could you please provide a justification of why a time horizon of 24 months is used in this study? Generally, the long term conditions such as Diabetes, CHD last over the life time and depression may be recurrent in patients with these long term conditions. It may be possible that the value of the intervention (collaborative care) in terms of costs and outcomes may differ with longer terms such as 5 years or 10 years or possibly a life time. You have referenced something similar in page 6 lines 16-21. I agree there may be some project specific constraints but this could be discussed as a limitation. 3. Page 8, lines 42-46: “Data on the use of other health…….collected by questionnaire completed by participants at initial (4 –month) follow-up”. Could you please discuss on any potential biases arising out of this method of assessing the resource utilisation? 4. In page 9, first para, you mention “Participants were also asked about support from family and friends……for this resource”. Had this information been included in the analysis, the results could have been possibly different. This should be discussed as a potential limitation.

	5. Page 8, Line 47: “The services ……., patient costs and expenses, and ….”. Could you please elaborate what was included in the patient costs and expenses? In addition, could you please tabulate the unit costs of each resource use considered, along with the reference to their source? Table 1 included in this manuscript does not provide the breakdown of resource utilisation and unit costs. 6. Though transition probabilities were varied as a part of sensitivity analysis, the manuscript could have elaborated on the potential impact of patient characteristics on the costs and outcomes. For example, would the results be same in the sub group of patients? Example the young and elderly, those with fewer comorbidities and those with more number of comorbidities. Depression may be more prevalent with increase in the number of morbidities and resource utilisation may increase with increase in the number of morbidities.

REVIEWER	Bernd Löwe University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
REVIEW RETURNED	28-May-2016

GENERAL COMMENTS	The paper investigates the cost-effectiveness of a collaborative care treatment for patients with depression and comorbid diabetes or cardiovascular disease. The design of the study, entitled COINCIDE randomized clinical trial, was published in 2012 and 2013 (pub #16 and #17), and the primary clinical outcomes were published in 2015 (pub #19). The current paper focuses on the health economic outcomes of the COINCIDE trial. The collaborative care intervention was delivered over three months by a practice nurse and a psychologist. The study question, i.e. the cost-effectiveness of this low-intensity psychological intervention, addresses an important topic. Altogether, the paper is well written, and no major methodological flaws were identified. However, I think the presentation of the study could be improved. Suggestions for improvement include: INTRODUCTION: p. 5, 6: The introduction is fine; however it does not describe why the study is important. Please include a statement saying what is new about your study and why you think it is important for the readership. p. 6: The aims of your study and the study questions are missing in the last paragraph of the introduction. Please include the study aims and the study questions in the last paragraph of the introduction. The aim of your study, as reported in the methods section (p. 6), is not detailed enough and should be reported in the introduction section of your paper. METHODS: p. 6, 7: the COINCIDE trial is described in detail in the methods section. However, given that study design and study results are already published elsewhere, I suggest substantial shortening of this

	section. p. 8 to 11: The economic evaluation is well described, but at the same time this section appears lengthy. Please shorten. RESULTS: p. 12: I think it is not correct to state that the mean (unadjusted) costs of health services used during the trial period was higher for the collaborative care group than usual care, because the confidence intervals of the costs in both groups overlap substantially. I do not think that there is a significant difference between the two groups. The same applies to the comparison of the QALYs in both groups. Please clarify. DISCUSSION: p. 13, 14: The discussion is fine.

VERSION 1 – AUTHOR RESPONSE

Many thanks to both reviewers for their helpful and constructive comments. Our responses (denoted by **) are below.

Reviewer: 1
1. Introduction section, second paragraph page 5: How does the usual care differ from the collaborative care? Could you please state clearly?
**This text relates to findings reported in a definitive Cochrane review of collaborative care (Archer at al, 2012). In that review usual care is defined as on either: no additional intervention; the same additional intervention applied to both study arms (effects potentially cancelled out), or enhanced usual care (a non-collaborative intervention that the collaborative care arm did not receive). We have added this text to the introduction (page 5, last paragraph).

**In the COINCIDE trial, usual care consisted of standard care provided by the patient's general practitioner. This can vary but should include the components of the NICE stepped care model for depression which includes GP support, referral for a range of low to high intensity psychological interventions and/or antidepressant therapy dependent on severity of depression, patient preference and prior experience. Because this trial was a pragmatic evaluation no restrictions were made on the type of usual care that might have been offered to participants in the control arm. We have also expanded our explanation of what usual care means in the context of this evaluation in the methods section (page 8, paragraph 2).

2. Could you please provide a justification of why a time horizon of 24 months is used in this study? Generally, the long term conditions such as Diabetes, CHD last over the life time and depression may be recurrent in patients with these long term conditions. It may be possible that the value of the intervention (collaborative care) in terms of costs and outcomes may differ with longer terms such as 5 years or 10 years or possibly a life time. You have referenced something similar in page 6 lines 16-21. I agree there may be some project specific constraints but this could be discussed as a limitation.
**We agree that as with conditions such as CHD and diabetes, depression is also a condition that can have a chronic course, with the risk of relapse and recurrence of symptoms higher among those who have had one or more episodes of depression.

**The time horizon for the primary analysis was 24 months, 12 and 36 month horizons were also explored in sensitivity analyses. We elected to use these time horizons because they were used to denote medium, long, and very long term follow-up in comparable trials of collaborative care included in the definitive Cochrane review of collaborative care (Archer at al, 2012). Furthermore, it was felt that to extrapolate from 4 months of trial data to, for example 10 years, would stretch the evidence from the trial too far, limiting robustness and increasing uncertainty around the estimates.

**We have now discussed this as a limitation of this analysis (page 15, paragraph 1).

3. Page 8, lines 42-46: “Data on the use of other health……..collected by questionnaire completed by participants at initial (4 –month) follow-up”. Could you please discuss on any potential biases arising out of this method of assessing the resource utilisation?
**Reliance on patient-reported data increases the likelihood of recall bias and there was a moderate level of participants with missing data for at least one category of healthcare use. Multiple imputation was used to account for missing data. Without data from medical records (accessed to records not agreed in the COINCIDE trial) it was not possible to verify patient reports.

**We have now included this as a limitation in the discussion (page 14, last paragraph).

4. In page 9, first para, you mention “Participants were also asked about support from family and friends……for this resource”. Had this information been included in the analysis, the results could have been possibly different. This should be discussed as a potential limitation.
**Collaborative care was associated with a different profile of healthcare resource use to usual care and it is possible that the use of informal care was also different between the study arms. However, it is not possible to estimate the magnitude or direction of any difference based on available data.

**We have discussed this as a limitation of this analysis (page 15, paragraph 1).

5. Page 8, Line 47: “The services ……., patient costs and expenses, and ….”. Could you please elaborate what was included in the patient costs and expenses? In addition, could you please tabulate the unit costs of each resource use considered, along with the reference to their source? Table 1 included in this manuscript does not provide the breakdown of resource utilisation and unit costs.
**Patient costs were related to health/healthcare and included travel/parking to attend healthcare appointments and private healthcare costs exceeding £50 (e.g. private reflexology, physiotherapy etc). We have added this text to the methods section (page 9, paragraph 1).

**We have added a supplementary table of unit costs and resource utilisation by healthcare category (Supplementary Table 1). We have referenced this table in the Methods (page 9, paragraph 1) and Results sections (page 12, paragraph 2) of the main text.

6. Though transition probabilities were varied as a part of sensitivity analysis, the manuscript could have elaborated on the potential impact of patient characteristics on the costs and outcomes. For example, would the results be same in the sub group of patients? Example the young and elderly, those with fewer comorbidities and those with more number of comorbidities. Depression may be more prevalent with increase in the number of morbidities and resource utilisation may increase with increase in the number of morbidities.
**There is limited evidence on which to select meaningful sub-groups that the clinical effectiveness or cost-effectiveness of collaborative care is likely to be different. As such, no sub-groups were defined a priori and the sample size in COINCIDE was not powered for this. Accordingly results from sub-group analyses here must be interpreted with caution.

**We have conducted sub-group analyses on the basis of age and number of comorbidities as

suggested.

**Based on the mean age of the sample (58 years), and the (former) age of retirement for women in England (60 years) was used to define two sub-groups: under 60 years and 60+. In the 60+ group, usual care was associated with lower costs and collaborative care with higher costs than in the under 60 group, resulting in a notably higher net cost in the 60+ group (£1,032 vs £468). The 60+ group gained marginally more QALYs from collaborative care than the under 60s (0.04 vs. 0.03). The resulting ICERs for both groups (<60s: £16,891/QALY; 60+: £23,358/QALY) were below £30,000/QALY and so decision-makers could consider implementing collaborative care for both groups.

**Based on the mean number of long-term conditions reported (other than diabetes or CHD), two sub-groups were defined: fewer than 6 conditions and 6+ conditions. The net cost of collaborative care was smaller in participants with fewer than 6 conditions than those with more than 6 (£489 vs. £849). Participants with fewer conditions also gained more QALYs from collaborative care than those with more than 6 (0.05 vs. 0.03). Therefore collaborative care is may be less likely to be cost-effective for patients with many multi-morbidities.

**Supplementary tables of model parameters and results has been added and key results described in the main text (page 13, second to last paragraph).

Reviewer: 2
INTRODUCTION:
p. 5, 6: The introduction is fine; however it does not describe why the study is important. Please include a statement saying what is new about your study and why you think it is important for the readership.
**This study is important because it makes a robust contribution to economic evidence about estimated costs and benefits of implementing collaborative care in the English healthcare system (NHS England). Existing evidence is limited to studies conducted in the US healthcare system which may not be relevant to the implementation of collaborative care in the NHS. Emerging evidence from a single English complete-case analysis suggests that collaborative care may be cost-effective in this context over 12-months. However it is still unknown whether these findings are likely to translate to longer time horizons. This analysis uses an economic model to estimate the cost-effectiveness of collaborative care in the context of the NHS at 12, 24, and 36 months. This has not been done previously. Furthermore, this is the first analysis of the cost-effectiveness of collaborative care in the NHS for patients with long-term physical conditions alongside depression (multi-morbidity). We have added this detail to the introduction (page 6, last paragraph).

p. 6: The aims of your study and the study questions are missing in the last paragraph of the introduction. Please include the study aims and the study questions in the last paragraph of the introduction. The aim of your study, as reported in the methods section (p. 6), is not detailed enough and should be reported in the introduction section of your paper.
**The overall aim of this study was to estimate the cost-effectiveness of collaborative care compared to usual care, over a long-term time horizon in a UK primary care setting. The key objectives were to:
• Develop an economic model to represent the key health states and events observed during the COINCIDE trial of collaborative versus usual care
• Estimate the costs of health and social care in the collaborative care and usual care groups
• Assess whether there are differences in costs between collaborative care and usual care
• Estimate the health status and quality adjusted life years (QALYs) of patients in the collaborative care and usual care groups
• Assess whether there are differences in health status and QALYs between collaborative care and usual care

• Estimate the long-term cost-effectiveness of collaborative care, compared to usual care

**The aim and detailed objectives have been moved to the end of the introduction (page 7).

METHODS:
p. 6, 7: the COINCIDE trial is described in detail in the methods section. However, given that study design and study results are already published elsewhere, I suggest substantial shortening of this section.
**We have retained sufficient detail of the COINCIDE trial in order to meet the requirements of the CHEERS checklist: "11a Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data." But have shortened where possible.

p. 8 to 11: The economic evaluation is well described, but at the same time this section appears lengthy. Please shorten.
**We have shortened this section as requested.

RESULTS:
p. 12: I think it is not correct to state that the mean (unadjusted) costs of health services used during the trial period was higher for the collaborative care group than usual care, because the confidence intervals of the costs in both groups overlap substantially. I do not think that there is a significant difference between the two groups. The same applies to the comparison of the QALYs in both groups. Please clarify.
**We have clarified that although the mean costs and QALYs were numerically higher for the collaborative care group, they are not significantly different, as demonstrated by the substantial overlap of the confidence intervals (page 12, paragraph 2).

VERSION 2 – REVIEW

REVIEWER	Nawaraj Bhattarai Health Economics Group, Institute of Health & Society, Newcastle University, Newcastle upon Tyne, United Kingdom
REVIEW RETURNED	12-Jul-2016

GENERAL COMMENTS	It is well written. I am happy with this revised version. Best wishes.

REVIEWER	Bernd Löwe Department of Psychosomatic Medicine and Psychotherapy University Medical Centre Hamburg-Eppendorf Hamburg, Germany
REVIEW RETURNED	24-Jul-2016

GENERAL COMMENTS	The authors have well addressed the reviewers' comments. Thank you. I have no further suggestions for improvement.