PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it was re-reviewed and accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Telemonitoring-based service redesign for the management of uncontrolled hypertension (HITS): Cost and cost-effectiveness analysis of a randomised controlled trial
AUTHORS	McKinstry, Brian; Stoddart, Andrew; Hanley, Janet; Wild, Sarah; Pagliari, Claudia; Paterson, Mary; Lewis, Steff; Sheikh, Aziz; Krishan, Ashma; Padfield, Paul

VERSION 1 - REVIEW

REVIEWER	Steventon, Adam Nuffield Trust
REVIEW RETURNED	03-Aug-2012

GENERAL COMMENTS	Overall this appears to be an informative study that adds to the literature in this area and should be of interest to BMJ readers. There is growing interest in telehealth among clinicians and policy makers. Other forms of telehealth (such as vital signs monitoring for people with chronic obstructive pulmonary disease, heart failure and diabetes) is not always cost effective. This paper gives a more promising finding in relation to blood pressure monitoring, albeit for an intermediate outcome (blood pressure). I have compared the article against the CONSORT statement and have found that, in some areas, the description of the study lacks some of the recommended details. These details may be included in the companion paper [1] but this has not been made available to me, so I cannot form a judgement about the reliability of the study at the current time. I would like to see some of these details included in this paper, regardless of the content of the companion paper, so my recommendation to the editor is that the paper should be revised and resubmitted. Comments: 1. The main additional item I would like to see included is a comparison of the baseline characteristics of treatment groups (either a table or a summary of findings from the companion paper, and including minimisation variables). This becomes more important as the trial did not record baseline resource use. The generalised linear model used to estimate incremental costs is a useful addition to the paper, but it misses many of the variables known to be predictive of resource use (for a discussion in relation to secondary care, see [2]). Therefore the paper largely relies on randomisation to balance out baseline costs between groups. A comparison of

	baseline characteristics will help the reader judge the reasonableness of this approach. 2. The family and link function for the generalised linear model need to be specified. 3. Although the incremental costs are adjusted using a generalised linear model, this does not appear to have been done for the basic cost analysis (however, see further comments below). Differences in baseline costs could therefore have a greater impact on the estimates of cost than incremental costs. 4. The article should state the primary endpoint of the study and how the trial was powered. This is necessary to what extent this article constitutes "secondary" analysis. For example, if the trial was powered on the basis of daytime ambulatory blood pressure (but costs were secondary), I would have more confidence in the results than if both blood pressure and costs were secondary measures. The article should state when this analysis was conceived, as it does not seem to have been planned as part of the original protocol. 5. The article should describe the source of data. Are the resource data from administrative data sets or patient report? How was blood pressure measured at baseline and 6-month follow up and was it measured in the same way for both treatment groups? If follow-up readings came from the telemonitoring device for intervention patients but from some other device for controls, the implications for the study should be discussed. Similarly if baseline and follow-up readings were measured in different ways. 6. Resource use included consultations with GPs, practice nurses, district nurses, NHS24 and out of hours GPs and nurses; medication; and A&E visits. However, hospital admissions and outpatient attendances were not included. Data on hospital admissions were collected but were not included in the analysis as "there was a risk of overwhelming the more robust estimates of other cost factors with unreliable, and likely unrelated, admission costs." The evidence that these costs are unrelated comes from the adverse events log, but at the moment this is not convincing as the completeness of the adverse events log is not discussed. Further, the discussion argues strongly that better blood pressure control can have an impact on cardiovascular events and therefore admission costs, albeit over much longer time frames. Therefore I would like to see some univariate analysis of the number of admissions, even if they cannot be costed or included in the cost-effectiveness analysis. 7. Univariate analysis of admission costs will also inform the discussion, which at the moment does not include critical reflection on the range of services covered (this is very impressive but there may be some exclusions – community matrons?) 8. The discussion about imputation should indicate the independent variables used. 9. Some more information about the intervention would be useful in places: a. Where and when were blood pressure readings taken? A statement about place would be interesting as, in the more general telehealth literature, distinctions are often made between mobile and

	home-based interventions [3]. b. What are the “same treatment protocols” referred to at the top of page 5? c. How often was the optional automated patient decision support used? 10. Can the authors clarify whether those recruiting patients were blinded to allocation status? 11. Are the authors happy there is no double counting in the calculation of intervention cost and resource use? The cost of the intervention (Table 2) includes a one-off 20 minutes of practice nurse time, followed by an extra 1 minute of practice nurse time per week. Impacts on resource use (Table 3) include an increase in practice nurse phone consultations of 0.68 consultations. Does the latter exclude monitoring time included in the cost of the intervention? 12. Table 2 does not include a source for the assumptions about practice nurse time. Were these based on diaries or discussions with practice nurses? If there is uncertainty, the link to the sensitivity analysis could be made more explicit. 13. Please can the authors state changes in blood pressure for both groups (and not just the overall difference in difference estimate)? Or even state baseline and follow-up readings separately. This would ease comparison with other studies [4]. Also, the use of the difference-in-difference estimator was not described in the methods. 14. Given the chequered history of telehealth research, some discussion as to why this study has found different results to others [4] would be helpful. 15. The discussion does not currently elaborate on all of the strengths and weaknesses of this study. For example, on: a. The significance of this trial being post-hoc, secondary analysis. (When was the decision to analyse the data on this way made? Was it planned or only done because indications of promising findings had already been observed?) b. Implications of missing baseline data on resource use. c. Possible scope of selection bias and adequacy of case-mix adjustment d. How generalisable these findings are likely to be to other settings. 16. Can the authors justify the phrase “modestly more expensive” in the abstract? The increase in costs of £119.28 over six months is 68% increase in control group costs (£174.91). This may not seem modest to everyone. 17. The abstract should state that clinical gains may need to be maintained for ten or more years for the additional costs to be compensated, if this is the case. Also, the abstract should state that further research is required to determine the impact of sustained blood pressure improvement on cost effectiveness, as this is what the authors argue in the discussion. 18. The CONSORT statement also requires the article title to specify that this is an RCT. A flow diagram showing patient recruitment might also be a useful addition. The statement also recommends

	extra detail in the abstract in places (that minimisation algorithm used, that outcomes assessment was blinded, numbers randomised in each group). 19. Was the analysis done intention to treat? Was there any loss to follow up? 20. Were there any exclusion criteria (about language?) Minor drafting comments • The minimisation algorithm should be described earlier in the article, on page 4 when discussing allocations. Currently it is described on page 7 when discussing the specification of one of the models, and this comes as a surprise. • Page 7 refers to “multiple regression” – do the authors mean ordinary least squares, linear regression? • The article alternates in its use of the terms “usual care” and “normal care” and these could be standardised. • “HBPM” not defined in Table 2. • On page 5 “Assumptions were made on an ad hoc basis” – it would be useful to remind reader at this point that this was done while researchers were blinded to treatment group. • Page 11 “the difference observed [in blood pressure] in this analysis was slightly higher than in the clinical analysis .... due to the values used in this analysis having been imputed to account for additional missing cost data” – imputation was done for both cost and blood pressure, so suggest edit to say “for additional missing data”. • Page 9: some of these figures (e.g. 0.55 additional practice nurse phone consultations) do not appear to match the tables. Have they been adjusted in some way? • The statement that recruitment was from “socio-economically diverse general practices” should be somewhere justified, though this may be in the companion paper. I hope these comments will be useful. References [1] McKinstry B, Hanley J, Wild S et al. Telemonitoring-based service redesign for the management of difficult-to-control hypertension (HITS): a multi-centre randomised controlled trial. Submitted BMJ. [2] Dixon J, Smith P, Gravelle H, Martin S, Bardsley M, Rice N et al. A person based formula for allocating commissioning funds to general practices in England: development of a statistical model. BMJ 2011; 343 doi: 10.1136/bmj.d6608 [3] http://www.newhamwsdtrial.org/telehealth/thinkpositive [4] Madsen LB, Kirkegaard P, Pedersen EB. Blood pressure control during telemonitoring of home blood pressure. A randomized controlled trial during 6 months. Blood Press 2008;17:78-86.

REVIEWER	Turner, Barbara

	Univ of Texas Health Science Center San Antonio, Medicine
REVIEW RETURNED	11-Sep-2012

GENERAL COMMENTS	This cost-effectiveness analysis of telemonitoring to improve blood pressure control uses data from an unpublished short-term randomized controlled trial in 20 Scottish primary care practices. The study has a timely "pragmatic" design, reflecting an increased international focus on comparative effectiveness research relevant to everyday clinical practice. Few studies have attempted to evaluate cost-effectiveness of short term interventions of blood pressure control, in part because it is challenging to evaluate whether the blood pressure will stay in control over a sufficiently long period of time realize the well-described benefits of blood pressure reduction on morbidity and mortality. Strengths: The cost effectiveness analysis (CEA) was performed well. The payer perspective (NHS) is relevant and clearly stated. Discounting was not performed because of the short time horizon, which is appropriate in this case but limits the possibility of comparing with other interventions. The uncertainty around the ICER was measured using bootstrapping methods, and the CEAC is presented with sensitivity analyses. Thus, the analysis is very well done from a technical standpoint. Weaknesses: This trial is relatively short term – only 6 months. Because the original trial has not been published, this paper leaves the reader with many unanswered questions about the methods and results of the trial. The patients were identified using ambulatory blood pressure monitoring which is not widely available – thus making it less 'pragmatic'. It is not clear how many patients would have to have had to have their blood pressure monitored using this technology to identify the sample of eligible persons – this should have been described in the report of the trial. The cost of using this technology to identify patients may need to be considered. It is difficult to evaluate the study population without knowing what would have been Table 1 of the paper reporting the results of the trial. If this paper is not paired with the results of the trial, it needs to include these data. Presumably all eligible subjects were on antihypertensive therapy, because it might not be justified to use this intervention in patients who have never had the benefit of being started on antihypertensive therapy. Information about the baseline distribution of blood pressures in the study population is needed. If most patients had a blood pressure of 160/100 or greater (stage 2) then an intervention that reduces systolic blood pressure by 4-5 mmHg has little value. The authors need to address the relative impact of this intervention compared with others that may be more costly but deal with the problem of poor adherence to therapy. It might not have been appropriate to intensify medication -- which appears to be the primary approach that this intervention promotes – without evaluating adherence to the current regimen. If the patient is not taking the drug(s) as directed, just prescribing more is not the answer. Indeed, a US trial of combined home monitoring and behavioral support achieved a much greater mean reduction in blood pressure (systolic reduced by 14.8 mm after one year) among persons with baseline poor control (Bosworth HB, Powers BJ, Olsen MK, McCant F, Grubber J, Smith V, Gentry PW, Rose C, Van Houtven C, Wang V, Goldstein MK, Oddone EZ. Home blood pressure management

	and improved blood pressure control: results from a randomized controlled trial. Arch Intern Med. 2011 Jul 11;171(13):1173-80). Another study using a pharmacist for adherence support also resulted in a greater average reduction in systolic BP (7mmHg) after 6 months (e.g. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA. 2006 Dec 6;296(21):2563-71). Thus, this trial of telemonitoring resulted in relatively small effect on blood pressure. It would have been useful to have some measure of patient compliance with the home monitoring interventions. Inability to estimate QALYs is a limitation that they acknowledge -- they mention but do not try to model mathematically longer term costs and benefits (page 12). Minor points: The investigators reasonably use 130/85 as the lower cut point for eligibility based on the most recent NICE guidelines (NICE clinical guideline 127). For a non-UK audience, they should have cited these guidelines for elevated ambulatory blood pressure as the justification for this cut point. The methods stated that they planned on considering the cost of hospitalizations - it is not surprising that they decided not to use these data since few hospitalizations could be expected to be averted by using this intervention. Possibly it would have been worthwhile the study had focused on persons with severely elevated hypertension. Although the cost of antihypertensive drug intensification was small, this would be a much bigger issue if the intervention were to be adopted in the US. For the cost effectiveness analysis - I asked Christopher Hollenbeak PhD, Professor Penn State University to review this paper also (he has no conflicts to declare either).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Recommendation:

Comments:
Comments from Adam Steventon, Senior Research Analyst, The Nuffield Trust.

Overall this appears to be an informative study that adds to the literature in this area and should be of interest to BMJ readers. There is growing interest in telehealth among clinicians and policy makers. Other forms of telehealth (such as vital signs monitoring for people with chronic obstructive pulmonary disease, heart failure and diabetes) is not always cost effective. This paper gives a more promising finding in relation to blood pressure monitoring, albeit for an intermediate outcome (blood pressure).

I have compared the article against the CONSORT statement and have found that, in some areas, the description of the study lacks some of the recommended details. These details may be included in the companion paper [1] but this has not been made available to me, so I cannot form a judgement about the reliability of the study at the current time. I would like to see some of these details included in this paper, regardless of the content of the companion paper, so my recommendation to the editor is that the paper should be revised and resubmitted.

Comments:

1. *The main additional item I would like to see included is a comparison of the baseline characteristics of treatment groups (either a table or a summary of findings from the companion paper, and including minimisation variables). This becomes more important as the trial did not record baseline resource use. The generalised linear model used to estimate incremental costs is a useful addition to the paper, but it misses many of the variables known to be predictive of resource use (for a discussion in relation to secondary care, see [2]). Therefore the paper largely relies on randomisation to balance out baseline costs between groups. A comparison of baseline characteristics will help the reader judge the reasonableness of this approach.*
We agree. A baseline characteristics table is now included

2. *The family and link function for the generalised linear model need to be specified.*
A paragraph has been added describing the family and link function selected and the process used to derive them.

3. *Although the incremental costs are adjusted using a generalised linear model, this does not appear to have been done for the basic cost analysis (however, see further comments below). Differences in baseline costs could therefore have a greater impact on the estimates of cost than incremental costs.*
The generalised linear model based multivariate estimates for total cost in each trial arm have now been incorporated into the text these are the same estimates used to calculate the incremental costs. The figures are very similar to those in the univariate analysis suggesting that (assuming the measures taken to combat the absence of baseline costs are reasonable – see discussion) this is not the case.

4. *The article should state the primary endpoint of the study and how the trial was powered. This is necessary to what extent this article constitutes "secondary" analysis. For example, if the trial was powered on the basis of daytime ambulatory blood pressure (but costs were secondary), I* would *have more confidence in the results than if both blood pressure and costs were secondary measures. The article should state when this analysis was conceived, as it does not seem to have been planned as part of the original protocol.*
The trial was powered to detect differences in mean systolic blood pressure but also collected resource use data as a secondary outcome for which it was not deliberately powered. The analysis presented here is post hoc in the sense that it was opportunistically conceived after the trials completion and was not part of the original trial protocol though it was conceived prior to completion of the primary clinical analysis for the trial. These points have now been clarified in the text.

5. *The article should describe the source of data. Are the resource data from administrative data sets or patient report? How was blood pressure measured at baseline and 6-month follow up and was it measured in the same way for both treatment groups? If follow-up readings came from the telemonitoring device for intervention patients but from some other device for controls, the implications for the study should be discussed. Similarly if baseline and follow-up readings were measured in different ways.*
Resource use data collection is now clarified in text under cost estimation section. Measurement of blood pressure was taken using a Spacelabs 90207 Ambulatory BP Monitor prior to randomisation and at follow up. While this was previously mentioned in the text it may have not been clear and as such we have attempted to clarify this.

6. *Resource use included consultations with GPs, practice nurses, district nurses, NHS24 and out of hours GPs and nurses; medication; and A&E visits. However, hospital admissions and outpatient attendances were not included. Data on hospital admissions were collected but were not included in the analysis as "there was a risk of overwhelming the more robust estimates of other cost factors with unreliable, and likely unrelated, admission costs." The evidence that these costs are unrelated comes from the adverse events log, but at the moment this is not convincing as the completeness of the adverse events log is not discussed. Further, the discussion argues strongly that better blood pressure control can have an impact on cardiovascular events and therefore admission costs, albeit over much longer time frames. Therefore I would like to see some univariate analysis of*

the number of admissions, even if they cannot be costed or included in the cost-effectiveness analysis.
Univariate analysis of the costs of hospital admissions have now been added. (See response to the second point raised above)

7. *Univariate analysis of admission costs will also inform the discussion, which at the moment does not include critical reflection on the range of services covered (this is very impressive but there may be some exclusions – community matrons?)*
Comments have been added to the discussion which consider admission costs and acknowledges that some factors may not have been accounted for. With regard to community matrons (the local Scottish equivalent are called impact nurses) specifically, they were not involved in the management of this group of participants.

8. *The discussion about imputation should indicate the independent variables used.*
The paragraph relating to multiple imputation has now been re-written to give more detail including the covariates used in the regressions.

9. *Some more information about the intervention would be useful in places:*
a. Where and when were blood pressure readings taken? A statement about place would be interesting as, in the more general telehealth literature, distinctions are often made between mobile and home-based interventions [3].
We have provided a detailed description of the intervention in a new. Please see Box.

b. What are the "same treatment protocols" referred to at the top of page 5?
This too is covered in the text in Box 1
c. *How often was the optional automated patient decision support used?*
The automated support was taken up by around 50% of patients and a small number asked for it to be discontinued. We do not know to what extent it was acted on, in the qualitative process analysis it was clear that some found it irritating particularly when their BP was only a mmHg or 2 above target.

10. *Can the authors clarify whether those recruiting patients were blinded to allocation status?*
It was not possible to blind researchers as the intervention comprised providing telemetric equipment. However randomisation was undertaken using a secure randomisation system provided remotely by Edinburgh Clinical Trials Unit. This has now been clarified in the text.

11. *Are the authors happy there is no double counting in the calculation of intervention cost and resource use? The cost of the intervention (Table 2) includes a one-off 20 minutes of practice nurse time, followed by an extra 1 minute of practice nurse time per week. Impacts on resource use (Table 3) include an increase in practice nurse phone consultations of 0.68 consultations. Does the latter exclude monitoring time included in the cost of the intervention?*
We are happy that there has been no double counting. The research nurses who assisted in the administration of the resource use surveys had access to GP records and would not have included the initial clinical visit in which was a trial related appointment where baseline trial measurements were undertaken and telemonitoring equipment was demonstrated in the survey. We have now clarified in the table that the 1 min per week is an assumption and that this relates to data monitoring time only as opposed to any patient contact time which would then be included in the survey. This should hopefully now be clearer to the reader.

12. *Table 2 does not include a source for the assumptions about practice nurse time. Were these based on diaries or discussions with practice nurses? If there is uncertainty, the link to the sensitivity analysis could be made more explicit.*
The assumed durations were based on our pilot work. This has now been explained in Table 3. A reference to Table 3 has also been added in the paragraph in the methods section which introduces the sensitivity analysis in order to make the connection between the two matters more explicit.

13. *Please can the authors state changes in blood pressure for both groups (and not just the overall difference in difference estimate)? Or even state baseline and follow-up readings separately.*

This would ease comparison with other studies [4]. Also, the use of the difference-in-difference estimator was not described in the methods.
Detail of baseline and follow up SABP has now been included in text and a short description of the difference in difference estimator added.

14. *Given the chequered history of telehealth research, some discussion as to why this study has found different results to others [4] would be helpful.*
We agree, a section comparing our results to those of other home BP telemonitoring studies has been added.

15. T*he discussion does not currently elaborate on all of the strengths and weaknesses of this study. For example, on:*

a. The significance of this trial being post-hoc, secondary analysis. (When was the decision to analyse the data on this way made? Was it planned or only done because indications of promising findings had already been observed?)
Now clarified - See reply to point 4.
b. Implications of missing baseline data on resource use.
c. Possible scope of selection bias and adequacy of case-mix adjustment
d. How generalisable these findings are likely to be to other settings.
In response to items 15 b to d, all three are now considered in the discussion, thank you for bring them to our attention.

16. Can the authors justify the phrase "modestly more expensive" in the abstract? The increase in costs of £119.28 over six months is 68% increase in control group costs (£174.91). This may not seem modest to everyone.
While the intervention may appear self-evidently "modest" in cost to our own eyes, we acknowledge that the term "modestly" is a subjective interpretation. The term has now been removed and now simply states "more expensive" leaving readers free to interpret the scale of the cost for themselves.

17. The abstract should state that clinical gains may need to be maintained for ten or more years for the additional costs to be compensated, if this is the case. Also, the abstract should state that further research is required to determine the impact of sustained blood pressure improvement on cost effectiveness, as this is what the authors argue in the discussion.
The abstract now has now been amended to differentiate these results from possible longer term effects and now includes recommendation for modelling to determine longer term impact of treatment. We have avoided specific reference to the timescale of "10 or more years" as it is as yet unclear specifically how long the benefits need to be maintained in order to outweigh the upfront cost. Longer term modelling may enlighten us as to how long benefits may need to be maintained to be cost-effective. Please note that the original paper didn't claim benefits needed to be maintained for 10 years for longer term cost effectiveness to be achieved, it merely used the example of a 10 year reduction to highlight the link with cardiovascular events.

18. The CONSORT statement also requires the article title to specify that this is an RCT. A flow diagram showing patient recruitment might also be a useful addition. The statement also recommends extra detail in the abstract in places (that minimisation algorithm used, that outcomes assessment was blinded, numbers randomised in each group).
Title now changed to reflect that this was an RCT. Comments regarding minimisation used, the numbers randomised to each arm and blinded outcome assessment have been added to abstract.

19. Was the analysis done intention to treat? Was there any loss to follow up?
Yes analysis was undertaken on an intention to treat basis. This is now clarified in the text. Patients lost to follow up are now stated alongside the missing data figures and have had their follow up data imputed (see new section on missing data).

20. Were there any exclusion criteria (about language?)
Information on exclusion criteria is now included alongside details of randomisation.

Minor drafting comments

- *The minimisation algorithm should be described earlier in the article, on page 4 when discussing allocations. Currently it is described on page 7 when discussing the specification of one of the models, and this comes as a surprise.*

Minimisation is now described alongside details of randomisation in the methods section.

- *Page 7 refers to "multiple regression" – do the authors mean ordinary least squares, linear regression?*

Yes, this has now been clarified in the text.

- *The article alternates in its use of the terms "usual care" and "normal care" and these could be standardised.*

We agree. Terms have now standardised to usual care.

- *"HBPM" not defined in Table 2.*

Now defined within the table.

- *On page 5 "Assumptions were made on an ad hoc basis" – it would be useful to remind reader at this point that this was done while researchers were blinded to treatment group.*

We agree. This has now been clarified.

- *Page 11 "the difference observed [in blood pressure] in this analysis was slightly higher than in the clinical analysis .... due to the values used in this analysis having been imputed to account for additional missing cost data" – imputation was done for both cost and blood pressure, so suggest edit to say "for additional missing data".*

We agree. The word "cost" has now been removed as suggested.

- *Page 9: some of these figures (e.g. 0.55 additional practice nurse phone consultations) do not appear to match the tables. Have they been adjusted in some way?*

This appears to have been a typographical error which slipped through. The table has now been redrafted following some reanalysis and checked for errors. Values now add up correctly in the table.

- *The statement that recruitment was from "socio-economically diverse general practices" should be somewhere justified, though this may be in the companion paper.*

This has now been clarified alongside details of recruitment.

Reviewer: 2

Recommendation:

Comments:
This cost-effectiveness analysis of telemonitoring to improve blood pressure control uses data from an unpublished short-term randomized controlled trial in 20 Scottish primary care practices. The study has a timely "pragmatic" design, reflecting an increased international focus on comparative effectiveness research relevant to everyday clinical practice. Few studies have attempted to evaluate cost-effectiveness of short term interventions of blood pressure control, in part because it is challenging to evaluate whether the blood pressure will stay in control over a sufficiently long period of time realize the well-described benefits of blood pressure reduction on morbidity and mortality.

Strengths:
The cost effectiveness analysis (CEA) was performed well. The payer perspective (NHS) is relevant and clearly stated. Discounting was not performed because of the short time horizon, which is appropriate in this case but limits the possibility of comparing with other interventions. The uncertainty around the ICER was measured using bootstrapping methods, and the CEAC is presented with sensitivity analyses. Thus, the analysis is very well done from a technical standpoint.

Thank you.

Weaknesses:
This trial is relatively short term – only 6 months.
This limitation is recognised in the text and our interpretation of the results have been phrased carefully to highlight that longer term follow up/modelling is required to overcome this limitation.

Because the original trial has not been published, this paper leaves the reader with many unanswered questions about the methods and results of the trial.
We have now made several amendments to the descriptions of the methodology used in answer to comments from reviewer 1 which should hopefully have addressed this concern.

The patients were identified using ambulatory blood pressure monitoring which is not widely available – thus making it less 'pragmatic'. It is not clear how many patients would have to have had to have their blood pressure monitored using this technology to identify the sample of eligible persons – this should have been described in the report of the trial. The cost of using this technology to identify patients may need to be considered.
ABPM is now recommended for the diagnosis of Hypertension by NICE (guideline 127). While this was perhaps not "pragmatic" at the time of study design as you rightly identify, this may fortunately no longer be the case. Another benefit to this is that we might now reasonably expect it to be equally applied in both care pathways considered (usual care or HBPM) thus not incurring an additional cost. Comments around the generalizability of these results in light of the use of ABPM have now been added.

It is difficult to evaluate the study population without knowing what would have been Table 1 of the paper reporting the results of the trial. If this paper is not paired with the results of the trial, it needs to include these data. Presumably all eligible subjects were on antihypertensive therapy, because it might not be justified to use this intervention in patients who have never had the benefit of being started on antihypertensive therapy. Information about the baseline distribution of blood pressures in the study population is needed. If most patients had a blood pressure of 160/100 or greater (stage 2) then an intervention that reduces systolic blood pressure by 4-5 mmHg has little value.
Baseline measurements table now added which includes details of this.

The authors need to address the relative impact of this intervention compared with others that may be more costly but deal with the problem of poor adherence to therapy. It might not have been appropriate to intensify medication -- which appears to be the primary approach that this intervention promotes – without evaluating adherence to the current regimen. If the patient is not taking the drug(s) as directed, just prescribing more is not the answer.
There may have been some confusion here. While medication was intensified during the course of the trial in the intervention group, the intervention itself did not include or actively encourage intensification of medication. We suggest that it is possible that the intensification observed may have been due to a reduction in therapeutic inertia, that is to say the improved information available to GPs regarding their patients BP may have made GPs less reluctant to alter prescribing patterns. Presumably any GP making such changes would take into account medication adherence in such a decision. Also the intervention did not seem to affect self-reported adherence.

Indeed, a US trial of combined home monitoring and behavioral support achieved a much greater mean reduction in blood pressure (systolic reduced by 14.8 mm after one year) among persons with baseline poor control (Bosworth HB, Powers BJ, Olsen MK, McCant F, Grubber J, Smith V, Gentry PW, Rose C, Van Houtven C, Wang V, Goldstein MK, Oddone EZ. Home blood pressure management and improved blood pressure control: results from a randomized controlled trial. Arch Intern Med. 2011 Jul 11;171(13):1173-80). Another study using a pharmacist for adherence support also resulted in a greater average reduction in systolic BP (7mmHg) after 6 months (e.g. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA. 2006 Dec 6;296(21):2563-71). Thus, this trial of telemonitoring resulted in relatively small effect on blood pressure.
A section comparing the trial to others in home BP telemonitoring has now been added. Please note that a more detailed consideration specifically focused on the BP result has been provided in our primary clinical paper.

It would have been useful to have some measure of patient compliance with the home monitoring interventions.
Similarly this has been covered in our clinical paper. Most patients complied well with the regime.

Inability to estimate QALYs is a limitation that they acknowledge -- they mention but do not try to model mathematically longer term costs and benefits (page 12).
We have plans to model the longer term costs and benefits of the intervention which will be based on a cost per QALY basis. As the aim of this paper is to present the within trial results, such modelling is outwith the scope of the paper. It does however provide rationale for the follow up work.

Minor points: The investigators reasonably use 130/85 as the lower cut point for eligibility based on the most recent NICE guidelines (NICE clinical guideline 127). For a non-UK audience, they should have cited these guidelines for elevated ambulatory blood pressure as the justification for this cut point.
Box 1 has been added which provided greater detail of the intervention. Specific reference is now made to these guidelines in the text.

The methods stated that they planned on considering the cost of hospitalizations - it is not surprising that they decided not to use these data since few hospitalizations could be expected to be averted by using this intervention. Possibly it would have been worthwhile the study had focused on persons with severely elevated hypertension.
Following comments from reviewer 1 and the meeting/cover letter we have now included some sensitivity analysis around hospital costs. These come with heavy caveats for the reasons highlighted above,

Although the cost of antihypertensive drug intensification was small, this would be a much bigger issue if the intervention were to be adopted in the US.
This is indeed very likely to be true as insurance systems are considerably different between for example the UK and USA. Similarly many other factors may quite reasonably be expected to differ in both price weight and counts of resource utilisation, particularly where some element of co-payment is in place. As a result such extrapolation to other health care systems may not be straightforward and is outwith the scope of this analysis having specified an NHS perspective. Caveats regarding the generalisability to other healthcare systems have been briefly incorporated in the discussion section to make this clear to readers unfamiliar with this.

We would like to than the reviewers for their helpful comments. We hope we have satisfactorily addressed these

Yours sincerely

Brian McKinstry

References
[1] McKinstry B, Hanley J, Wild S et al. Telemonitoring-based service redesign for the management of difficult-to-control hypertension (HITS): a multi-centre randomised controlled trial. Submitted BMJ.
[2] Dixon J, Smith P, Gravelle H, Martin S, Bardsley M, Rice N et al. A person based formula for allocating commissioning funds to general practices in England: development of a statistical model. BMJ 2011; 343 doi: 10.1136/bmj.d6608 [3] http://www.newhamwsdtrial.org/telehealth/thinkpositive
[4] Madsen LB, Kirkegaard P, Pedersen EB. Blood pressure control during telemonitoring of home blood pressure. A randomized controlled trial during 6 months. Blood Press 2008;17:78-86.

VERSION 2 – REVIEW

REVIEWER	Adam Steventon Senior Research Analyst

	The Nuffield Trust, UK
REVIEW RETURNED	20-Mar-2013

THE STUDY	The supplemental documents did not raise issues for the work.
REPORTING & ETHICS	I am concerned that the extra information provided about the one patient in the intervention arm with repeated admissions might be identifiable. This requires only a small change to the manuscript (perhaps omitting the reason for admission).
GENERAL COMMENTS	I believe the authors have satisfactorily addressed the comments I gave in a previous peer review. I have only a small number of minor comments that could be dealt with easily: 1. p-values do not need to be specified to 4 decimal places, so perhaps replace <0.0001 with <0.001 in the abstract and elsewhere. 2. In some cases, data on service use was collected by research nurses from GP records. Please can the authors state whether the nurses involved were blinded to treatment allocations for the data collection (I suspect they were not, and this is a necessary limitation of trials in this area). This could be done simply in the paragraph in the Overview section that deals with the randomisation. 3. Ideally, the number of intervention and control patients whose data were sourced from GP records as opposed to a survey should be stated. Relative over/under reporting of contacts is associated with patient characteristics, so there is theoretically a small risk of bias if the balance between survey and administrative data differed between trial arms. 4. The results section states that differences in mean daytime SABP were adjusted for baseline mean daytime SABP and minimisation factors. The methods section says that adjustment was by minimisation factors only, so needs to be amended. 5. In the discussion, the authors quote relative risk reductions of 15 and 10% in stroke and coronary heart disease. Ideally, absolute risks would be given, however perhaps this information is not available. 6. Please can the authors include their estimated ICC, as this may be useful for future investigators designing trials in this area. I was not sure that the authors meant "cluster analysis" - perhaps a better way of putting it would be to say that the GLM was modified to allow for clustering (perhaps using a random effect?). 7. On page 14 the authors state that "However, the fact that point estimates were still in favour of the intervention..." - please can the authors clarify which point estimates these are (consultation and medical costs?) 8. In Table 1, the units for HbA1c are specified as "%" but the figures are quite high. Do the authors mean "mmol/mol"? 9. In Table 3, the heading for "mean difference" should be changed to "mean cost difference" or similar. 10. On page 4, the authors state that the Spacelabs 90207 ABPM was used to collect baseline data - was the same device used to collect data at 6 months? I would like confirmation that the same

	device was used in both groups, and that the intervention group data did not come from the telemonitoring. We discussed this in a previous review and the authors responded saying that the information is already included in the manuscript - apologies if I'm missing it! This is an important contribution to the field and my remaining comments are relatively minor. I recommend that the article is accepted.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer comments:

I am concerned that the extra information provided about the one patient in the intervention arm with repeated admissions might be identifiable. This requires only a small change to the manuscript (perhaps omitting the reason for admission).
RESPONSE: Thank you for bringing this to our attention. The reason for admission has now been removed

I believe the authors have satisfactorily addressed the comments I gave in a previous peer review. I have only a small number of minor comments that could be dealt with easily:

1. p-values do not need to be specified to 4 decimal places, so perhaps replace <0.0001 with <0.001 in the abstract and elsewhere.
RESPONSE: All P-values throughout the manuscript have now been respecified to 3 decimal places as requested.

2. In some cases, data on service use was collected by research nurses from GP records. Please can the authors state whether the nurses involved were blinded to treatment allocations for the data collection (I suspect they were not, and this is a necessary limitation of trials in this area). This could be done simply in the paragraph in the Overview section that deals with the randomisation.
RESPONSE: In order to maintain blinding of outcome assessment (including data collected on resource use), patients were asked not to reveal their treatment group allocation to the research nurse undertaking the assessment; however it is not possible to rule out unblinding where patients did not adhere to this. We have now clarified this in the overview section.

3. Ideally, the number of intervention and control patients whose data were sourced from GP records as opposed to a survey should be stated. Relative over/under reporting of contacts is associated with patient characteristics, so there is theoretically a small risk of bias if the balance between survey and administrative data differed between trial arms.

RESPONSE: We believe there may have been a misunderstanding caused by our use of the word “survey” in this section. All such data collected were actually collected from GP records at follow up on forms which we were referring to as surveys. The section has now been rephrased removing the word survey to prevent confusion to readers.

4. The results section states that differences in mean daytime SABP were adjusted for baseline mean daytime SABP and minimisation factors. The methods section says that adjustment was by minimisation factors only, so needs to be amended.
RESPONSE: Thank you for bringing this to our attention. All sections now correctly describe adjustments as being made for baseline SABP and all minimisation factors.

5. In the discussion, the authors quote relative risk reductions of 15 and 10% in stroke and coronary heart disease. Ideally, absolute risks would be given, however perhaps this information is not available.
RESPONSE: We agree absolute risk reductions would be beneficial here if they were available. However Laws et at [1] who provide the most up-to-date meta-analysis on the matter only offer relative risks.

6. Please can the authors include their estimated ICC, as this may be useful for future investigators designing trials in this area. I was not sure that the authors meant "cluster analysis" - perhaps a better way of putting it would be to say that the GLM was modified to allow for clustering (perhaps using a random effect?).
RESPONSE: Thank you for pointing out that we had not fully described our sensitivity analysis where we allowed for potential clustering. We have now removed this paragraph from the paper, as all the details are in the main trial paper, and we do not think it adds anything specifically to the health economic paper. The interested reader can read the main trial paper for these details.

7. On page 14 the authors state that "However, the fact that point estimates were still in favour of the intervention..." - please can the authors clarify which point estimates these are (consultation and medical costs?)
RESPONSE: This was referring to the point estimates for change in SABP in Madsen et al [2] and has been clarified in the text.

8. In Table 1, the units for HbA1c are specified as "%" but the figures are quite high. Do the authors mean "mmol/mol"?
RESPONSE: Thank you for bringing this to our attention. The figure did indeed refer to mmol/mol and the heading has been corrected on the table.

9. In Table 3, the heading for "mean difference" should be changed to "mean cost difference" or similar.
RESPONSE: Thank you for bringing this to our attention. The heading has now been amended to clarify that this is difference in costs

10. On page 4, the authors state that the Spacelabs 90207 ABPM was used to collect baseline data - was the same device used to collect data at 6 months? I would like confirmation that the same device was used in both groups, and that the intervention group data did not come from the telemonitoring. We discussed this in a previous review and the authors responded saying that the information is already included in the manuscript
- apologies if I'm missing it!
RESPONSE: Please accept our apologies if this was not clear. A line has now been added to the effect variable section which explains that the Spacelabs 90207 ABPM was used for all measurements of SABP at both timepoints.

This is an important contribution to the field and my remaining comments are relatively minor. I recommend that the article is accepted.
RESPONSE: Thank you for the recommendation.

References:
1. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338: b1665.
2. Madsen LB, Kirkegaard P, Pedersen EB. Blood pressure control during telemonitoring of home blood pressure. A randomized controlled trial during 6 months. Blood Press 2008;17:78–86.