PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	TELEMONITORING AFTER DISCHARGE FROM HOSPITAL WITH HEART FAILURE - COST-EFFECTIVENESS MODELLING OF ALTERNATIVE SERVICE DESIGNS
AUTHORS	Thokala, Praveen; Baalbaki, Hassan; Brennan, Alan; Pandor, Abdullah; Stevens, John; Gomersal, Tim; Wang, Jenny; Bakhai, Ameet; Al-Mohammad, Abdallah; Cleland, John; Cowie, Martin; Wong, Ruth

VERSION 1 - REVIEW

REVIEWER	Fukumoto, Yoshihiro Tohoku University Graduate School of medicine, Cardiovascular Medicine
REVIEW RETURNED	26-May-2013

THE STUDY	This manuscript is a clinical study regarding cost-effectiveness analyses, which suggested that home telemonitoring was an optimal strategy in most scenarios of heart failure. This report is clinically important; however, this reviewer has some major criticism for publication. Major comments: 1. First, what is the study population? It seems that this study was based on Home-HF study (ref. 12); however, the study population may be different. The authors should clearly indicate how they enrolled the patients. 2. The authors divided the patients into 4 groups, which was different form ref. 12. Thus, they should show the data of patient baseline characteristics and outcome measurement.

REVIEWER	Stoddart, Andrew The University Of Edinburgh, Edinburgh Clinical Trials Unit
REVIEW RETURNED	10-Jun-2013

THE STUDY	The authors use markov modelling techniques to assess the cost-effectiveness of 3 forms of remote monitoring (RM) strategies to usual care of patients following discharge from hospital for heart failure (HF). The paper makes good use of a recent network-meta-analysis to populate key parameters where possible with appropriate sensitivity analyses around key parameters. The paper is generally well presented and the techniques applied are inline with recommended practice. However I still have a short list of concerns predominantly surrounding modelling assumptions, or matters which may require more clarity. Please note that I have answered “no” to the following questions as the option “it is unclear” was not available and an answer of “yes” would have been misleading. Is the overall study design appropriate and adequate to answer the research question? Are the methods adequately described? Comments: 1) Page 4 of the paper states that the model consists of two states: “alive at home” and “dead”. “Alive at home”, however, incorporates the probability of hospitalisation and associated impact on health related quality of life and costs as well as alive at home without further incedent. The paper would benefit from a more detailed description of the model in this respect. In particular the authors recognise that the probability of mortality is varies by time since discharge from hospital, with the highest risk of mortality immediately after discharge (Table 1). While the authors state clearly that patients were at least initially assigned a probability of mortality based on their time since discharge and treatment group, it is unclear whether this is incorporated into the model/reset for patients who are re-admitted. If so I am unsure how this has been done and I am unable to comment on the suitability of the approach used. If not, it may be possible to include this by separating alive at home into “tunnelled” states denoting time since admission. 2) The model also explicitly attempts to model the impact of non HF related readmissions by applying a hazard ratio relative to usual care to the probability of readmission dependent on the intervention group patients are in. A cost for such admissions are applied but due to the absence of literature on the rates of disutility from non HR admissions, the model assumes no disutility occurs. Thus non HF related admissions are expected to vary between intervention groups and this variation is reflected in the cost side of the ICER equation but not in the QALYs. While this limitation is recognised in the paper, sensitivity analysis around this may be beneficial. 3) Page 7 refers to an expert advisory group who were consulted to derive cost estimates for each of the interventions. While I have no reason to expect this group to have been inappropriate, the paper lacks detail on their credentials in this, and neither I nor the reader are in a position to assess how appropriate the approach was. The paper would benefit from a short description. 4) There are several issues of modelling uncertainty which it may not be possible to address at present due to gaps in the literature. In addition to those detailed above these would include matters such as:

	a. the heterogeneity of the nature of interventions grouped into each of the four treatment categories (UC, STS HM, STS HH and TM), b. the need to use clinical opinion to derive some cost parameters, c. the inability to model repeat interventions after rehospitalisation for HF, or d. the absence of data on subgroups who are more or less responsive to a given form of intervention. The very nature of model uncertainty such as these prevent their impact on the overall results from being tested formally, though the authors do offer sensitivity analyses for some of them. However I find some of the results stated to be stated in overly assertive terms and may need to be rephrased. For example on Page 11 (bottom) the sentence "implemented effectively as part of a whole system redesign of care, TM can alleviate pressure on long term NHS costs and improve people's quality of life through better self-care at home" should perhaps be rephrased by something as simple as swapping "can" for "may" to reflect the limitations of the model. 5) Similarly at the bottom of page 10, carrying over onto page 11, the sentence "In situations with a limited number of devices, it is cost-effective to treat all patients using TM for 6 months than using TM for 12 months on half of the patients…" may only be true of a homogenous patient group. If a subgroup of more responsive patients could be found, then the possibility that offering the more responsive group the TM for the full 12 months could be cost-effective over offering all patients TM for 6 months, depending on the rate of improved response. Other minor issues: • The results in the abstract do not appear to match those presented in table 5 as the base case results, in particular an ICER of 9,552/QALY for TM vs UC where Table 5 quotes: 11,873/QALY or 6,942/QALY depending on whether the Home HF study is included in the meta-analysis. • Page 6, last line of first paragraph: "this consideration predominantly affects the hazard ratios around the telemonitoring intervention only and does not impact significantly on the [STS] interventions". The word "significantly" here is presumably being used in the colloquial sense rather than the scientific. Might I suggest swapping it for something like "substantially" to make it clear no formal statistical testing has been done, or has it? • Page 6: Acronym NYHA (presumably the New York Heart Association) is not defined. • Table 5: The acronyms for Usual Care (UC), Net benefit (NB) defined in footer but not used in table and could be removed to save space.
REPORTING ETHICS	As detailed in the previous section, there are occasional instances where the broad interpretation of the results is correct it is stated in an overly assertive manor which can easily be amended.
RESULTS AND CONCLUSIONS	I have no concerns on the above matters.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments

1. First, what is the study population? It seems that this study was based on Home-HF study (ref. 12); however, the study population may be different. The authors should clearly indicate how they enrolled

the patients. This study is decision analysis modelling of cost-effectiveness using secondary data from different sources.

Authors response: Sorry to have been a little unclear about the characteristics of the study populations in these data sources. We have amended the text to clarify characteristics of patients in CHARM study which provides an estimate of the baseline mortality. Similarly, we have added the details of the patients in Klersy et al, which provided baseline hospitalisation rates and the network meta-analysis of 21 studies, which provided the effectiveness of interventions.

2. The authors divided the patients into 4 groups, which was different form ref. 12. Thus, they should show the data of patient baseline characteristics and outcome measurement. There was no primary outcome measurement as part of this study. The model utilised a hypothetical cohort of HF patients discharged from the hospital within 28 days and used secondary data from various sources to estimate the cost-effectiveness.

Authors response: We have amended the text to clarify characteristics of patients in these data sources (please see response for comment 1)

Reviewer 2 Comments:
1) Page 4 of the paper states that the model consists of two states: “alive at home” and “dead”. “Alive at home”, however, incorporates the probability of hospitalisation and associated impact on health related quality of life and costs as well as alive at home without further incedent. The paper would benefit from a more detailed description of the model in this respect. In particular the authors recognise that the probability of mortality is varies by time since discharge from hospital, with the highest risk of mortality immediately after discharge (Table 1). While the authors state clearly that patients were at least initially assigned a probability of mortality based on their time since discharge and treatment group, it is unclear whether this is incorporated into the model/reset for patients who are re-admitted. If so I am unsure how this has been done and I am unable to comment on the suitability of the approach used. If not, it may be possible to include this by separating alive at home into “tunnelled” states denoting time since admission. The reviewer brings up an important point that we considered quite extensively during the model development stage.

Authors response: Our cohort model uses a monthly probability of death based on the time since discharge and the type of treatment. However, this is not incorporated into the model for patients who are re-admitted for HF. This is because the parameters used in the model represent an average of many different pathways (as with any cohort model), that is, the overall cohort includes a group of patients who have never been hospitalised and a group of patients who receive multiple hospitalisations and the mean rate of hospitalisation is a weighted average of these groups. Thus, to incorporate mortality based on their time since discharge for re-admitted patients would need more detailed evidence on baseline risks and effectiveness in these different groups. For example, this would need information on the effectiveness of telemonitoring in reducing mortality for patients who have had, say, 3 hospitalisations in the previous 12 months. This detailed granularity of evidence is not available and thus, an overall cohort approach was deemed as sufficient for the decision problem. Further research is necessary to develop evidence to address this impact of heterogeneity of patients on the effectiveness of the interventions. If this type of evidence was available, the mortality risk in the model can be reset for patients who are re-admitted by using individual level patient simulation or by using tunnelled states as suggested by the reviewer.

We feel that this is an important point and that it is useful to clarify this issue in the paper. Thus, we

have amended the text in the discussion section (see below)

“Repeat interventions after repeat hospital admissions for heart failure are not modelled and the mortality risk is not reset for patients who are re-admitted as this would need detailed evidence on baseline risks and effectiveness in different patient groups. As this detailed evidence is not available, the cohort model uses evidence about the overall average of the patients to estimate the cost-effectiveness.”

2) The model also explicitly attempts to model the impact of non HF related readmissions by applying a hazard ratio relative to usual care to the probability of readmission dependent on the intervention group patients are in. A cost for such admissions are applied but due to the absence of literature on the rates of disutility from non HR admissions, the model assumes no disutility occurs. Thus non HF related admissions are expected to vary between intervention groups and this variation is reflected in the cost side of the ICER equation but not in the QALYs. While this limitation is recognised in the paper, sensitivity analysis around this may be beneficial.

Authors response: Good point. As there is little or no direct evidence on impact of non-HF related re-hospitalisations, we have performed deterministic sensitivity analysis to see how much impact the assumptions on disutility of hospitalisation affects the results. Similarly, sensitivity analysis was also performed using a lower estimate of the disutility of HF-related hospitalisations. The results are robust to the variations in the disutility of hospitalisation i.e the ICER values in these analyese are similar to that in the basecase. This is made explicit in the results section of the paper.

3) Page 7 refers to an expert advisory group who were consulted to derive cost estimates for each of the interventions. While I have no reason to expect this group to have been inappropriate, the paper lacks detail on their credentials in this, and neither I nor the reader are in a position to assess how appropriate the approach was. The paper would benefit from a short description.

Authors response: The four clinicians named on this paper formed the expert advisory group. This is made explicit in the paper by amending the text just after the reference to the expert group in Page 7 (see below)

“A high cost usual post discharge care scenario was also developed based on discussions with the clinical expert group (AB, AAM, JC and MRC).”

4) There are several issues of modelling uncertainty which it may not be possible to address at present due to gaps in the literature. In addition to those detailed above these would include matters such as:
a. the heterogeneity of the nature of interventions grouped into each of the four treatment categories (UC, STS HM, STS HH and TM),
b. the need to use clinical opinion to derive some cost parameters,
c. the inability to model repeat interventions after rehospitalisation for HF, or
d. the absence of data on subgroups who are more or less responsive to a given form of intervention.

The very nature of model uncertainty such as these prevent their impact on the overall results from being tested formally, though the authors do offer sensitivity analyses for some of them. However I find some of the results stated to be stated in overly assertive terms and may need to be rephrased. For example on Page 11 (bottom) the sentence “implemented effectively as part of a whole system redesign of care, TM can alleviate pressure on long term NHS costs and improve people’s quality of life through better self-care at home” should perhaps be rephrased by something as simple as swapping “can” for “may” to reflect the limitations of the model. Agree, as the reviewer pointed out, there are gaps in literature and any limitations in the evidence base also manifest as limitations of the cost-effectiveness model. These limitations are explicit in the discussion section.

Authors response: The text in conclusions is rephrased from “can” for “may” so that the wording is not overly assertive.

5) Similarly at the bottom of page 10, carrying over onto page 11, the sentence “In situations with a limited number of devices, it is cost-effective to treat all patients using TM for 6 months than using TM for 12 months on half of the patients…” may only be true of a homogenous patient group. If a subgroup of more responsive patients could be found, then the possibility that offering the more responsive group the TM for the full 12 months could be cost-effective over offering all patients TM for 6 months, depending on the rate of improved response.

Authors response: Agree. The text in discussion section is amended to reflect this (see below)

“In situations with a limited number of TM devices, assuming a homogenous patient group, it is cost-effective to treat all patients using TM for six months than using TM for 12 months on half the patients with the other half of the patients under usual care.”

6) The results in the abstract do not appear to match those presented in table 5 as the base case results, in particular an ICER of 9,552/QALY for TM vs UC where Table 5 quotes: 11,873/QALY or 6,942/QALY depending on whether the Home HF study is included in the meta-analysis.

Authors response: This is an error. The text in the abstract is amended.

“TM was the most cost-effective strategy in the scenario using these base case costs. Compared with usual care, TM had an estimated incremental cost effectiveness ratio (ICER) of £11,873/QALY, whereas STS HH had an ICER of £228,035/QALY against TM.”

7) Page 6, last line of first paragraph: “this consideration predominantly affects the hazard ratios around the telemonitoring intervention only and does not impact significantly on the [STS] interventions”. The word “significantly” here is presumably being used in the colloquial sense rather than the scientific. Might I suggest swapping it for something like “substantially” to make it clear no formal statistical testing has been done, or has it

Authors response: Agree. Text amended to “substantially”.

8) Page 6: Acronym NYHA (presumably the New York Heart Association) is not defined.

Authors response: Agree. NYHA is now defined in the text

9) Table 5: The acronyms for Usual Care (UC), Net benefit (NB) defined in footer but not used in table and could be removed to save space

Authors response: Agree. UC and NB are removed from the Table 5

VERSION 2 - REVIEW

REVIEWER	Stoddart, Andrew The University Of Edinburgh, Edinburgh Clinical Trials Unit
REVIEW RETURNED	26-Jul-2013

THE STUDY	While I have answered No to "Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?" this is obviously a positive reasonce given the phrasing of the question. (please see below comments)
GENERAL COMMENTS	I have reviewed the article carefully in light of the authors responses to my previous comments and I am happy to confirm that my previous concerns have now been addressed. While the modelling approach taken still lacks a certain degree of detail which would be desirable to address the research question in its fullest, for example data on re-admissions or differential severity groupings. This is, as the authors make clear in the paper, due to the limited data available in the literature and a more sophisticated approach is not thought to be possible at this time. As such the model offers perhaps a simplified picture but one which arguably offers the best estimate possible given the state of present knowledge. Where the model has limitations, the authors highlight them clearly and reflect this uncertainty in conclusions in an appropriate manor. All minor/typographical errors raised previously appear to have been amended and I have not spotted any more.