PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adherence management for cancer patients on capecitabine: a prospective two-arm cohort study
AUTHORS	Jaehde, Ulrich; Krolop, Linda; Ko, Yon-Dschun; Schwindt, Peter; Schumacher, Claudia; Fimmers, Rolf

VERSION 1 - REVIEW

REVIEWER	Bernard Vrijens Chief Science Officer, MWV Healthcare Belgium I am an employee of MWV Healthcare
REVIEW RETURNED	13-May-2013

THE STUDY	In general, the paper is well written and address the important topic of patient adherence to oral anticancer drug therapy. Please find here below some minor comments/suggestions to improve the manuscript: 1) In the abstract, define a cycle as 2 weeks on treatment and 1 week off. 2) In the sample size calculation, please specify which statistical tests are used and how sample size is estimated for the non inferiority test in the initially adherent patients. Note also that "error of first kind" should read 'type I error". 3) A recent systematic review published in DRUGS (Demonceau et al. Drugs (2013) 73:545–562) has demonstrated the benefit of feeding back to the patient electronically compiled adherence data. This reference should be added as an introduction to the feedback proposed in module 3. 4) In the present study, my impression is that the Standard Of Care (SOC) was quite good as all patients received module 1&2. The paper would benefit from a brief description of the SOC and how it could have impacted the conclusion. See for example: de Bruin et al. (Arch Intern Med. 2010;170(3):240-250) 5) This paper addresses primarily the implementation element of adherence. It should be clearly defined as such according to the recently published taxonomy (Vrijens et al., Br J Clin Pharmacol / 73:5 / 691–705)
GENERAL COMMENTS	I think that the paper would benefit from a brief discussion of the metrics used to quantify adherence to on/off therapies. In this research, the authors have used "daily adherence" and "daily intake adherence" with an arbitrary cut-off at 90%. This approach was used previously and is fine for the objectives of this paper. It would however be good to discuss how one could improve the quality of the metrics so that they better reflect the longitudinal aspect of the adherence data. A call for future research.

REVIEWER	Claire Easthall MRPharmS, School of Pharmacy, University of East Anglia, Norwich, UK I have no competing interests
REVIEW RETURNED	14-May-2013

GENERAL COMMENTS	This is an intersting article an provides novel data on an important topic. It is generally well written and has been an enjoyable read. I have taken the time to make additional comments that I feel will improve the manuscript and this is attched as a seperate file. **General comments** • The key messages are good but I'd be inclined to emphasise the importance of establishing that if patient's start off adherent, they stay so. This is a really important point allows it allows targeting of support to those who'll actually benefit from it. • I'm not sure the objectives of the abstract quite match what is reported here as they mention the development of the intervention yet there is very little information about this in the manuscript. • The intervention is described as multi-professional yet the actual intervention (in addition to standard care) was only delivered by one professional, a pharmacist. • Within the results I would perhaps expect to see a little more information about the intervention itself, how long the third module lasted on average, how many follow ups were received, how patients perceived this etc. • The introduction is generally well written and an enjoyable read. My only advice for improvement here would be that the section reviewing previous studies is a slightly cumbersome read. Minor amendments and restructuring may improve this. • The methods section is generally well written and methodologically sound. Minor points for improvements are mentioned below. One point of minor concern with the methods however, is that all patients received modules 1 and 2 in addition to standard care. Can we sure that the "adherers" would have been so without receipt of these two modules? Information on the theoretical basis of the modules contents and process by which they were developed would also be useful. • The results are generally well written but some of the figures are quite complex and may therefore benefit from additional explanations. • The conclusion is very well written with a good identification of the studies limitations **Specific minor points** • Page two lines 15-16: This doesn't quite read right, I wonder if it should read "...aimed to develop and evaluate.." OR "This was a prospective...". Either would be fine but as it reads it's not quite

	right. • Page three, line 19: is this standard pharmaceutical care? It may be useful to clarify this. • Page three, line 30: I'd expect to see whether this was a statistically significant increase in adherence • Page four, lines 36-37: I know what this statement means but I wonder if it could be better articulated, it took a few readings to become clear. • Page five, line 6: I think a little more detail on the "intensified multidisciplinary pharmaceutical care programme" would be useful here to add context and aid understanding • Page six, line 20: Who asked the patients to participate? I would like to know this information so that I can evaluate whether there may have been any sense of coercion by the patients being directly asked to participate by their healthcare providers. • Page six, lines 40-43: "Participants were provided with a MEMS container and asked to use it for storage of capecitabine medication during the study". To me this wording could infer that patients were not aware that their adherence was being monitored. This being so, surely there are ethical considerations in deceiving the patients with regard to the purpose of the MEMS container? It is however an ideal means of overcoming the Hawthorne effect which plagues medication adherence research. I think this is quite an important point to clarify within the manuscript. • Page seven, lines 19-27: This is another awkward paragraph that is hard to work through. I think there is some ambiguity here that would benefit from clarification. It might be helpful to clearly articulate that these were the different measures of adherence perhaps? • Page seven, line 43: "Modular medication management" as this is the first time that this term has been introduced, I think it would benefit from a little explanatory introduction at an earlier stage. If found myself stumbling over whether this was the name of the adherence support intervention. This comes later, but it felt confusing in the beginning. • Page ten, line 6: 97 patients were assessed for eligibility, is all of the patients that could have been assessed during the data collection period? Presumably so but this isn't clear. • Page ten, lines 21-22: Very minor point but I'd normally expect to see percentages with the raw numbers too, i.e. 58 patients (79.5%) were initially adherent. • Page 11, table 1: It's not clear what comparison each p-value relates to. It looks like all of the different sub-classifications (for example ages) have been combined somehow, and the difference summarised in one p-value, but this isn't what I was expecting from the methods section. This is very confusing. Also with the table, is it necessary to say that 76% were female and 24% were male? Surely if the readers are provided with the information that 76% were female it is intuitive to work out the percentage that was male? This only a very minor point but I

	mention it because it could be a useful means of decreasing the volume of text in the table as it is quite 'busy'. Also with the number of prescribed drugs, it might be useful to stipulate whether this was all regular medication or included PRN drugs. Also, I'm not certain how many of your readers will have a specific interest in knowing exactly which drug the capecitabine was combined with. If this is not essential information perhaps the table could be simplified to just say monotherapy or combined therapy? This might make the table easier to digest. • Page 12, line 23: Figure 3, I wonder if all of your readers (and those of general medical readership) will be familiar with this type of plot and what it specifically shows; I certainly wasn't. A small amount of additional information about what each aspect of the chart represents might help readers with less familiarity with this. • Page 12, lines 25-26: "Median daily adherence was 100% in every cycle. Average daily adherence decreased from 98.9% in cycle one to 97.3% in cycle 6" – what does this mean? The term 'average daily adherence' is very confusing as one would normally assume this refers to a mean or median, this being so it contradicts the proceeding sentence. This ambiguity requires clarification. (NB now that I have seen online table A this is clearer – I would advise replacing the term 'average' with 'mean' to avoid confusing your readers). As an additional thought, is it common practice to report both the mean and median? Surely either or is more common according to whether the data is normally distributed? If there is a justifiable rationale for using both measures this should be articulated. • Page 12, lines 29-30: I don't think it's fair to say that the modular medication management led to consistently high adherence in the initially adherent group, there is no data to suggest it was the modular medication management that led to the high adherence rates, they may have been high anyway. I believe this inference is therefore incorrect. • Page 12, line 34: It's not clear to me what online figures A and B actually show. I assume each different coloured line represents a different patient but these are quite complex figures to work through. Your readers may appreciate a little further explanation. • Page 12, line 59: I'd expect to see actual figures (and percentages) here rather than just saying twice as high. Also you say number of adherence patients but the chart refers to percentages, be consistent and accurate. • Page 13, line 13: Number of adherent patients remained relatively constant in later cycles too (again this should be % not number). I'd say 'relatively' is a bit of a lose term here as some may argue there was a bit of a dip after cycle four, perhaps you could quantify this statement by saying it only ranged between X and Y over the observation period after the intervention? • Page 13, line 29: Online table B, same comments re showing both mean and median • Page 13, line 44: The potential predictors adherence, what is

	data shown for age and gender but not any other variables, could this all be presented in a table? • Page 14, line 3: Again a percentage here would be helpful to so that drop-out in the two groups can be compared more easily. Also is it worth making a comparison of whether the drop-out/discontinuation rates were similar between the two groups? • Page 15, lines 44-50: I disagree with the statement that it would be easier to identify non-adhering patients by means of possible predictors and indeed you go onto contradict this statement by saying we haven't really got any predictors. I think what you may have meant is that using MEMS is both costly and labour intensive. However, it remains our gold-standard of adherence assessment. My advice we be to not put down the use of MEMS, I think it's great that you used the gold standard and it strengthens your study but adding robustness and credibility to the reported data. • Page 16, lines 46-49. The sentence beginning with 'however' and ending with 'alone', I'm not sure at all what this is saying. It may benefit from re-phrasing to articulate this point with greater clarity. • Page 16, line 49/50: 8/15, again, I'd expect a percentage in brackets here please. • Page 16, line 54/55: The statement "patients have to be educated in detail..." is non-specific. The fact the 53.3% of patients are getting their capecitabine break wrong in some way is a big deal (I also think you should make more of this finding which represents novel and useful data), what would your specific recommendations be to remedy this be? • Page 17, lines 20/21: Again I'd prefer to see something more specific than 'further research is needed'. What techniques are there to change adherence behaviours in those who are intentionally non-adherent, how can we identify intentional non-adherence? It doesn't need to be much (after all this would be the subject of the further work recommended) but I'd like to see a little further development of what further work could be explored.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
In general, the paper is well written and addresses the important topic of patient adherence to oral anticancer drug therapy. Please find here below some minor comments/suggestions to improve the manuscript:

1. In the abstract, define a cycle as 2 weeks on treatment and 1 week off.
- We have clarified the definition of one capecitabine cycle in the abstract.

2. In the sample size calculation, please specify which statistical tests are used and how sample size is estimated for the non inferiority test in the initially adherent patients. Note also that "error of first kind" should read 'type I error".

- We have added information on the statistical tests in the methods section. Moreover, we changed “error of first kind” to “type I error” throughout the manuscript.

3. A recent systematic review published in DRUGS (Demonceau et al. Drugs (2013) 73:545–562) has demonstrated the benefit of feeding back to the patient electronically compiled adherence data. This reference should be added as an introduction to the feedback proposed in module 3.
- We added the reference in the methods section describing module 3.

4. In the present study, my impression is that the Standard Of Care (SOC) was quite good as all patients received module 1&2. The paper would benefit from a brief description of the SOC and how it could have impacted the conclusion. See for example: de Bruin et al. (Arch Intern Med. 2010;170(3):240-250).
- Modules 1 and 2 are based on the pharmaceutical care model developed in a previous study by Simons et al. which has shown to enhance adherence (Support Care Cancer 2011;19:1009–18). This certainly explains the high level of adherence even without specific adherence support (module 3). We have extended this aspect in the discussion.

5. This paper addresses primarily the implementation element of adherence. It should be clearly defined as such according to the recently published taxonomy (Vrijens et al., Br J Clin Pharmacol / 73:5 / 691–705)
- We included this information at the end of the introduction.

6. I think that the paper would benefit from a brief discussion of the metrics used to quantify adherence to on/off therapies. In this research, the authors have used "daily adherence" and "daily intake adherence" with an arbitrary cut-off at 90%. This approach was used previously and is fine for the objectives of this paper. It would however be good to discuss how one could improve the quality of the metrics so that they better reflect the longitudinal aspect of the adherence data. A call for future research.
- We agree and have added this aspect to the discussion.

Reviewer #2
This is an interesting article and provides novel data on an important topic. It is generally well written and has been an enjoyable read.
- Thanks, we are happy to read this!

General comments
1. The key messages are good but I’d be inclined to emphasise the importance of establishing that if patient’s start off adherent, they stay so. This is a really important point allows it allows targeting of support to those who’ll actually benefit from it.
- We agree with this comment and emphasised this finding by rephrasing the third key message.

2. I’m not sure the objectives of the abstract quite match what is reported here as they mention the development of the intervention yet there is very little information about this in the manuscript.
- The contents of the three modules were based on a detailled literature review. We included more information on the development of the intervention in the methods section.

3. The intervention is described as multi-professional yet the actual intervention (in addition to standard care) was only delivered by one professional, a pharmacist.
- We agree with the reviewer that the description in the methods section regarding the delivery of the modular medication management was misleading. Modules 1 and 2 were provided by the pharmacist in collaboration with physicians and nurses. Module 3 was delivered by the pharmacist only. We changed the corresponding section to clarify this issue.

4. Within the results I would perhaps expect to see a little more information about the intervention itself, how long the third module lasted on average, how many follow ups were received, how patients perceived this etc.
- This would be very interesting but we did not document these issues systematically, unfortunately.

5. The introduction is generally well written and an enjoyable read. My only advice for improvement here would be that the section reviewing previous studies is a slightly cumbersome read. Minor amendments and restructuring may improve this.
- The part of the introduction section reviewing previous studies has been amended, revised and restructured. We hope that it is better readable now.

6. The methods section is generally well written and methodologically sound. Minor points for improvements are mentioned below. One point of minor concern with the methods however, is that all patients received modules 1 and 2 in addition to standard care. Can we sure that the “adherers” would have been so without receipt of these two modules?
- Modules 1 and 2 are based on the pharmaceutical care model developed in a previous study by Simons et al. which has shown to enhance adherence (Support Care Cancer 2011;19:1009–18). Therefore, modules 1 and 2 certainly had a beneficial effect on the adherence of all patients. We have extended this aspect in the discussion (see “Effect of modular medication management”).

Information on the theoretical basis of the modules contents and process by which they were developed would also be useful.
- This information has been added to the methods section of our manuscript.

7. The results are generally well written but some of the figures are quite complex and may therefore benefit from additional explanations.
- The figure legends have been extended.

8. The conclusion is very well written with a good identification of the studies limitations.
- Thanks!

Specific minor points
- We thank the reviewer for these valuable suggestions to improve the readability of our manuscript. In the following we only respond to some of the reviewer’s specific points. The others were implemented exactly as the reviewer suggested.

3. Page three, line 30: I’d expect to see whether this was a statistically significant increase in adherence
- According to our statistician, a test did not make sense here since there was no control. So he recommended us just to report the extent of increase in the initially non-adherent patients. This is in accordance with the comment of the managing editor that the analysis “should focus on association rather than cause-and-effect”.

9. Page seven, line 43: “Modular medication management” as this is the first time that this term has been introduced, I think it would benefit from a little explanatory introduction at an earlier stage. If found myself stumbling over whether this was the name of the adherence support intervention. This comes later, but it felt confusing in the beginning.
- The term “modular medication management” is now mentioned in the introduction section.

12. Page 11, table 1: It’s not clear what comparison each p-value relates to. It looks like all of the different sub-classifications (for example ages) have been combined somehow, and the difference

summarised in one p-value, but this isn't what I was expecting from the methods section. This is very confusing.
- Each p value relates to the result of the corresponding Fisher's exact test. Frequencies of socio-demographic and disease-related characteristics in initially adherent and non-adherent patients were tabulated in a contingency table and the relationship between two categorical variables was explored using the Fisher's exact test (i.e. does the group membership (initially adherent or initially non-adherent) relates to the patients' age/sex/number of additional drugs etc.). This approach was explained in the methods section ("Differences regarding socio-demographic and disease-related characteristics between initially adherent and non-adherent patients were tested using the Fisher's exact test for nominal data.").

14. Page 12, lines 25-26: "Median daily adherence was 100% in every cycle. Average daily adherence decreased from 98.9% in cycle one to 97.3% in cycle 6" – what does this mean? The term 'average daily adherence' is very confusing as one would normally assume this refers to a mean or median, this being so it contradicts the proceeding sentence. This ambiguity requires clarification. (NB now that I have seen online table A this is clearer – I would advise replacing the term 'average' with 'mean' to avoid confusing your readers). As an additional thought, is it common practice to report both the mean and median? Surely either or is more common according to whether the data is normally distributed? If there is a justifiable rationale for using both measures this should be articulated.
- The term 'average' was replaced by 'mean' throughout the manuscript. The mean was calculated additionally for both adherence groups since it is more sensitive to differences in daily adherence than the median.

20. Page 13, line 44: The potential predictors adherence, what is data shown for age and gender but not any other variables, could this all be presented in a table?
- Data for the relationship of daily adherence and age and gender, respectively, are shown in detail since these associations were considered as particularly interesting. To show data for the association between daily adherence and all further socio-demographic and disease-related characteristics a large table would be needed. Since there was no significant association between daily adherence and any of the further characteristics we think that it is not essential to show this data in the manuscript.

21. Page 14, line 3: Again a percentage here would be helpful to so that drop-out in the two groups can be compared more easily. Also is it worth making a comparison of whether the drop-out/discontinuation rates were similar between the two groups?
- We added the percentages to this part of the results section. The idea of making a comparison of the drop-out and discontinuation rates between the groups is very interesting. However, we think that due to the small sample size its validity would be limited.

VERSION 2 – REVIEW

REVIEWER	Claire Easthall, Research Pharmacist, School of Pharmacy, University of East Anglia, Norwich, Norfolk, NR4 7TJ, Norwich. No competeing interests
REVIEW RETURNED	10-Jun-2013

GENERAL COMMENTS	My original (minor) concerns have now been addressed by the revisions made an I am confident that this manuscript is suitable for publication. Although I have ticked accept, there are one or two VERY minor amendments which the authors amy with to consider: • Page 2 line 18: The change here still doesn't read quite right to me, perhaps there is a word missing, it feels like it should say 'a multi-professional medication management intervention' or 'programme'

	or something like that. It just doesn't quite make sense to me. • Page 3 line 16/17: As above • Page 3 line 30/31: I understand your rationale for not undertaking a statistical test here and was unsure myself whether it was possible, I just wanted to be sure the possibility had been explored. I wonder if, as a compromise and to help your readers, it would be possible to calculate confidence intervals around the data here, so that the readers can at least gauge whether the confidence intervals overlap. • Page 15 line 10: Again the wording doesn't quite work, it either needs to be 'a patient tailored modular medication management, programme' OR simply 'patient tailored modular medication management'. • Page 15, line 49: It reads, 'like, e.g', either would be fine but both look slightly odd • Page 17, line 37: Would it be possible to provide an example of what is meant by an 'advanced educational intervention' and perhaps a reference to back this up? If a patient is intentionally non-adherent and resistant to the modules already provided I wonder if further education will be beneficial. There is evidence to suggest that provision of education to patients that do not wish to receive simply evokes further resistance. Perhaps a newer approach such as Motivational Interviewing would be useful to explore and resolve the patient's ambivalence to adherence?