PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Community pharmacy-delivered interventions for public health priorities: a systematic review of interventions for alcohol reduction, smoking cessation, and weight management, including meta-analysis for smoking cessation.
AUTHORS	Brown, Tamara; Todd, Adam; O'Malley, Claire; Moore, Helen; Husband, Andy; Bambra, Clare; Kasim, Adetayo; Sniehotta, Falko; Steed, Liz; Smith, Sarah; Nield, Lucie; Summerbell, Carolyn

VERSION 1 - REVIEW

REVIEWER	Denns Raisch, John Rafi, Pharm D and Shannon Kindelien Dennis W. Raisch, PhD, MS, RPh Professor, College of Pharmacy University of New Mexico Health Sciences Center 1 University of New Mexico, MSC 09 5360 Albuquerque, NM 87131
REVIEW RETURNED	02-Oct-2015

GENERAL COMMENTS	The manuscript provides a good description of the search strategy, and is well-written. Key concerns: 1. Title: Specify that meta-analysis was only performed for tobacco cessation and specify the terms as alcoholism treatment and tobacco cessation (instead of alcohol and smoking) to be consistent with weight management. 2. The flow diagram indicates that almost 14,000 articles were excluded initially but the methods (or diagram) provide no information regarding exclusion criteria for those articles. 3. Cost effectiveness is mentioned repeatedly, yet very little evidence is reported to support cost effectiveness. What is shown is in an appendix table and the results are not reported consistently across studies or in a manner that supports the reader to compare to other public health interventions. 4. The meta-analysis of smoking cessation does not address study quality or the differences in duration of follow-up, which varies from 5 to 52 weeks. Since length of follow-up for tobacco cessation has an important impact on the measure of effectiveness, it is a problematic to combine these studies. Given these concerns, the editors should consider whether the meta-analysis should be deleted. 5. The discussion section, which is inadequate in light of the information reported, should include a critique (strengths and weaknesses) of this body of literature. The lack of cost effectiveness data should be noted as a concern, with recommendations for how these values should be reported. Recommendations regarding the importance of reporting predictors of success (and what those predictors might be, would strengthen the discussion. Furthermore there is literature on pharmacist-provided tobacco cessation interventions which describes these predictors, although these studies many not have been included in this manuscript because of

	lack of a control group. Those studies could, however, be mentioned in the discussion section to strengthen the discussion. Another point to consider for the discussion is to put the findings in perspective of other public health interventions that pharmacists provide, such as vaccinations. 6. The tobacco cessation therapies are limited to nicotine replacement interventions. The review does not address more modern and effective treatment modalities, such as varenicline or buproprion. This should be mentioned. 7. A description of whether the patients bear any costs of the interventions should be provided. In addition a discussion of pharmacists' reimbursement and motivations for providing these interventions is needed. 8. The limitations of this literature review manuscript should be addressed in the discussion. 9. The term "anthropometric measurements" appear to be misapplied in the manuscript, because the complete measurements required are not provided, only portions of them are given. 10. The authors should consider writing the manuscript on tobacco cessation only and another manuscript on alcohol counseling and weight reduction, since there were so few of those studies, they provide little additional information. 11. The summary tables of the studies should be combined so the outcomes are reported with the study descriptions because the reader has to go back and forth between tables to fully understand the studies. Columns should be deleted when the column is populated with NR for most studies. Instead of reporting numerator and denominator for outcome, report sample sizes and success rates. 12. It is unclear what constitutes a weak, moderate, or strong assessment of quality or how the global measure is determined. 13. Opening sentences on page 5, lines 4-18, appear to be copied from their previous publication entitled: "Community pharmacy interventions for public health priorities: protocol for a systematic review of community pharmacy-delivered smoking, alcohol and weight management interventions."

REVIEWER	Tania USA
REVIEW RETURNED	05-Oct-2015

GENERAL COMMENTS	I would like to congratulate the authors for such a high quality systematic review they have conducted. I would like to suggest its publication with enthusiasm and without any change.

REVIEWER	Michael Stoto Georgetown University, U.S.A.
REVIEW RETURNED	27-Oct-2015

GENERAL COMMENTS	This paper addresses an important issue, using appropriate systematic review methods, and obtains largely credible results that should be useful to policy makers and public health practitioners. The meta-analysis and meta-regression of the smoking cessation studies, however, is problematical in a number of results. First, it is not at all clear what the authors used as a metameter, the effect size that is common across all of the studies. Since ORs are reported

	presumably the metameter is the OR for cessation comparing the intervention and control groups at some point after the intervention, but that should be clearly stated. Without stating this clearly, a summary such as the "pooled odds ratio was 2.56 [95% CI 1.45 to 4.53]" (to quote from the abstract) is meaningless. Second, given the description of the studies on pages 19-22, it is apparent that there is substantial substantive heterogeneity in many respects. In addition to differences in populations studied and methodology, there would seem to be many differences in the nature and intensity of the intervention, nature of the comparator, duration and intensity of the intervention and when the cessation outcome was mentioned. The "72% unexplained differences" (p. 23, l. 9), if it is as I presume an I2 statistic, quantifies this uncertainty, but the is it not merely a statistical problem but demonstrates that this summary is meaningless. The authors, of course, go on to explore heterogeneity via meta-regression, but I am not confident that the issue is ever fully dealt with. Even though the final meta-regression model has an I2 of 27% and a non-significant Q statistic, these tests are known to be underpowered. Third, based on what appears in the abstract and conclusions, the subgroup analysis summarized in Figure 2. It would be useful to report whether the difference between the two groups was significant, and whether this dimension of heterogeneity was identified a priori. It should also be noted in the abstract and conclusion whether this was the primary comparison, or the result of a post hoc comparison. Fourth, the authors made the appropriate choice not to summarize the other outcomes in a meta-analysis. The summary tables, however, should indicate the comparison between intervention and control groups in each study (e.g. in Table 2, were both of the analyses differences of differences using the displayed intervention and control outcomes, or some adjusted difference) and whether these differences were statistically significant. Finally, it is not clear why, in the abstract, smoking interventions are declared effective without qualification, whereas are weight management interventions are compared to those delivered in primary care settings and those commercially provided.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Denns Raisch
University of New Mexico Health Sciences Center

Please note that John Rafi, Pharm D and Shannon Kindelien, graduate students in our program, assisted me in this review

Please leave your comments for the authors below See attachment
The manuscript provides a good description of the search strategy, and is well-written.

Key concerns:
1. Title: Specify that meta-analysis was only performed for tobacco cessation and specify the terms as alcoholism treatment and tobacco cessation (instead of alcohol and smoking) to be consistent with weight management.
RESPONSE: Thank you, the title has now been changed so that it is clear that meta-analysis was only performed for smoking cessation. The term we used throughout the paper was 'alcohol reduction'

so to be consistent this is what we have now used in the title. Both studies of ‘alcohol reduction’, excluded participants with ‘alcohol dependence’ so it was decided that ‘alcohol reduction’ better reflected the population under study.

2. The flow diagram indicates that almost 14,000 articles were excluded initially but the methods (or diagram) provide no information regarding exclusion criteria for those articles.
RESPONSE: We conducted and reported the systematic review according to PRISMA; Figure 1 states reasons for exclusion for the 49 articles that were excluded on reading of full-text articles.

3. Cost effectiveness is mentioned repeatedly, yet very little evidence is reported to support cost effectiveness. What is shown is in an appendix table and the results are not reported consistently across studies or in a manner that supports the reader to compare to other public health interventions.
RESPONSE: We agree that there is relatively little identified cost-effectiveness evidence; 7 of the 19 included studies reported on cost/cost-effectiveness (1/2 alcohol reduction, 4/12 smoking cessation and 2/5 weight management interventions). The review was primarily a review of effectiveness; however, cost-effectiveness analyses reported within the trial papers were assessed. With regard to the 4 smoking cessation studies that reported on cost-effectiveness we acknowledge on page 24: ‘Four studies reported cost-effectiveness analyses; the methods differed between the studies, making comparisons difficult.’
We agree that a lot of the information on cost-effectiveness is to be found within the appendices and is summarised within the tables in the main text alongside the effectiveness data. We attempt within the text to summarise the salient points from the cost-effectiveness data, for example with the smoking cessation studies, we briefly summarise to show that even with relatively low quit rates the cessation interventions appear cost-effective. Page 24: ‘Four studies reported cost-effectiveness analyses; the methods differed between the studies, making comparisons difficult. Three UK pharmacy-delivered interventions appeared cost-effective; there were relatively low quit rates in one intervention29 and a non-significant trend for cessation rates in another.38 The Australian study31 appeared cost-effective (and effective) in increasing quit rates amongst young adults who were shown the detrimental effects on their own facial physical appearance, of smoking, by using a computer-generated simulation.’
Two of the interventions (both weight management) directly compare costs across different types of interventions and we report the results on page 25: ‘The pharmacy-based group of the Jolly43 trial was not cost-effective compared with commercial weight management programmes’. We also attempt to compare the costs of both studies on page 25: ‘the costs reported in the study of GP versus pharmacy-based weight management programmes42 were broadly similar to that of the pharmacy-based group in the Jolly trial.’
We take on board the need to improve reporting of the cost-effectiveness data to help the reader and so we have extracted cost-effectiveness data in detail within a new Supplementary file 7 and have added some more detail to the text. In the Discussion we have added: ‘This review aimed to extract information on intervention costs and potential cost saving through intervention effects; however, it is not a review of economic evaluations and as such we do not critically appraise the methods of the economic evaluations; we simply report the results of the various types of economic evaluations that were conducted alongside included interventions.’
In summary, we have attempted to report cost-effectiveness data consistently across the different types of interventions (alcohol reduction, smoking cessation, weight management) and we have noted the limitations of the data, reporting comparisons across different types of public health interventions, where reporting has enabled us to do so.

4. The meta-analysis of smoking cessation does not address study quality or the differences in duration of follow-up, which varies from 5 to 52 weeks. Since length of follow-up for tobacco cessation has an important impact on the measure of effectiveness, it is a problematic to combine these studies. Given these concerns, the editors should consider whether the meta-analysis should be deleted.

RESPONSE: We agree with the reviewer that study quality and duration of follow up are important factors in smoking cessation. However, we disagree with reviewer that the meta-analysis results should be deleted because clinical and methodological diversity always occur in meta-analysis. We accounted for study quality in a meta-regression model together with study type and intervention duration, which together reduced variations between studies to about 27% (this is an acceptable level of heterogeneity based on Cochrane recommendation). We have now included a subgroup analysis by “study quality” and show that most variations between studies are from studies rated as moderate or weak quality. This was not included initially because it showed no significant difference in a meta-regression model, which may be due to lack of power given the small number of studies.

5. The discussion section, which is inadequate in light of the information reported, should include a critique (strengths and weaknesses) of this body of literature. RESPONSE: We have revised the discussion and attempted to describe in more detail the strengths and the limitations both of our review and the evidence.
The lack of cost effectiveness data should be noted as a concern, with recommendations for how these values should be reported. RESPONSE: We acknowledge within the discussion section on page 30: ‘….more research is needed on the cost effectiveness of community pharmacy-delivered alcohol, smoking, and weight management interventions compared with other providers.’ We have now added a sentence on page 30: ‘It appears that duration of intervention impacts on effectiveness and this is likely to impact on cost-effectiveness.’ Recommendations regarding the importance of reporting predictors of success (and what those predictors might be, would strengthen the discussion. Furthermore there is literature on pharmacist-provided tobacco cessation interventions which describes these predictors, although these studies many not have been included in this manuscript because of lack of a control group. Those studies could, however, be mentioned in the discussion section to strengthen the discussion. RESPONSE: We acknowledge that predictors of success are very important but as you say, due to a lack of control group, these sorts of studies were not picked up by this review. We decided not to embark on discussing possible types of predictors but we have highlighted potential predictors from the evidence we did include, for example on duration of intervention which may also vary according to type of setting.
Another point to consider for the discussion is to put the findings in perspective of other public health interventions that pharmacists provide, such as vaccinations. RESPONSE: We agree that it would be worthwhile comparing the results of our review to results from other public health interventions delivered by community pharmacies. However, as public health is a relatively new role for community pharmacies the evidence for these interventions is, at best, poor. Many reviews published in these areas contain uncontrolled studies of low quality and a high risk of bias. We therefore feel that it would be inappropriate to compare these to our review. For the example of vaccination and community pharmacy, to the authors’ knowledge, there is no systematic review in this area owing to the lack of primary research in this area. The rationale for choosing alcohol, smoking and weight management as review areas was, in many cases, because our pilot searches showed these were the most developed public health services in terms of an evidence base. We now reference a Cochrane review which is in progress which will hopefully enable comparisons, particularly in terms of implementation, organisation and delivery; with other types of public health interventions carried out in the pharmacy (Steed et al. 2014)

6. The tobacco cessation therapies are limited to nicotine replacement interventions. The review does not address more modern and effective treatment modalities, such as varenicline or buproprion. This should be mentioned.
RESPONSE: Many thanks for this comment. Our search was not limited by the ‘type’ of smoking cessation intervention. If we found any controlled studies (meeting our inclusion criteria) describing a community pharmacist intervention in relation to varenicline or bupropion, we would have included them in our review.
Similarly, for the weight management and alcohol aspects of the review, we would have included

studies involving pharmaceutical interventions (e.g. the supply of orlistat or disulfarim). Of note, we did include a study in relation to weight management that involved the supply of orlistat (see Malone, 2003)
Unfortunately we did not any studies in relation to varenicline or bupropion (or indeed any other smoking pharmacological intervention). We were not surprised by this given these agents are relatively new in the context of community pharmacy interventions and, in the majority of countries these drugs are only available with a prescription written by an appropriate practitioner. We would, however, expect these studies to be published in the future and possibly included in future updates of this review.

7. A description of whether the patients bear any costs of the interventions should be provided. In addition a discussion of pharmacists' reimbursement and motivations for providing these interventions is needed.
RESPONSE: Thank you for raising this point. Rather than specifically address this information in the main text of the manuscript, we decided to include it as a supplementary file. Please see P15 - Supplementary file 4: Organisation and delivery of interventions – last column 'resources' states where products were provided for free to the participants. See also Implementation of the interventions (Supplementary file 3). See also Behaviour Change (Supplementary file 5) and text on page 16: 'In addition, interventions that included the provision of NRT or commercial weight management programmes or products, free of charge, were also deemed to include 'incentivisation'. We have now made it clear to the reader that this information is provided in the Supplementary files. We do not feel a discussion of pharmacists' reimbursement and motivations would add value to the manuscript given that pharmacists are no different to other primary healthcare provider. We accept that the mechanisms of payment may differ (private insurance, national health service) but the overall concept remains the same.

8. The limitations of this literature review manuscript should be addressed in the discussion.
RESPONSE: Thank you. We have revised the discussion and attempted to describe the limitations of our review in this section.

9. The term "anthropometric measurements" appear to be misapplied in the manuscript, because the complete measurements required are not provided, only portions of them are given.
RESPONSE: We believe that the use of the term 'anthropometric' has been used correctly; we use the term to encompass any type of anthropometric method for estimating body fat (e.g.skinfolds, height and weight, circumferences, etc), so that we do not have to list each type of measurement individually throughout the report. We don't imply that each individual study has measured all possible types of anthropometric measurement. We hope this clarifies the matter.

10. The authors should consider writing the manuscript on tobacco cessation only and another manuscript on alcohol counseling and weight reduction, since there were so few of those studies, they provide little additional information.
RESPONSE: We did consider writing separate papers based on the type of intervention (i.e. alcohol reduction, smoking cessation, weight management) however the paper is based on a systematic review which was funded by the National Institute for Health Research (NIHR) Public Health Research programme; the original remit was to review the effectiveness of community pharmacy based public health interventions for the three most significant modifiable risk factors for morbidity/mortality in the UK. Therefore, we felt that it was important to keep this 'intact' and reflect the state of the evidence within one paper, highlighting that there is scant evidence (so far) for alcohol reduction and for weight management services carried out within community pharmacy settings. As far as we are aware, this is the first systematic review that brings together community pharmacy-delivered alcohol, smoking and weight management interventions within one review. The evidence demonstrates that the community pharmacy is an appropriate and feasible setting to deliver a range

of public health interventions.

11. The summary tables of the studies should be combined so the outcomes are reported with the study descriptions because the reader has to go back and forth between tables to fully understand the studies. Columns should be deleted when the column is populated with NR for most studies. Instead of reporting numerator and denominator for outcome, report sample sizes and success rates.
RESPONSE: Thank you for this comment, in order to improve reading of the paper we have done as you suggest and merge study descriptions and outcomes for each type of intervention. We have kept NR so that it is clear where this evidence was not reported (this demonstrates how very little data was reported particularly on inequalities). We have reported percentages alongside quit rates (for the smoking cessation studies) which also demonstrates the sample size; we have also reported p values for each study, these have been extracted directly from the papers.

12. It is unclear what constitutes a weak, moderate, or strong assessment of quality or how the global measure is determined.
RESPONSE: Thank you for pointing this oversight out – an explanation for grading of quality has been added to bottom of the tables within the main paper and supplementary file 7; we have also added this detail to pages 7-8: 'Studies were assessed for quality using six criteria: selection bias, study design, confounders, blinding, data collection methods and withdrawals/dropouts. Each study was given an overall (global) rating based on the ratings for the six criteria ('strong' = no 'weak' ratings, 'moderate' = one 'weak' rating and 'weak' = two or more 'weak' ratings).'

13. Opening sentences on page 5, lines 4-18, appear to be copied from their previous publication entitled: "Community pharmacy interventions for public health priorities: protocol for a systematic review of community pharmacy-delivered smoking, alcohol and weight management interventions."
RESPONSE: This repetition was purposeful. We were keen to make it clear to a reader, who might check whether we did what we said we would do, that we followed our published a priori protocol.

Reviewer: 2
Tania B. Huedo-Medina
University of Connecticut
Please leave your comments for the authors below I would like to congratulate the authors for such a high quality systematic review they have conducted. I would like to suggest its publication with enthusiasm and without any change. RESPONSE: Thank you, we are very grateful for your comments.

Reviewer: 3
Michael Stoto
Georgetown University, U.S.A.

Please leave your comments for the authors below This paper addresses an important issue, using appropriate systematic review methods, and obtains largely credible results that should be useful to policy makers and public health practitioners.
The meta-analysis and meta-regression of the smoking cessation studies, however, is problematical in a number of results. First, it is not at all clear what the authors used as a metameter, the effect size that is common across all of the studies. Since ORs are reported presumably the metameter is the OR for cessation comparing the intervention and control groups at some point after the intervention, but that should be clearly stated. Without stating this clearly, a summary such as the "pooled odds ratio was 2.56 [95% CI 1.45 to 4.53]" (to quote from the abstract) is meaningless.
RESPONSE: We thank the reviewer for this comment. The "metameter" are odds ratio between the

intervention and the control post intervention. This has been clarified in the article.
Second, given the description of the studies on pages 19-22, it is apparent that there is substantial substantive heterogeneity in many respects. In addition to differences in populations studied and methodology, there would seem to be many differences in the nature and intensity of the intervention, nature of the comparator, duration and intensity of the intervention and when the cessation outcome was mentioned. The “72% unexplained differences” (p. 23, l. 9), if it is as I presume an I2 statistic, quantifies this uncertainty, but the is it not merely a statistical problem but demonstrates that this summary is meaningless.
RESPONSE: We thank the reviewer for this comment. The “72% unexplained differences” is I2 and show substantial heterogeneity. However, individual heterogeneities for the subgroup analysis are around 50% for study type and ranges between 0% - 88.9% for study quality. While statistical significance may not necessarily translate to context meaningfulness or relevance, the pooled effect shows significant intervention effect despite the substantial heterogeneity based on random effect model. We presented this as a highlight of what could have been in an ideal case of homogenous studies. We also exercised the necessary caution by only presenting the subgroup pooled effect for the active comparator in our abstract. There is no simple solution to solving heterogeneity problem, the option of not doing meta-analysis solely due to “statistical heterogeneity” seems too generously recommended and it prevents the opportunity to explore sources of variations, while subgroup analysis alone is also problematic due to potential danger of accidental false conclusion.
The authors, of course, go on to explore heterogeneity via meta-regression, but I am not confident that the issue is ever fully dealt with. Even though the final meta-regression model has an I2 of 27% and a non-significant Q statistic, these tests are known to be underpowered.
RESPONSE: We agree with the reviewer that the tests are known to be under powered. We also agree that the issue of heterogeneity cannot solely be addressed by statistical analysis. However, it is important and advisable to always explore sources of variation in a meta-analysis because there will always be variation between studies. While there is no “hard” threshold for acceptable I2, there is a consensus that I2 less than 50% is less problematic (Schroll et al. 2011). The magnitude of heterogeneity between studies is more important than its associated p-value. Our approach considered a holistic framework for meta-analysis and follows Cochrane guidelines on dealing with substantial heterogeneity with respect to methodology. Meta-regression is important to minimise the associated problem with subgroup analysis, which is needed due to the substantial heterogeneity in the overall pooled effect.
Third, based on what appears in the abstract and conclusions, the subgroup analysis summarized in Figure 2. It would be useful to report whether the difference between the two groups was significant, and whether this dimension of heterogeneity was identified a priori. It should also be noted in the abstract and conclusion whether this was the primary comparison, or the result of a post hoc comparison.
RESPONSE: We thank the reviewer for this comment. Subgroup analyses for mediators are pre-specified in the protocol. The table below shows the meta-regression results for separate analysis of study type, intervention duration and Quality. There was a marginally significant difference between study types and a significant positive association with intervention duration. There was no significant difference between study quality categories, which is why we did not include its subgroup analysis in the paper. However, non-significance effect of quality rating may be due to lack of power as a result of small sample size and three categories of quality ratings.

Table 1: Mete-regression exploratory of association between intervention effects and study type, study quality and intervention duration.

Variable
Study type (Active Comparator vs non-active comparator)
Estimate: -0.6433 95% CI lower: -1.2857, upper:-0.0010
Quality

Moderate vs Weak
Estimate: -0.0637 95% CI lower: -1.3749, upper: 1.2475
Strong vs weak
Estimate: -0.2751 95% CI lower: -1.4725, upper: 0.9223
Intervention duration
Estimate: 0.0301 95% CI lower: 0.0128, upper: 0.0475

Fourth, the authors made the appropriate choice not to summarize the other outcomes in a meta-analysis. The summary tables, however, should indicate the comparison between intervention and control groups in each study (e.g. in Table 2, were both of the analyses differences of differences using the displayed intervention and control outcomes, or some adjusted difference) and whether these differences were statistically significant.
RESPONSE: We thank the reviewer for this comment. However, we have already provided this information. Underneath the summary tables within the main text of the paper it states: *effectiveness was assessed using between group differences on whether the comparisons between interventions and control groups were significant or not. ↓: intervention not effective; ↑: intervention effective; ↔: no statistically significant between group difference; ?: unable to assess effectiveness;
There is much more detail in supplementary file 6 on whether differences between groups were adjusted or not and if so, which variables were adjusted. We have now added p values to the tables, where possible, and these have been extracted directly from the papers.
Finally, it is not clear why, in the abstract, smoking interventions are declared effective without qualification, whereas are weight management interventions are compared to those delivered in primary care settings and those commercially provided.
RESPONSE: Thank you for pointing this out, we have now made clear in the discussion that there is little evidence directly comparing different settings for smoking cessation. The results section of the abstract also provides the odds ratio of pharmacy-delivered smoking cessation compared to usual care (also set within the pharmacy).

References:
1. Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons Ltd; 2008.
http://handbook.cochrane.org/chapter_9/9_5_3_strategies_for_addressing_heterogeneity.htm
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2. Jeppe B Schroll, Rasmus Moustgaard, Peter C Gøtzsche (2011) Dealing with substantial heterogeneity in Cochrane reviews. Cross-sectional study. BMC Medical Research Methodology 2011, 11:22. http://www.biomedcentral.com/1471-2288/11/22
3. Steed L, Kassavou A,Madurasinghe VW, Edwards EA, Todd A, Summerbell CD,NkansahN, Bero L,Durieux P, Taylor SJC, Rivas C,Walton RT. Community pharmacy interventions for health promotion: effects on professional practice and health outcomes. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD011207. DOI: 10.1002/14651858.CD011207.

VERSION 2 – REVIEW

REVIEWER	Michael Stoto Georgetown University, USA
REVIEW RETURNED	28-Dec-2015

GENERAL COMMENTS	The authors have responded well to the concerns that the reviewers raised, and the paper is much improved.