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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. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The use of individual patient level data (IPD) to quantify the impact of pre-treatment predictors of response to treatment in chronic hepatitis B patients: A Cohort Study
AUTHORS	Mealing, Stuart; Ali, Shehzad; Hawkins, Neil; Lescrauwaet, Benedicte; Bjork, Stefan; Mantovani, Lorenzo; Lampertico, Pietro

VERSION 1 - REVIEW

REVIEWER	Elizabeth Boxall Consultant Clinical Scientist recently retired from HPA Laboratory Birmingham, UK A possible conflict of interest is that I am currently part of the NICE hepatitis B guideline development group (as the virologist) and have been looking at network analysis work done by the NICE team of researchers
REVIEW RETURNED	10-Jul-2012

THE STUDY	Not qualified to comment on the statistical methods
RESULTS & CONCLUSIONS	as I am not sure how the results have been derived - I can't say if they are credible or answer the research question. the summary conclusions seem obvious and indisputable.
GENERAL COMMENTS	I am returning this paper as I do not feel qualified to review it properly - see comments for editor While I am familiar with chronic hepatitis B and the antiviral treatment options, the nature of the response to treatment, how it is measured and how baseline characteristics and length of follow up can influence outcome; I am struggling to understand this paper and wish to return it to be reviewed by a health economist or a statistician. Observations: It opens with a very good description of a network meta-analysis and why we need them. The problem of comparison of studies carried out by different drug manufacturers at different times and with different subject variables is also well laid out. I am aware that network analysis methods are required to compare and evaluate treatment studies, as studies of new drugs are not compared with placebo, but with the 'standard of care treatment' - which in studies

	<p>of hepatitis B is Lamivudine. I can also appreciate that any drug will work 'less well' in patients who are sicker or with more advanced disease. Hence the need to only review papers describing RCTs where patient variables should be randomised. The problems with meta-analyses is that different studies may have a different range of patient variables and the hence the need for network analysis approach to synthesise all possible data. This study re-analyses data from 2 RCTs comparing Entecavir and Lamivudine in HBeAg+ and HBeAg -ve subjects. I can follow the paper as far as page 10 of the results, then a variable called 'z' is introduced into the data tables, without definition or explanation. 'z' may be well know to statisticians or health economists, but as a general reader I have no idea what its relevance might be. It is not referred to in the text or is its relevance discussed. From then on I am lost and not ashamed to admit to it and therefore suggest that this paper is either, not suitable for a general BMJ readership, or requires considerable more explanation and revision to be generally understandable. e.g. in the abstract the primary outcome measures are "Odds ratios(OR) at one year", the general reader might well stop there and not go any further. The paper may be more suitable for the Journal of Extreme Statistics</p>
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REVIEWER	Andrea Messori, PharmD Area Vasta Toscana Centro Regional Health Service 50126 Firenze ITALY
REVIEW RETURNED	13-Jul-2012

GENERAL COMMENTS	<p>This article poses a difficult question because two different issues have been addressed at the same time.</p> <p>The objective of this article is in fact two-fold. On the one hand, an analysis of treatments for hepatitis B is presented and, on the other, a substantial part of the article is focused on the statistical technique adopted as well as on the merits of this sophisticated method of analysis.</p> <p>In my view, the paper could benefit from a more explicit declaration of its main objective and, in my view, a single primary objective should be unequivocally chosen and declared.</p> <p>In more detail, the choice could be between these two alternatives:</p>
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	<p>(1) The main objective of this paper is the analysis of the effectiveness data of treatments for hepatitis B. Accordingly, the statistical approach firstly is described in the Methods section without excessive details. In addition, since this statistics is quite sophisticated and offers a number of specific clues, an appendix –if necessary- could be added at the end of the article in which the authors present a more complete description of their statistics.</p> <p>or</p> <p>(2) Given that this statistics of indirect comparisons incorporating co-variables has rarely been applied in the previous literature and can therefore be seen as an original finding, the main objective of this paper is to offer a thorough examination of this statistical topic. In this framework, the case of hepatitis B is presented just as an example, and it would probably be useful to add another example to better describe the pros and the cons of the statistical approach.</p> <p>In my view, this paper deals, in either case, with an interesting issue. Before suggesting further comments, my preliminary opinion is that, in the first place, the paper should be reorganised according to either approach, i.e. Approach (1) or Approach (2). Thereafter, I am afraid that a further review of the paper is likely to be needed particularly if the paper does not perfectly fit, in its second draft, the objectives indicated as Objective (1) or Objective (2)</p> <p>I personally have no specific preference on whether Approach (1) or Approach (2) should be given priority.</p> <p>SPECIFIC COMMENTS</p> <p>In my view, it is premature to offer specific comments because it is crucial to know which of the two approaches the authors feel to be their priority.</p>
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REVIEWER	Gane, Edward Auckland City Hospital, New Zealand Liver Unit
REVIEW RETURNED	26-Sep-2012

REPORTING & ETHICS	<p>This paper by Ali et al is a complicated analysis of the predictive value of treatment choice and baseline predictors of response in CHB. This represents a well designed study. Although the methodology of network-meta-analysis (NMA) technique is complex, the BMJ Open would seem a suitable forum for this work, to enable other researchers in the field of pharmaco-economic modeling, and policy generation to digest this analysis.</p> <p>However, the following minor issues need to be addressed before this paper can be considered acceptable for publication in the BMJ. The Authors need to expand the discussion, to include a succinct interpretation of the analyses for the reader with less understanding of network-meta-analysis (NMA) techniques. Does this analysis tell us that entecavir is more cost effective than lamivudine in all</p>
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	<p>scenarios? in more general terms so that it is interpretable by the general readership of this journal.</p> <p>The Authors do not include either HbeAg seroconversion in HbeAg positive CHB, or HBSAg clearance in all CHB as a primary endpoint for the analysis.</p> <p>The significance of the analysis is limited by the fact that only 2 antivirals are included. The Authors should include in the Discussion whether they would expect different outcomes for agents such as adefovir which is less potent than lamivudine (and hence slower HBV DNA decline) but higher barrier to resistance? Or tenofovir which is as potent as lamivudine but with high barrier to resistance? It should be repeated with the inclusion of tenofovir and adefovir. What impact does the price of the drug have – i.e. is this analysis influenced by the country where it is performed?</p> <p>In summary, once these issues have been addressed in the revised manuscript, then this paper should be suitable for publication in the BMJ Open.</p>
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REVIEWER	Dr Claudia Geue Research Associate Health Economics and Health Technology Assessment University of Glasgow United Kingdom
REVIEW RETURNED	16-Oct-2012

THE STUDY	<p>Information on the number of participants in each of the trials would be helpful. I notice these are mentioned in the abstract, but the authors may want to include these information in the main text.</p> <p>The authors state in their abstract the 'OR at one year' as their primary outcome measure. It is not quite clear how this translates into results presented in the main text (48 weeks).</p> <p>The STROBE checklist supplied as supplementary material does not seem to have page numbers assigned to each of the checklist items.</p>
RESULTS & CONCLUSIONS	Perhaps the authors could provide some model fit statistics. When describing results a reference to the appropriate table would be helpful.

VERSION 1 – AUTHOR RESPONSE

Review 1

Reviewer Comment Author response

In my view, the paper could benefit from a more explicit declaration of its main objective and, in my view, a single primary objective should be unequivocally chosen and declared.

In more detail, the choice could be between these two alternatives:

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(1) The main objective of this paper is the analysis of the effectiveness data of treatments for hepatitis B. Accordingly, the statistical approach firstly is described in the Methods section without excessive details. In addition, since this statistics is quite sophisticated and offers a number of specific clues, an appendix –if necessary- could be added at the end of the article in which the authors present a more

complete description of their statistics.
or

(2) Given that this statistics of indirect comparisons incorporating co-variables has rarely been applied in the previous literature and can therefore be seen as an original finding, the main objective of this paper is to offer a thorough examination of this statistical topic. In this framework, the case of hepatitis B is presented just as an example, and it would probably be useful to add another example to better describe the pros and the cons of the statistical approach.

While we are appreciative of the time and effort put in by the reviewers of our manuscript, and thank all three for their comments we would respectfully disagree with the key comment from reviewer one.

The purpose of this paper is neither to assess the efficacy of interventions for CHB nor to provide an overview of covariate adjustment techniques in NMA. Instead we look to identify and quantify the impact of baseline characteristics, in particular baseline disease severity, on the relative efficacy of interventions for CHB. Hence, in the language of meta-analysis, we aimed to identify which covariates interacted with treatment effect to act as treatment effect modifiers and to quantify the magnitude of this interaction effect in CHB treatment. We believe we are the first authors to undertake such an analysis in the area of CHB. We have explained this objective on page 6. Some editing has been done to clearly explain this.

As such, we believe that the paper is structured in an appropriate manner for the task undertaken.

The journal may be interested to know that the effectiveness data of entecavir vs lamivudine in CHB has already published and referenced in the paper – this is the first alternative proposed by reviewer 1. Regarding the second alternative objective, in our opinion, it is an entirely different paper and one that is currently under development by the authors. This second paper utilises the results from the manuscript submitted to BMJ Open in order to assess the impact of adjusting for the interaction on all CHB treatments. Once complete, we would of course consider submitting to BMJ Open and would be happy for reviewer one to provide an external review. The presence of this second paper highlights again the importance of the work presented in the current paper as a standalone piece of research and also points to impracticalities of trying to do everything in one manuscript.

Finally, as an aside, we note that two of the three reviewers raised no issue with the structure and objective of the manuscript under consideration

In my view, it is premature to offer specific comments because it is crucial to know which of the two approaches the authors feel to be their priority. None

Reviewer 2

The Authors need to expand the discussion, to include a succinct interpretation of the analyses for the reader with less understanding of network-meta-analysis (NMA) techniques. Does this analysis tell us that entecavir is more cost effective than lamivudine in all scenarios? in more general terms so that it is interpretable by the general readership of this journal. The reviewer raises an interesting point in terms of the impact of covariate adjustment on cost-effectiveness (and hence reimbursement) but this is the subject of a future piece of research. The current manuscript represents a statistical analysis of patient level data which identifies treatment effect modifiers on the relative efficacy of interventions for CHB and as such no statements about cost-effectiveness can be made. However, this analysis will be the cornerstone of the forthcoming NMA and the economic model based on the effectiveness data. Therefore, we have not provided a detailed discussion of the NMA methods in this paper.

The Authors do not include either HbeAg seroconversion in HbeAg positive CHB, or HBsAg clearance in all CHB as a primary endpoint for the analysis. The reviewer is correct in this observation. We focussed solely on undetectable viral load. The identification of treatment effect modifiers on these

two endpoints would be an interesting piece of research but is beyond the scope of the current manuscript. The reason for choosing undetectable viral load is that it is commonly reported in clinical trials and has been used in previous NMA of CHB.

The significance of the analysis is limited by the fact that only 2 antivirals are included. The Authors should include in the Discussion whether they would expect different outcomes for agents such as adefovir which is less potent than lamivudine (and hence slower HBV DNA decline) but higher barrier to resistance? Or tenofovir which is as potent as lamivudine but with high barrier to resistance? It should be repeated with the inclusion of tenofovir and adefovir.

Text amended to highlight the fact that data from only two interventions was available.

We sympathise with the comments made by the reviewer and in an ideal world we would have used all available patient level data. Due, however, to the patents for the compounds being held by multiple companies, the provision of patient-level data required for such analysis would require several research teams to provide confidential data which is highly unlikely to happen due to commercial confidentiality.

We have now noted in the paper that the interaction effects observed in this study may not be constant across all treatment comparisons.

What impact does the price of the drug have – i.e. is this analysis influenced by the country where it is performed? The paper contains a statistical analysis of clinical trial data and as such issues such as drug pricing will not influence the results.

In summary, once these issues have been addressed in the revised manuscript, then this paper should be suitable for publication in the BMJ Open. Noted with thanks.

Reviewer three

Information on the number of participants in each of the trials would be helpful. I notice these are mentioned in the abstract, but the authors may want to include these information in the main text.

Text amended in line with reviewer comments

The authors state in their abstract the 'OR at one year' as their primary outcome measure. It is not quite clear how this translates into results presented in the main text (48 weeks).

Text amended in line with reviewer comments. Unit of time now consistent throughout manuscript

The STROBE checklist supplied as supplementary material does not seem to have page numbers assigned to each of the checklist items.

Page numbers or comments added to all elements of checklist

When describing results a reference to the appropriate table would be helpful.

References to tables now clearly identifiable in the text.

VERSION 2 – REVIEW

REVIEWER	Andrea Messori HTA Unit and University of Firenze Regional Health Service Firenze ITALY
REVIEW RETURNED	29-Nov-2012

REPORTING & ETHICS	I initially had some concerns of unclear design and/or redundant publication, but the last explanations offered by the authors have been quite convincing.
GENERAL COMMENTS	COMMENTS INCLUDED IN MY PREVIOUS REVIEW: “In my view, the paper could benefit from a more explicit declaration of its main objective and, in my view, a single primary objective should be unequivocally chosen and declared. In more detail, the choice could be between these two alternatives:

(1) The main objective of this paper is the analysis of the effectiveness data of treatments for hepatitis B. Accordingly, the statistical approach firstly is described in the Methods section without excessive details. In addition, since this statistics is quite sophisticated and offers a number of specific clues, an appendix –if necessary- could be added at the end of the article in which the authors present a more complete description of their statistics.

or

(2) Given that this statistics of indirect comparisons incorporating co-variables has rarely been applied in the previous literature and can therefore be seen as an original finding, the main objective of this paper is to offer a thorough examination of this statistical topic. In this framework, the case of hepatitis B is presented just as an example, and it would probably be useful to add another example to better describe the pros and the cons of the statistical approach.”

RESPONSE BY S. ALI AND CO-WORKERS:

While we are appreciative of the time and effort put in by the reviewers of our manuscript, and thank all three for their comments we would respectfully disagree with the key comment from reviewer one.

The purpose of this paper is neither to assess the efficacy of interventions for CHB nor to provide an overview of covariate adjustment techniques in NMA. Instead we look to identify and quantify the impact of baseline characteristics, in particular baseline disease severity, on the relative efficacy of interventions for CHB. Hence, in the language of meta-analysis, we aimed to identify which covariates interacted with treatment effect to act as treatment effect modifiers and to quantify the magnitude of this interaction effect in CHB treatment. We believe we are the first authors to undertake such an analysis in the area of CHB. We have explained this objective on page 6. Some editing has been done to clearly explain this. As such, we believe that the paper is structured in an appropriate manner for the task undertaken.

The journal may be interested to know that the effectiveness data of entecavir vs lamivudine in CHB has already published and referenced in the paper – this is the first alternative proposed by reviewer 1. Regarding the second alternative objective, in our opinion, it is an entirely different paper and one that is currently under development by the authors. This second paper utilises the results from the manuscript submitted to BMJ Open in order to assess the impact of adjusting for the interaction on all CHB treatments. Once complete, we would of course consider submitting to BMJ Open and would be happy for reviewer one to provide an external review. The presence of this second paper highlights again the importance of the work presented in the current paper as a standalone piece of research and also points to impracticalities of trying to do everything in one manuscript.

Finally, as an aside, we note that two of the three reviewers raised no issue with the structure and objective of the manuscript under consideration

FURTHER COMMENTS BY ANDREA MESSORI (REVIEWER 1):

The response on this point by the authors poses a number of questions. In my previous review, I suggested a quite profound revision of this paper to better select a single objective of the study (rather than two objectives altogether). This single objective could be

	<p>either the presentation of the original results of the clinical analysis (with the methods description confined to a technical appendix) or the presentation of a novel method of analysis (that incidentally used the clinical data mainly as an example of its application).</p> <p>The authors stick to their initial choice in that they confirm their preference for a paper pursuing the two objectives at the same time. They also are honest in indicating that three separate papers could be produced from this overall this body of data, namely: a) the first clinical paper that has already been published; b) the present paper submitted to BMJ Open; c) a future paper that could be specifically focused on the original methodology of this type of analysis. In my view, whether or not paper (c) will eventually be considered as a duplicate paper presenting again part of the findings already published in papers (a) or (b) is outside the purposes of the present review. So, I concentrate only on the degree of redundancy between paper (a) and paper (b), i.e. the present manuscript.</p> <p>As regards this latter point, Ali et al. now present a series of quite convincing arguments (“... we look to identify and quantify the impact of baseline characteristics, in particular baseline disease severity, on the relative efficacy of interventions for CHB. Hence, in the language of meta-analysis, we aimed to identify which covariates interacted with treatment effect to act as treatment effect modifiers and to quantify the magnitude of this interaction effect in CHB treatment. We believe we are the first authors to undertake such an analysis in the area of CHB. We have explained this objective on page 6. Some editing has been done to clearly explain this.”) to support the view that the clinical results described in the present paper are an original finding that had not been reported in their previous article, i.e. in paper (a).</p> <p>I agree with Ali et al. that, in general, all articles should preferably be designed as “a standalone piece of research” and I also agree, to a certain extent, on “impracticalities of trying to do everything in one manuscript.”</p> <p>This is the reason why, given that the issue of redundant publication of the clinical data does not seem to apply, the rewording of some sentences, in my view, continues to be needed to avoid giving some impression that the development of sophisticated NMAs is one of the objectives of this study.</p> <p>I appreciate that some (minimal) changes on this point have been introduced (e.g. on page 6: “The objective of this study is to explore and quantify the relationship between treatment effect and patient characteristics, in particular baseline disease severity and time of response measurement, in predicting response to CHB treatment”). A little additional effort in this direction could however be useful.</p> <p>Finally, the abstract does not report any 95% confidence interval. This index could be preferable as opposed to presenting the exact p-values for the various statistics.</p>
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REVIEWER	<p>Claudia Geue, PhD Research Associate University of Glasgow, UK</p> <p>No competing interest declared.</p>
REVIEW RETURNED	22-Nov-2012

REPORTING & ETHICS	The authors have clearly addressed the issue raised in my last review. I recommend acceptance without changes.
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VERSION 2 – AUTHOR RESPONSE

Reviewer Comment	Author response
<p>In my view, the paper could benefit from a more explicit declaration of its main objective and, in my view, a single primary objective should be unequivocally chosen and declared.</p> <p>In more detail, the choice could be between these two alternatives: ></p> <p>(1) The main objective of this paper is the analysis of the effectiveness data of treatments for hepatitis B. Accordingly, the statistical approach firstly is described in the Methods section without excessive details. In addition, since this statistics is quite sophisticated and offers a number of specific clues, an appendix –if necessary- could be added at the end of the article in which the authors present a more complete description of their statistics.</p> <p>or</p> <p>(2) Given that this statistics of indirect comparisons incorporating co-variables has rarely been applied in the previous literature and can therefore be seen as an original finding, the main objective of this paper is to offer a thorough examination of this statistical topic. In this framework, the case of hepatitis B is presented just as an example, and it would probably be useful to add another example to better describe the pros and the cons of the statistical approach.</p>	<p>While we are appreciative of the time and effort put in by the reviewers of our manuscript, and thank all three for their comments we would respectfully disagree with the key comment from reviewer one.</p> <p>The purpose of this paper is neither to assess the efficacy of interventions for CHB nor to provide an overview of covariate adjustment techniques in NMA. Instead we look to identify and quantify the impact of baseline characteristics, in particular baseline disease severity, on the relative efficacy of interventions for CHB. Hence, in the language of meta-analysis, we aimed to identify which covariates interacted with treatment effect to act as treatment effect modifiers and to quantify the magnitude of this interaction effect in CHB treatment. We believe we are the first authors to undertake such an analysis in the area of CHB. We have explained this objective on page 6. Some editing has been done to clearly explain this.</p> <p>As such, we believe that the paper is structured in an appropriate manner for the task undertaken.</p> <p>The journal may be interested to know that the effectiveness data of entecavir vs lamivudine in CHB has already published and referenced in the paper – this is the first alternative proposed by reviewer 1. Regarding the second alternative objective, in our opinion, it is an entirely different paper and one that is currently under development by the authors. This second paper utilises the results from the manuscript submitted to BMJ Open in order to assess the impact of adjusting for the interaction on all CHB treatments. Once complete, we would of course consider submitting to BMJ Open and would be happy for reviewer one to provide an external review. The presence of this second paper highlights again the importance of the work presented in the current paper as a standalone piece of research and also points to impracticalities of trying to do everything in one</p>

	<p>manuscript.</p> <p>Finally, as an aside, we note that two of the three reviewers raised no issue with the structure and objective of the manuscript under consideration</p>
<p>In my view, it is premature to offer specific comments because it is crucial to know which of the two approaches the authors feel to be their priority.</p>	<p>None</p>

Reviewer 2

<p>The Authors need to expand the discussion, to include a succinct interpretation of the analyses for the reader with less understanding of network-meta-analysis (NMA) techniques. Does this analysis tell us that entecavir is more cost effective than lamivudine in all scenarios? in more general terms so that it is interpretable by the general readership of this journal.</p>	<p>The reviewer raises an interesting point in terms of the impact of covariate adjustment on cost-effectiveness (and hence reimbursement) but this is the subject of a future piece of research. The current manuscript represents a statistical analysis of patient level data which identifies treatment effect modifiers on the relative efficacy of interventions for CHB and as such no statements about cost-effectiveness can be made. However, this analysis will be the cornerstone of the forthcoming NMA and the economic model based on the effectiveness data. Therefore, we have not provided a detailed discussion of the NMA methods in this paper.</p>
<p>The Authors do not include either HbeAg seroconversion in HbeAg positive CHB, or HBsAg clearance in all CHB as a primary endpoint for the analysis.</p>	<p>The reviewer is correct in this observation. We focussed solely on undetectable viral load. The identification of treatment effect modifiers on these two endpoints would be an interesting piece of research but is beyond the scope of the current manuscript. The reason for choosing undetectable viral load is that it is commonly reported in clinical trials and has been used in previous NMA of CHB.</p>
<p>The significance of the analysis is limited by the fact that only 2 antivirals are included. The Authors should include in the Discussion whether they would expect different outcomes for agents such as adefovir which is less potent than lamivudine (and hence slower HBV DNA decline) but higher barrier to resistance? Or tenofovir which is as potent as lamivudine but with high barrier to resistance? It should be repeated with the inclusion of tenofovir and adefovir.</p>	<p>Text amended to highlight the fact that data from only two interventions was available.</p> <p>We sympathise with the comments made by the reviewer and in an ideal world we would have used all available patient level data. Due, however, to the patents for the compounds being held by multiple companies, the provision of patient-level data required for such analysis would require several research teams to provide confidential data which is highly unlikely to happen due to</p>

	<p>commercial confidentiality.</p> <p>We have now noted in the paper that the interaction effects observed in this study may not be constant across all treatment comparisons.</p>
<p>What impact does the price of the drug have – i.e. is this analysis influenced by the country where it is performed?</p>	<p>The paper contains a statistical analysis of clinical trial data and as such issues such as drug pricing will not influence the results.</p>
<p>In summary, once these issues have been addressed in the revised manuscript, then this paper should be suitable for publication in the BMJ Open.</p>	<p>Noted with thanks.</p>

Reviewer three

<p>Information on the number of participants in each of the trials would be helpful. I notice these are mentioned in the abstract, but the authors may want to include these information in the main text.</p>	<p>Text amended in line with reviewer comments</p>
<p>The authors state in their abstract the 'OR at one year' as their primary outcome measure. It is not quite clear how this translates into results presented in the main text (48 weeks).</p>	<p>Text amended in line with reviewer comments. Unit of time now consistent throughout manuscript</p>
<p>The STROBE checklist supplied as supplementary material does not seem to have page numbers assigned to each of the checklist items.</p>	<p>Page numbers or comments added to all elements of checklist</p>
<p>When describing results a reference to the appropriate table would be helpful.</p>	<p>References to tables now clearly identifiable in the text.</p>