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)	Cross Sectional Study of Prescribing Errors in Patients Admitted to Nine Hospitals Across North West England
AUTHORS	Seden, Kay; Kirkham, Jamie; Kennedy, Tom; Lloyd, Michael; James, Sally; McManus, Aine; Ritchings, Andrew; Simpson, Jennifer; Thornton, Dave; Gill, Andrea; Coleman, Carolyn; Thorpe, Bethan; Khoo, Saye

VERSION 1 - REVIEW

REVIEWER	Professor Bryony Dean Franklin Centre for Medication Safety and Service Quality Imperial College Healthcare NHS Trust / UCL School of Pharmacy London UK No competing interests
REVIEW RETURNED	21-Sep-2012

THE STUDY	I found the methods to be unclear in parts - see comments below Completed STROBE checklist refers to stating how the sample size was arrived at, and key elements of the study design being presented early in the paper, but I could not find these aspects stated explicitly in the main paper.
RESULTS & CONCLUSIONS	Overall message of the paper, particularly in terms of what this adds to previous work, could be made stronger - see comments and suggestions below.
GENERAL COMMENTS	I enjoyed reading this paper, but have both some general comments and specific comments on each section. General comments: 1. Importantly, for a study of prescribing errors, no explicit definition of a prescribing error is given. There can be confusion among pharmacists as to the extent to which prescribing errors and pharmacists' interventions are synonymous (while the literature suggests that although there is some overlap, they are clearly not synonymous) and so providing a clear definition of a prescribing error to the pharmacist data collectors would have been essential. It's not currently clear what definition was used. The last few sentances of the introduction imply that errors in clinical decision

	making were not included, and so I assume that only "prescription writing" errors were included, but this does not tally with the examples and tables presented later. 2. It's not very clear what this study adds to what has already been done in this area - what is new? What was the gap in the literature that this study was intended to fill? 3. Some details of the UK setting are needed for international readers, specifying for example the model of ward pharmacy used, how many participating hospitals used electronic prescribing and how many used paper drug charts, etc. 4. The methodological approach to data collection is not clear to me. If the idea was to study all of the patient's inpatient and dischage medication to explore the risk to the patient, how were these data collected during the patient stay without recording patient identifiers (as per ethics statement)? Or were there mulitple snapshots for each patient, depending when they were seen by the pharmacist? And if the latter, how were previously screened prescription items handled - were they counted again, or was it just the new unscreened items that were included subsequently? Were all types of inpatient medication order (including IV fluids, when required medicaiton, and once only medication) included? 5. I also felt that much of the discussion was not directly linked to the results and implications of the present study, eg second half of thrd para, second half of fourth para. Depending on the guidelines for this journal, I wondered if the discussion would benefit from more structure and subheadings, to create more focus on the present study and how it adds to the literature. Specific comments on each section: Article summary - key messages - it's not clear what is meant by "complete prescriptions" without reading the full paper Artilce summary - strengths and limitations - you state that you determined the rate of errors in complete prescriptions "rather than" individual items - but elsewhere you give the rate per individual item. Should this be "as well as" individual items? Introduction - in line with comments above, I felt that this would benefit from being more focused towards the present study and the gap in the literature that it is intended to fill. The second half of the first paragraph discusses inpatient ADRs, without explaining how these are related (or not?) to prescribing error. The second para is not particularly relevant to the rest of the paper. The third para relates to grade of prescriber, ward area, etc as being "causes" of prescribing error whereas they are probbaly more accurately described as factors associated with prescribing error. Second half

	of third para also not directly relevant to the present study. Introduction - third para - it is stated that newly qualified doctors are twice as likely to make errors than more senior doctors. Please state whether or not this is taking into account the fact that junior doctors do far more prescribing, by volume, than more senior doctors. Methods - several aspects of the second para are not clear. Were data collected on alternate days as stated, or once a week on rotating days as implied by the Monday - Tuesday - Wednesday example? The statements relating to a separate form for drug histories also confused me - is this part of usual clinical practice in these hospitals, or was this something done as part of data collection for the present study? These issues would be clearer if a separate explanation of the setting was given, as suggested above, to make clear what was usual work flow and clinical practice. The data collection section than then focus on what was done for the present study. Methods - classificaiton of errors - how were these allocations decided where there was some overlap between categories? Eg how would you decide if lack of clear directions for administration was category (2) or category (9)? Methods - the data on classificaiton and independent reasessment of the errors would better fit in the results section Methods - analysis - (line 29/30) it is stated that where there was one error per prescription, only one was counted in the analysis. But if the objectives were to analyse errors per whole prescription sheet, doesn't this lose data? I wonder if some of this analysis is actually per medication order, and some per prescription sheet, but it's not very clear at present Results - was the findings relating to error severity vs grade of prescriber statisticaly significant? Results - abbreviations used in tables should be defined, eg TI, pot, CD, TTO - international readers will not be familiar with some of these terms Results - table 4 - what does n refer to here? Doctors? prescription sheets? medication orders? Discussion - the statement about severity assessment being based on what would have happened if the error were not rectified, would fit better in the methods section Discussion - the findings relating to missing data would be better in the results section rather than being presented "de novo" in the

	dicussion

REVIEWER	Dr Penny Lewis, Clinical Lecturer, University of Manchester, England. I have no competing interests
REVIEW RETURNED	30-Sep-2012

GENERAL COMMENTS	The title should use the plural, prescribing errors as the study is investigating more than one error. There are a few examples of this throughout the paper and, although a very minor point, it can be distracting. **Introduction** Page 4 Line 5&45: As above- 'prescribing errors are common' not 'prescribing error is common'. Line 18: Reference 8 is a study set in Netherlands. I think that this should be noted as there will be differences in healthcare systems and the setting of other studies discussed in this section are all highlighted. Line 31: The start of this sentence talks about the causes of error but the examples given e.g. type of medication, ward area are not really causes but rather descriptions of the nature and type of errors found. Causes implies something deeper regarding the origin of the error i.e. it was a lack of knowledge about a certain type of medication that caused the error rather than for example antibiotics are a cause of error. On the whole I think the introduction could be shortened as some points raised do not add anything to the case for the study- e.g. I'm not sure of the relevance of the section on line 35 discussing undergraduate training and teaching in UK medical schools as it doesn't really lead into the aims and objectives of the study. Line 44: 'Complete prescriptions' - this description could be confusing as a prescription can be just one item or one medication order that is complete i.e. has all the necessary information such as dose, formulation etc. If what is meant is a prescription form containing multiple items then this should be clearly stated. Line 47: There appears to be two parts to the aim of this study given in this section. Firstly to examine the prevalence, type and

	severity of errors made by different categories of prescriber (I would state prescribing errors not just errors to make this clearer) and secondly, to examine the prevalence, type and severity of prescribing errors at admission, discharge and in different ward areas. However, in the results you perform multivariate analysis and therefore are testing hypotheses regarding specific factors being associated with prescribing errors yet this is not written in the aims. There are a few results presented that are not mentioned within these aims. I do note that the aim given in the article summary is a better reflection of the work. Line 52: It is stated that only errors concerned with issuing of a prescription were recorded and that errors in clinical decision making or downstream errors in executing the prescription were excluded. Firstly, I would like to know about what is meant by downstream errors. Do you mean dispensing errors or errors in transcription – I just think this requires a little more clarity. Secondly, I would think that errors in clinical decision making make up an important proportion of prescribing errors, for example, not prescribing a drug when it is clearly indicated or prescribing a drug that is contra-indicated due to hepatic or renal insufficiency. I may be misunderstanding what you mean by clinical decision making but to me this reads as though you are only examining errors in writing the prescription e.g. omitting a dose. I think that this can be easily clarified. **Methods** Data collection: within this first paragraph the terms survey and audit are used interchangeably, I would stick with one term. Page 5 Line 15: The data collection process is described as ward pharmacists recording errors at the point of checking admission and discharge prescriptions. So only prescriptions written at these points are recorded in the study- is that correct as the first aim was to examine the prevalence, type and severity of errors made by different categories of prescriber- which I assumed meant all prescribing errors at any point e.g. during inpatient stay. Perhaps the aim can be made clearer to make this explicit. Line 19: I am not sure whether a separate form is completed on acute admission to allow for emergency prescribing as part of normal practice or whether this was carried out for the purposes of

	the study. Could you make this clearer. Line 24: Hospitals were advised to complete the study on alternate days so that patients would not be caught twice. This suggests that data collection days are every second day, however, days appear to be chosen to get an even spread of days of the week and occur only once weekly, so double auditing of patients from an admission ward to another ward would not occur anyway. Again, this just needs explaining better. Line 33&34: The use of capital letters requires some attention. Line 36: Other and unknown seem to overlap here – there are doctors for whom grade was not recorded and also an unknown category in which information was not recorded. Is there a difference between these categories? Line 43: I am not sure what was involved in the process of exclusion and inclusion of errors into EQUIP study error types and what was done in the case of overlap. Could you explain? Line 48: Severity ratings were assigned according to three factors: the modified EQUIP study criteria, the pharmacists grading and also by reference to licensing information of the medication. How were these three reconciled? I am also very interested to know the role that licensing information had on assignment of severity ratings. Line 52: The authors developed 10 error groups including one which was safety errors – I would argue that all of these errors are safety errors. Line 57: I'm not familiar with the term 'over-call'- do you mean overestimate? Line 60: I would like to know what a standard error is and how this was decided. <u>Page 6</u> Line 4: It is stated that 14 standard errors were decided upon but it appears that only six were given to each of the six pharmacists. Line 9-13: There are some results presented here regarding the concordance of pharmacist ratings with the gold standard and perhaps these should be in the results section or at least in their own sub-section. Line 18: One hundred and forty three should be in words and not

	figures as it starts the sentence. Line 19-21: These are results and hence would sit better in the next section. Line 31-32: Here, the factors that were explored for their association with errors are described yet they are not stated in the aims and objectives section. It might be useful in the methods section to state how a prescribing error was defined for the purposes of the study. <u>Results</u> I think the total number of days on which data was collected should be presented here. The term incidence is used rather than prevalence which was stated in the aims- was this intended? <u>Page 7</u> Line 48: Multivariate analysis was conducted examining the risk of error with the number of items on a prescription form – this was a significant finding yet there was no mention of this being part of the aims of the study in the introduction. Line 56: It is stated that no significant differences were found in errors rates between different prescribed grades – this should perhaps state 'Compared to newly qualified doctors…' as this was the reference used. **<u>Discussion</u>** <u>Page 8</u> Line20-21: There is some discussion about the relationship between hospital type and number of errors. It would be useful to have a table detailing the types of hospitals included in the study e.g DGH, teaching, paediatric hospital etc. Line35: One of the analyses carried out looked at Liverpool graduates vs other graduates yet the decision to explore this was not discussed in the introduction and it would be good to know the rationale for this analysis. Line 37-41: Are these findings significant? They are certainly interesting Line 45: It is stated that a rate of 10.9% was observed- should this

	figure be included in the results section? Line 49-51: This section reads as though you have data on paediatric patients vs. adult patients but this is not presented in the results section which is a little confusing. Line 52-54: It is stated that a study reported that errors were more common in prescribing s`amongst men than women but I was uncertain as to how this relates to the results that were presented in the paper. Line 55-page 9 line 8: The literature discussed here is interesting but I think it would be better if it was discussed in relation to what was found in this study. <u>Page 9</u> Line 5: It's stated that the paper by Dean et al examined errors on prescriptions however the term prescription in your paper refers to entire prescription forms with multiple medications but Dean's paper examined errors per medication order. I would just ensure that a distinction is made. Line 20-22: You state that errors were grouped according to their origin and cause yet I did not see any mention in the methods about determining the cause of errors. Perhaps this could be clarified. Line 31-33: The distinction between 'emergency prescribing' and errors which could have been prevented is a very positive aspect of the study. Line 38-40: The sensitivity analysis showed a drop in error rate with exclusion of omission errors- what implications does this have for practice? Could there be more discussion about the implications of the findings for practice. Line 43: Incorrect use of capital letters. Line 56: This sentence implies that analysis was conducted into differences between handwritten and electronic prescriptions. <u>Page 14</u> Figures 1a and 1b: These forest plots are good but perhaps they should be separate figures as they show different results and then they can be presented in order in the text. (at the moment figure 2 comes before figure 1b). I would also like to see a key for the

	hospital types. Page 16 Table 1: The numbering in the original EQUIP error category is confusing, perhaps it's not needed. Under the heading 'writing errors' no signature is given a rating of significant as it's a governance issue- I was wondering what this meant in relation to the potential severity to the patient? Patient harm e.g having to wait for the prescription to be signed and therefore a delay in receiving medication can't be any more severe for other errors in this category i.e missing dose. Page 23 Table 4: I had some difficulty reading this table as percentages run down columns but differences are examined across columns – perhaps this could be explained somewhere for the reader. Discharge/admission should be the other way around. On the whole I think the results of this study are interesting and worthy of publication however, there needs to be a clear setting of aims and objectives and more coherence between different sections. The paper would benefit from greater clarity of terms and concepts and requires some significant rewriting in parts. I would be very happy to read subsequent revisions.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Professor Bryony Dean Franklin Centre for Medication Safety and Service Quality Imperial College Healthcare NHS Trust / UCL School of Pharmacy London UK

No competing interests

I found the methods to be unclear in parts - see comments below

• Completed STROBE checklist refers to stating how the sample size was arrived at, and key elements of the study design being presented early in the paper, but I could not find these aspects stated explicitly in the main paper.

We agree these were not stated. Information concerning the sample size has now been added to the Data Collection section of the methods

• Overall message of the paper, particularly in terms of what this adds to previous work, could be made stronger - see comments and suggestions below.

I enjoyed reading this paper, but have both some general comments and specific comments on each section.

General comments:

1. Importantly, for a study of prescribing errors, no explicit definition of a prescribing error is given. There can be confusion among pharmacists as to the extent to which prescribing errors and pharmacists' interventions are synonymous (while the literature suggests that although there is some overlap, they are clearly not synonymous) and so providing a clear definition of a prescribing error to the pharmacist data collectors would have been essential. It's not currently clear what definition was used. The last few sentances of the introduction imply that errors in clinical decision making were not included, and so I assume that only "prescription writing" errors were included, but this does not tally with the examples and tables presented later.

The final sentence has been removed from the introduction. Errors in 'clinical decision making' which were excluded was intended to encompass aspects such as an item not in the hospital formulary being prescribed, which as pointed out above, could be a pharmacist intervention although not considered a true prescribing error. The following has been added to the methods section: 'We adopted the following definition of prescribing errors for the study, which excludes adherence to local prescribing policy and guidelines: "A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice".'

2. It's not very clear what this study adds to what has already been done in this area - what is new? What was the gap in the literature that this study was intended to fill?

We aimed to audit complete prescriptions in order to determine the number of patients at risk from prescribing errors. This differs from much of the current literature, which evaluates prescribing error rates per prescribed item.

3. Some details of the UK setting are needed for international readers, specifying for example the model of ward pharmacy used, how many participating hospitals used electronic prescribing and how many used paper drug charts, etc.

A section describing the setting has been added to the methods section.

4. The methodological approach to data collection is not clear to me. If the idea was to study all of the patient's inpatient and dischage medication to explore the risk to the patient, how were these data collected during the patient stay without recording patient identifiers (as per ethics statement)? Or were there mulitple snapshots for each patient, depending when they were seen by

the pharmacist? And if the latter, how were previously screened prescription items handled - were they counted again, or was it just the new unscreened items that were included subsequently? Were all types of inpatient medication order (including IV fluids, when required medicaiton, and once only medication) included?

Multiple snapshots were taken for each patient. The audit was carried out over intervals of a week (this is now clarified in the methods section ie Monday of week 1, Tuesday of week 2 etc) so if patients were audited twice, there would be an interval of at least one week, unless their acute admission/inpatient /discharge prescription were audited on the same day. If items on prescriptions had been previously screened, they would be counted again in any subsequent auditing , though there would be a one week interval since previous auditing, or the patient would be a different stage of hospital admission. All types of inpatient medication order were audited, including IV fluids, when required and once only medication. This has been clarified in the methods section

5. I also felt that much of the discussion was not directly linked to the results and implications of the present study, eg second half of thrd para, second half of fourth para. Depending on the guidelines for this journal, I wondered if the discussion would benefit from more structure and subheadings, to create more focus on the present study and how it adds to the literature.

The discussion has been amended as suggested

The literature in the discussion has now been linked to the results observed. Implications have been further discussed

Specific comments on each section:

• Article summary - key messages - it's not clear what is meant by "complete prescriptions" without reading the full paper

This has been clarified in the article summary: ‘Prescriptions frequently contain multiple medications, but data about errors on complete prescriptions (all prescribed items on an inpatient chart or discharge prescription), which give a better estimate of numbers of patients at risk of harm, are lacking’

• Artilce summary - strengths and limitations - you state that you determined the rate of errors in complete prescriptions "rather than" individual items - but elsewhere you give the rate per individual item. Should this be "as well as" individual items?

This is correct and the sentence has been amended as suggested

• Introduction - in line with comments above, I felt that this would benefit from being more focused towards the present study and the gap in the literature that it is intended to fill. The second half of the first paragraph discusses inpatient ADRs, without explaining how these are related (or not?) to prescribing error. The second para is not particularly relevant to the rest of the paper. The third para relates to grade of prescriber, ward area, etc as being "causes" of prescribing error whereas they are

probbaly more accurately described as factors associated with prescribing error. Second half of third para also not directly relevant to the present study.

The final paragraph of the introduction has been amended and now gives more details of the aims of the study. The first statement and reference relating to ADRs has been removed. The second paragraph is intended to give a general background on human error, related to prescribing error. The third paragraph has been amended as suggested

• Introduction - third para - it is stated that newly qualified doctors are twice as likely to make errors than more senior doctors. Please state whether or not this is taking into account the fact that junior doctors do far more prescribing, by volume, than more senior doctors.

This sentence has been amended as follows: 'Existing data suggest that newly qualified and junior doctors are twice as likely to make prescribing errors than senior doctors, taking into account the larger volume of prescriptions written by more junior prescriber grades.'

• Methods - several aspects of the second para are not clear. Were data collected on alternate days as stated, or once a week on rotating days as implied by the Monday - Tuesday - Wednesday example? The statements relating to a separate form for drug histories also confused me - is this part of usual clinical practice in these hospitals, or was this something done as part of data collection for the present study? These issues would be clearer if a separate explanation of the setting was given, as suggested above, to make clear what was usual work flow and clinical practice. The data collection section than then focus on what was done for the present study.

The information in this paragraph has been clarified. A description of the setting has been added to the methods section as suggested.

• Methods - classificaiton of errors - how were these allocations decided where there was some overlap between categories? Eg how would you decide if lack of clear directions for administration was category (2) or category (9)?

Category 9 relates specifically to the directions for administration of a medicine, whereas category 2 relates to any other error in writing the prescription. It has now been clarified in the text that the modification and definition of error categories and severities was undertaken by two members of the study team (KS, SK) and agreed by a third (TK).

• Methods - the data on classificaiton and independent reasessment of the errors would better fit in the results section

This section has been moved to the results section as suggested

• Methods - analysis - (line 29/30) it is stated that where there was one error per prescription, only one was counted in the analysis. But if the objectives were to analyse errors per whole prescription sheet, doesn't this lose data? I wonder if some of this analysis is actually per medication order, and some per prescription sheet, but it's not very clear at present

We thank the reviewer for this comment. In the regression analysis we are making the key assumption that each error is independent. Of course when a prescription is implicated with many errors this assumption cannot hold. We also have the problem of multiplicity. Each prescription will mostly have one set of risk factor data which will be the same for each error should a prescription contain more than one error. Analysing in this way would have the effect of overestimating the effect of any risk factor. To overcome this, for the analysis of risk factors, data collected on the most severe error only was included. As the reviewer correctly points out this will cause a lack of data but this approach was required to meet the model assumptions in this instance. The model essentially answers the question "What is the magnitude of effect of each of the concerned risk factors when an error occurs on a prescription?" The aim is to reduce all errors but if a prescription contains more than one, then it makes sense to consider the most severe error as this is the one we would be most concerned about in terms of overall outcome to the patient. The following has been added to the methods section: 'For the formal statistical analysis, when there was more than one error on a prescription, only the most severe error was included. This approach was used to ensure that the errors included in the analysis were independent'

• Results - was the findings relating to error severity vs grade of prescriber statisticaly significant?

Using a chi-squared statistic for trend considering only prescribers: new, junior, mid and senior and crosstab them by number of significant errors or above (excluding minor), then the p-value for trend is $p<0.001$. The sentence now reads: 'The proportion of errors categorised with severity as significant or higher by prescriber grade were as follows: all prescribers 58.0%, newly qualified 51.2%, junior 60.8%, mid grade 66.4%, senior 57.6% (X^2_{trend} $p<0.001$ for univariate analysis, although this association disappeared when corrected for other potential confounders)(Table 3).'

• Results - abbreviations used in tables should be defined, eg TI, pot, CD, TTO - international readers will not be familiar with some of these terms

Abbreviations have been clarified as suggested

• Results - table 4 - what does n refer to here? Doctors? prescription sheets? medication orders?

In this table n refers to number of prescriptions. This has been clarified by addition of a footnote

• Discussion - the statement about severity assessment being based on what would have happened if the error were not rectified, would fit better in the methods section

This statement has been added to the methods section

• Discussion - the findings relating to missing data would be better in the results section rather than being presented "de novo" in the dicussion

Missing data has now also been mentioned in the risk factor analysis section of the results

Reviewer: Dr Penny Lewis, Clinical Lecturer, University of Manchester, England.

I have no competing interests

Thank you for the opportunity to review this paper. Studies such as these are very important to understanding the nature of prescribing errors, enabling us to begin to develop solutions to what is a key patient safety issue. I think the study generates some interesting findings but I have some concerns, mainly around the writing of the paper, that need addressing before it would be of a publishable standard. These I have outlined below:
Title
• The title should use the plural, prescribing errors as the study is investigating more than one error. There are a few examples of this throughout the paper and, although a very minor point, it can be distracting.

This has been amended as suggested

Introduction
Page 4
• Line 5&45: As above- 'prescribing errors are common' not 'prescribing error is common'.

This has been amended as suggested

• Line 18: Reference 8 is a study set in Netherlands. I think that this should be noted as there will be differences in healthcare systems and the setting of other studies discussed in this section are all highlighted.

The sentence now reads: 'A study in the Netherlands evaluating medication omission errors in elderly patients admitted to hospital reported adverse consequences in 21% of 100 patients'

• Line 31: The start of this sentence talks about the causes of error but the examples given e.g. type of medication, ward area are not really causes but rather descriptions of the nature and type of errors found. Causes implies something deeper regarding the origin of the error i.e. it was a lack of knowledge about a certain type of medication that caused the error rather than for example antibiotics are a cause of error.

The sentence has been amended and now reads: 'Data on factors which may contribute to prescribing errors, for example differences between grades of prescriber, ward area, admission or discharge and type of medication prescribed are sparse.'

• On the whole I think the introduction could be shortened as some points raised do not add anything to the case for the study- e.g. I'm not sure of the relevance of the section on line 35 discussing undergraduate training and teaching in UK medical schools as it doesn't really lead into

the aims and objectives of the study.

This section relating to teaching and training in medical schools was discussed here, as we were evaluating error rates for different grades of prescriber, ie do newly qualified doctors make more errors than more experienced prescriber grades. The point concerning newly qualified doctors being adequately prepared to prescribe drugs and manage risk at the point of graduation appeared relevant to this analysis.

• Line 44: 'Complete prescriptions' - this description could be confusing as a prescription can be just one item or one medication order that is complete i.e. has all the necessary information such as dose, formulation etc. If what is meant is a prescription form containing multiple items then this should be clearly stated.

This has been clarified as follows: 'Whilst previous studies have evaluated error for individual medications, few studies have systematically evaluated complete prescriptions (all items included on a single prescription chart or discharge prescription at the time of clinical pharmacist check) to evaluate factors associated with prescribing error'

• Line 47: There appears to be two parts to the aim of this study given in this section. Firstly to examine the prevalence, type and severity of errors made by different categories of prescriber (I would state prescribing errors not just errors to make this clearer) and secondly, to examine the prevalence, type and severity of prescribing errors at admission, discharge and in different ward areas. However, in the results you perform multivariate analysis and therefore are testing hypotheses regarding specific factors being associated with prescribing errors yet this is not written in the aims. There are a few results presented that are not mentioned within these aims. I do note that the aim given in the article summary is a better reflection of the work.

This section has been revised and now reads: 'We undertook a prospective survey of prescribing errors in nine diverse National Health Service (NHS) hospitals in the North West of England, aiming to examine the differences in prescribing error rates between grades of prescriber, ward area, admission or discharge, hospitals and the type and number of medication prescribed. In order to further evaluate the role of undergraduate training, we also tested for a relationship between occurrence of error and medical school training of prescribers. Univariate analysis and multivariate logistic regression was used to evaluate factors associated with prescribing errors.'

• Line 52: It is stated that only errors concerned with issuing of a prescription were recorded and that errors in clinical decision making or downstream errors in executing the prescription were excluded. Firstly, I would like to know about what is meant by downstream errors. Do you mean dispensing errors or errors in transcription – I just think this requires a little more clarity. Secondly, I would think that errors in clinical decision making make up an important proportion of prescribing errors, for example, not prescribing a drug when it is clearly indicated or prescribing a drug that is contra-indicated due to hepatic or renal insufficiency. I may be misunderstanding what you mean by clinical decision making but to me this reads as though you are only examining errors in writing the prescription e.g. omitting a dose. I think that this can be easily clarified.

The final sentence referring to downstream errors and errors of the clinical decision making process has been removed from the introduction. Errors in 'clinical decision making' which were excluded was intended to encompass aspects such as an item not in the hospital formulary being prescribed, which as pointed out above, could be a pharmacist intervention although not considered a true prescribing error. The following definition has been added to the methods section: 'We adopted the following definition of prescribing errors for the study, which excludes adherence to local prescribing policy and guidelines: "A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice".'

Methods

• Data collection: within this first paragraph the terms survey and audit are used interchangeably, I would stick with one term.

'Survey' has now been replaced by 'audit' in the first paragraph

Page 5

• Line 15: The data collection process is described as ward pharmacists recording errors at the point of checking admission and discharge prescriptions. So only prescriptions written at these points are recorded in the study- is that correct as the first aim was to examine the prevalence, type and severity of errors made by different categories of prescriber- which I assumed meant all prescribing errors at any point e.g. during inpatient stay. Perhaps the aim can be made clearer to make this explicit.

Prescriptions were audited at any point during inpatient stay, not only at admission. The sentence now reads: 'Nominated ward-based clinical pharmacists prospectively documented prescribing errors at the point of checking inpatient or discharge prescriptions, during normal pharmacy working hours.'

• Line 19: I am not sure whether a separate form is completed on acute admission to allow for emergency prescribing as part of normal practice or whether this was carried out for the purposes of the study. Could you make this clearer.

The separate form referred to an audit form rather than a prescription form. Prescribing was carried out as per normal practice. This has been clarified in the text.

• Line 24: Hospitals were advised to complete the study on alternate days so that patients would not be caught twice. This suggests that data collection days are every second day, however, days appear to be chosen to get an even spread of days of the week and occur only once weekly, so double auditing of patients from an admission ward to another ward would not occur anyway. Again, this just needs explaining better.

This has been clarified as follows: ‘Hospitals were advised to complete the study on different days of the week throughout the period of the audit, in order to capture an even spread of days. For example data collection would occur weekly, on Monday in week one, Tuesday in week two, Wednesday in week three, in order to minimise inadvertent double auditing of the same patient on admission to hospital and subsequent admission to a ward.’

• Line 33&34: The use of capital letters requires some attention.

The capital letters in this sentence have been amended

• Line 36: Other and unknown seem to overlap here – there are doctors for whom grade was not recorded and also an unknown category in which information was not recorded. Is there a difference between these categories?

The sentence has been clarified as follows: ‘...other (for example locum doctors for whom grade was unclear) and unknown (no information concerning prescriber recorded).’

• Line 43: I am not sure what was involved in the process of exclusion and inclusion of errors into EQUIP study error types and what was done in the case of overlap. Could you explain?

It has now been clarified in the text that the modification and definition of error categories and severities was undertaken by two members of the study team (KS, SK) and agreed by a third (TK). Any specific ‘exclusions’ or ‘inclusions’ are described in table 2.

• Line 48: Severity ratings were assigned according to three factors: the modified EQUIP study criteria, the pharmacists grading and also by reference to licensing information of the medication. How were these three reconciled? I am also very interested to know the role that licensing information had on assignment of severity ratings.

The use of licensing information referred to the regarding of error severities from the study data, rather modification and definition of categories. This has been clarified in the methods section. The licensing information was referred to in order to determine potential implications of different degrees of overdose, underdose, of drug interactions, and also to confirm clinical contra-indications. The modification and definition of error categories and severities was undertaken by two members of the study team (KS, SK) and agreed by a third (TK). This has been clarified in the text.

• Line 52: The authors developed 10 error groups including one which was safety errors – I would argue that all of these errors are safety errors.

We agree that all the errors discussed are safety issues. The category has been re-named ‘clinical safety errors’, as these errors relate to clinical safety issues

• Line 57: I’m not familiar with the term ‘over-call’- do you mean overestimate?

‘over call’ has been amended to ‘over report’. There was a tendency to report factors of prescribing which were not true errors

• Line 60: I would like to know what a standard error is and how this was decided.

‘standard errors’ has been amended to ‘sample errors’. We selected a list of errors which a) were common in occurrence, and b) covered a broad range of categories and severities. This was discussed among members of the study team after analysis of the main study. This has been clarified in the text.

Page 6

• Line 4: It is stated that 14 standard errors were decided upon but it appears that only six were given to each of the six pharmacists.

The 14 sample errors were contained in six sample prescription scenarios; this has been clarified in the text.

• Line 9-13: There are some results presented here regarding the concordance of pharmacist ratings with the gold standard and perhaps these should be in the results section or at least in their own sub-section.

This has been moved to the results section as suggested

• Line 18: One hundred and forty three should be in words and not figures as it starts the sentence.

The sentence now reads: ‘A total of 143 errors were not considered true errors of the process of prescribing and were excluded.’

• Line 19-21: These are results and hence would sit better in the next section.

This section has been moved to the results as suggested by both reviewers

• Line 31-32: Here, the factors that were explored for their association with errors are described yet they are not stated in the aims and objectives section.

This has been added to the introduction as suggested

• It might be useful in the methods section to state how a prescribing error was defined for the purposes of the study.

A definition has been added to the methods section as suggested

Results

• I think the total number of days on which data was collected should be presented here. The term incidence is used rather than prevalence which was stated in the aims- was this intended?

'Incidence' has been amended to 'prevalence' in this sentence

Page 7

• Line 48: Multivariate analysis was conducted examining the risk of error with the number of items on a prescription form – this was a significant finding yet there was no mention of this being part of the aims of the study in the introduction.

This has been added to the introduction as suggested

• Line 56: It is stated that no significant differences were found in errors rates between different prescribed grades – this should perhaps state 'Compared to newly qualified doctors…' as this was the reference used.

This sentence has been amended as suggested

Discussion

Page 8

• Line20-21: There is some discussion about the relationship between hospital type and number of errors. It would be useful to have a table detailing the types of hospitals included in the study e.g DGH, teaching, paediatric hospital etc.

Table 1 has been added as suggested

• Line35: One of the analyses carried out looked at Liverpool graduates vs other graduates yet the decision to explore this was not discussed in the introduction and it would be good to know the rationale for this analysis.

This has been clarified in the introduction text.

• Line 37-41: Are these findings significant? They are certainly interesting

Using a chi-squared statistic for trend considering only prescribers: new, junior, mid and senior and crosstab them by number of significant errors or above (excluding minor), then the p-value for trend is $p<0.001$. The sentence now reads: 'The proportion of errors categorised with severity as significant or higher by prescriber grade were as follows: all prescribers 58.0%, newly qualified 51.2%, junior 60.8%, mid grade 66.4%, senior 57.6% (X^2trend $p<0.001$ for univariate analysis, although this association disappeared when corrected for other potential confounders)(Table 3).'

• Line 45: It is stated that a rate of 10.9% was observed- should this figure be included in the results section?

This figure has been included in the descriptive results section as suggested

• Line 49-51: This section reads as though you have data on paediatric patients vs. adult patients but this is not presented in the results section which is a little confusing.

This data has been added to the results section and clarified in the discussion

• Line 52-54: It is stated that a study reported that errors were more common in prescribing s`amongst men than women but I was uncertain as to how this relates to the results that were presented in the paper.

This data has been added to the results section and clarified in the discussion

• Line 55-page 9 line 8: The literature discussed here is interesting but I think it would be better if it was discussed in relation to what was found in this study.

This paragraph has been amended to include comparison with the data observed in our study

Page 9
• Line 5: It's stated that the paper by Dean et al examined errors on prescriptions however the term prescription in your paper refers to entire prescription forms with multiple medications but Dean's paper examined errors per medication order. I would just ensure that a distinction is made.

This has been clarified in the text

• Line 20-22: You state that errors were grouped according to their origin and cause yet I did not see any mention in the methods about determining the cause of errors. Perhaps this could be clarified.

We did not evaluate the causes of errors, the sentence has been amended as follows: 'Finally, by grouping errors into categories according to their origin, we sought to reduce misclassification as far as possible.'

• Line 31-33: The distinction between 'emergency prescribing' and errors which could have been prevented is a very positive aspect of the study.

• Line 38-40: The sensitivity analysis showed a drop in error rate with exclusion of omission errors- what implications does this have for practice? Could there be more discussion about the implications of the findings for practice.

Further discussion has been included as suggested

• Line 43: Incorrect use of capital letters.

This has been amended

• Line 56: This sentence implies that analysis was conducted into differences between handwritten and electronic prescriptions.

This has been clarified as follows: 'We did not formally evaluate differences in error rates between electronic prescribing and paper-based prescribing systems. Although one hospital (Hospital G) was utilising complete electronic prescribing systems on some wards at the time of the study, and many of the other hospitals were using electronically generated discharge summaries, we failed to observe any clear association with error rate, mainly because of the large variability in case mix which impacted directly on the number of items/prescription.'

Page 14
• Figures 1a and 1b: These forest plots are good but perhaps they should be separate figures as they show different results and then they can be presented in order in the text. (at the moment figure 2 comes before figure 1b). I would also like to see a key for the hospital types.

The figures have been separated and re-numbered as suggested

Page 16
• Table 1: The numbering in the original EQUIP error category is confusing, perhaps it's not needed.

These have been removed as suggested

• Under the heading 'writing errors' no signature is given a rating of significant as it's a governance issue- I was wondering what this meant in relation to the potential severity to the patient? Patient harm e.g having to wait for the prescription to be signed and therefore a delay in receiving medication can't be any more severe for other errors in this category i.e missing dose.

We accept that the impact on a patient of a prescription with no signature may be no more significant that a prescription with no dose specified, we felt that as a governance issue, not signing a prescription represented a more significant error, which is stated in table 1. Prescriptions without signatures accounted for 1% of total errors (37/3011), which would make negligible difference to the overall results if re-classified.

Page 23
• Table 4: I had some difficulty reading this table as percentages run down columns but differences are examined across columns – perhaps this could be explained somewhere for the reader.

For this Table (now table 5) we want to compare the number of errors vs. no errors for each variable of interest. So the reviewer is correct in that the differences are examined across columns. To avoid confusion, the 'n' in the error/ no error columns have been removed, as the statistical testing is not based on these numbers.

• Discharge/admission should be the other way around.

The result suggests there are on average 9% more errors in discharge group than admissions group. Switching the results around would suggest that there are 9% less errors in admissions than in discharge which is the same thing. Analysing them the other way round would switch the difference and CI to 9% (-6% to 12%) which is interpreted the same.

VERSION 2 – REVIEW

REVIEWER	Dr Penny Lewis, Clinical Lecturer, University of Manchester I have no competing interests
REVIEW RETURNED	04-Dec-2012

GENERAL COMMENTS	• I am not sure that you provided a sufficient explanation as to why differences between Liverpool graduates were explored versus other university graduates. Is there something unique to this course? If you were to explore other universities might the results be different? • In the results it is stated that the lowest rates of errors were reported for the paediatrics speciality – in table 4 this speciality was not explored individually so I take it you are referring to the paediatric hospital as oppose to paediatric patients from across the different hospitals? Or was this data collected from all paediatric patients seen across all hospitals? • Risk factor analysis: 'All factors considered appeared to show a significant difference except for medical school training'. Perhaps this should be 'except for whether a doctor was trained at Liverpool medical school or not' as the study only tested for a difference between Liverpool graduates and other medical school graduates. • One of the main findings of this study, as stated in the key messages, was that prescribing errors increased by 14% for every additional medication item prescribed but there is no discussion as to what this might mean for practice.

	• It is stated that 'A study in Spain compared paediatric wards with obstetrics found the paediatric patients had a fourfold higher risk of serious errors then maternity population' – and then stated that this is in line with own findings but I didn't see anything in the results regarding severity of errors across different patient groups. I think is a simple misconception due to the way the paragraph is phrased. • Finally by grouping errors into categories according to the origin we sought to reduce misclassification as far as possible – could you explain this further as I'm not sure what is meant by this. • The final conclusion of the paper states that removing safeguards such as pharmacists could lead to higher numbers of errors but the 'key messages' of the paper are that you found no difference in error rate by grade and the strongest predictor for prescribing error was the number of medicines. So I am not sure of the link between this and the overall aims/key messages. If this is the main conclusion then maybe there should be some mention of these safeguards in the introduction. • Overall, the study presents some very interesting data but I believe that the paper could be improved upon further, linking the key findings, introduction and discussion better and clarifying the important findings e.g. is the main message of the work that pharmacists should never be removed from their role or that there is no link between experience and number of errors made.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Dr Penny Lewis, Clinical Lecturer, University of Manchester

I have no competing interests

Thank you for responding to my comments. I think that the paper has improved significantly. However, there are a few comments I would like to make regarding this version.

• I am not sure that you provided a sufficient explanation as to why differences between Liverpool graduates were explored versus other university graduates. Is there something unique to this course? If you were to explore other universities might the results be different?

This has been clarified in the introduction. A large proportion of evaluated prescribers (30%) received undergraduate training at the University of Liverpool. The study was funded by the Mersey Deanery.

• In the results it is stated that the lowest rates of errors were reported for the paediatrics speciality – in table 4 this speciality was not explored individually so I take it you are referring to the paediatric hospital as oppose to paediatric patients from across the different hospitals? Or was this data collected from all paediatric patients seen across all hospitals?

This refers to the error rate observed for the paediatrics specialty hospital; this has been clarified in the text

• Risk factor analysis: 'All factors considered appeared to show a significant difference except for medical school training'. Perhaps this should be 'except for whether a doctor was trained at Liverpool medical school or not' as the study only tested for a difference between Liverpool graduates and other medical school graduates.

The wording has been changed as suggested

• One of the main findings of this study, as stated in the key messages, was that prescribing errors increased by 14% for every additional medication item prescribed but there is no discussion as to what this might mean for practice.

The following has been added to the discussion: 'In multivariate analysis, the strongest predictor for prescribing error was the number of medicines on each prescription, with risk for prescribing errors increasing by 14% for every additional medication item prescribed. Complex polypharmacy is becoming increasingly common, with patients potentially requiring management for multiple chronic conditions simultaneously. In these patients, vigilance for prescribing errors and pharmacist review is of particular importance.'

• It is stated that 'A study in Spain compared paediatric wards with obstetrics found the paediatric

patients had a fourfold higher risk of serious errors then maternity population' – and then stated that this is in line with own findings but I didn't see anything in the results regarding severity of errors across different patient groups. I think is a simple misconception due to the way the paragraph is phrased.

The paragraph has been rephrased and now reads: 'A study in Spain comparing paediatric wards with obstetrics found that paediatric patients had a fourfold higher risk of serious errors than the maternity population (2.3% vs 14.3%), which were mainly related to drug dosing. We observed a low error rate for the paediatrics specialty hospital, although this was likely due to a low number of prescribed items.'

• Finally by grouping errors into categories according to the origin we sought to reduce misclassification as far as possible – could you explain this further as I'm not sure what is meant by this.

This sentence has been altered and now reads: 'Finally, in order to limit the impact of error misclassification, the original 29 error categories were batched into 10 different types of error groups relating to key components of prescribing.'

• The final conclusion of the paper states that removing safeguards such as pharmacists could lead to higher numbers of errors but the 'key messages' of the paper are that you found no difference in error rate by grade and the strongest predictor for prescribing error was the number of medicines. So I am not sure of the link between this and the overall aims/key messages. If this is the main conclusion then maybe there should be some mention of these safeguards in the introduction.

The following sentence has been added to the introduction, in the paragraph relating to the background of error. 'Barriers which may prevent medication errors, or prevent errors from reaching the patient, may include electronic prescribing alerts, and prescription review by clinical pharmacists.'

The conclusion now states that as prescribing errors are prevalent in secondary care and are made by all grades of prescribers, removing safeguards (ie pharmacists) could lead to more errors actually reaching patients. We referred to the particular importance of pharmacists in clinical areas associated with high risk; patients with polypharmacy and admission areas are now given as examples. This now relates our key findings to the importance as pharmacists as 'safeguards'.

• Overall, the study presents some very interesting data but I believe that the paper could be improved upon further, linking the key findings, introduction and discussion better and clarifying the important findings e.g. is the main message of the work that pharmacists should never be removed from their role or that there is no link between experience and number of errors made.

The main message links both aspects. Our key findings are that grade of prescriber does not affect error rate and that increased number of prescribed items increases risk of errors. We conclude that prescribing errors are prevalent, regardless of the grade of prescriber, therefore a key role of clinical pharmacists is to ensure that errors are less likely to reach patients. Potential barriers to prescribing

errors have now been mentioned in the introduction. Further comment on number of prescribed items conferring higher risk for prescribing errors has been added to the discussion.