PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exploring the association of the discharge medicines review with patient hospital readmissions through national routine data linkage in Wales: a retrospective cohort study
AUTHORS	Mantzourani, E.; Nazar, Hamde; Phibben, Catherine; Pang, Jessica; John, Gareth; Evans, Andrew; Thomas, Helen; Way, Cheryl; Hodson, Karen

VERSION 1 – REVIEW

REVIEWER	James C. McElnay School of Pharmacy, Queen's University Belfast
REVIEW RETURNED	28-Aug-2019

GENERAL COMMENTS	This is an interesting paper, the findings of which are worthy of publication. It addresses an important matter, i.e. minimising rehospitalisation of patients within the first 90 days post-discharge. However, in the view of this reviewer, before publication, considerable redrafting and change in emphasis in places throughout the paper are required. Some areas that require improvement are as follows: 1. Abstract needs some redrafting to ensure it is a stand-alone piece. The conclusions and article summary sections of the abstract need particular attention. 2. Strengths and limitations of the study – the content of this section, as written, is very difficult to understand and needs to be rewritten. The limitation raised in page 11, i.e. failure to access data on other healthcare services, e.g. within General Practice, as part of the data linkage process, should be included as a study limitation. 3. Introduction, paragraph 2: Need to explain the community pharmacy services being described in more detail, particularly for an international audience. 4. Page 5, Outcome measures – these need to be stated much more clearly 5. There seems to be a conflict running throughout the paper as to what is the most important area of the research to emphasise within the text, the data linkage methodology or the outcomes (impact of DMR on rehospitalisation). To this reviewer the emphasis should be much more on the outcomes. With this in mind, I suggest that the data linkage piece on page 6 is simplified / inserted into the supplementary material. 6. The discussion section should have a greater focus on the impact of the new service on patient outcomes with comparison of current findings with other published post-discharge interventions designed to minimise rehospitalisation rates. Whereas the discussion on data linkage may be interesting regionally, it will be less interesting to international readers.

REVIEWER	Tamasine Grimes Trinity College Dublin Ireland
REVIEW RETURNED	20-Oct-2019

GENERAL COMMENTS	Thanks for the opportunity to review this manuscript addressing the association between activation of a DMR post-discharge and hospital readmission. The manuscript provides detail of service delivery and evaluation of the DMR, with evaluation supported by the linkage of multiple data sources. It provides important information to support further service development and delivery and the authors have clearly outlined opportunities and barriers to data linkage and analysis. Some considerations to support strengthening the manuscript: Does the data, as currently presented, support investigation of the impact or the effect of the DMR intervention? The authors acknowledge this themselves in the limitations, however, it may require the objectives and title of the study to be changed. Consider that the study describes an association between the intervention and readmission. 2. Is the abstract accurate, balanced and complete? Suggest revise the title and edit the abstract to reflect that the study describes an association between the intervention and outcome measure, rather than the impact or effect of. 4. Are the methods described sufficiently to allow the study to be repeated? The comparator group and the denominator are unclear. It would be helpful to state this explicitly. It seems the denominator was all inpatient referred for a DMR, the intervention group was those who activated part 1 of the DMR and the comparator was those referred for a DMR but who did not activate it. Is this correct? I am not familiar with the analysis approach chosen. I found myself unsure whether it was "confidence inference tree", "conditional inference tree" or something else. It would be helpful to provide a supporting reference and brief defence of this approach. This limited my ability to critique the multivariate analysis, or have confidence in understanding the influence of independent variables on the outcome. Why were deaths excluded from the survival analysis? 5. Are research ethics (e.g. participant consent, ethics approval) addressed appropriately? The authors have presented a complex and what appears challenging data linkage. GDPR and health research regulations are topical at present. It would be helpful to provide supporting evidence of the legislation or policy that enables this work without consent or the oversight of a consent waiver process. This will be important for an international audience with varying degrees of regulation. The work "de-anonymization" is somewhat concerning, and perhaps should be re-phrased to reflect that pseudonymised data were made identifiable. The data controllers for each dataset could be outlined, and the relationship between these - for example, who is the controller of the community pharmacy data? 7. If statistics are used are they appropriate and described fully?

	It would be helpful to provide more detail of the conditional inference tree. 11. Are the discussion and conclusions justified by the results? The conclusions outline the effect of the DMR on readmission. This does not seem to be supported by the data presented. There appears to be an association, but as the authors acknowledge, the limitations of imbalance between groups (deprivation decile) and the analysis of part 1 of the DMR only, make it difficult to claim causation. It would be worthwhile, through an implementation science lens, to investigate what supports or inhibits activation of part 1 of the DMR. The difference in deprivation decile likely represents much more than "health consciousness". Every best wish for completion of this work.

REVIEWER	Richard Woodman Flinders University Australia
REVIEW RETURNED	18-Nov-2019

GENERAL COMMENTS	Overall comments Whilst the study is original and potentially of interest there are a large potential for bias and the limitations of the study have not been adequately considered. In particular, multivariate analysis should be performed to better estimate the independent association between DMR use and readmission. Specific comments Removal of patients that died from the analysis is likely to introduce bias rather than remove it. These patients should have their follow-up time recorded and this variable adjusted for in the analysis – in either a logistic regression or a Cox regression survival analysis. The analysis needs to be adjusted for all other socio-demographic variables namely age, sex, SES, and diagnosis regardless of their significance with DMR. All are potential confounders of the association between DMR and readmission. Whilst a strobe checklist has been completed there are many fields that have not been adequately addressed and simply state NA. Specifically • Study size (a power calculation needs to be performed) • How were missing data addressed (how many patients were discharged but not linked to the DMR database, and how many patients that were linked with the DMR did not have information on readmission? What was done about theses missing data. Similarly did any of the patients have missing socioeconomic data and were they removed from the analysis). • How was loss to follow-up addressed? (was there missing data on readmissions for any patients?). • There are no confounder adjusted estimates provided • The limitations of the study are not adequately addressed. In particular, this is an observational cohort study, with enrolment with the DMR based on self-selection and/or clinician judgement. As such there is a large potential for bias. This bias should be addressed as far as possible with confounder adjusted analysis. The possibility of residual confounding should also be discussed.

	The cumulative incidence curve for readmission suggests non-proportional hazards since the curves do not separate further after 30 days. A test for non-proportional hazards should be performed if Cox regression is used to adjust for the confounders. Some adjustment for multiple comparisons should be performed with an appropriate Type 1 error rate used rather than $p<0.05$. The 3 main outcomes are all related to each other, and there are numerous categories of age considered separately for each outcome. It is concerning that ethics approval was not sought. Why is Cardiff University Ethics approval (senior author's affiliation) not required?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Reviewer Name: James C. McElnay, Institution and Country: School of Pharmacy, Queen's University Belfast	
This is an interesting paper, the findings of which are worthy of publication. It addresses an important matter, i.e. minimising rehospitalisation of patients within the first 90 days post-discharge. However, in the view of this reviewer, before publication, considerable redrafting and change in emphasis in places throughout the paper are required. Some areas that require improvement are as follows:	
1. Abstract needs some redrafting to ensure it is a stand-alone piece. The conclusions and article summary sections of the abstract need particular attention.	The abstract has been revised, as per the reviewer's suggestion. The article summary has been removed completely, as advised by the editor.
2. Strengths and limitations of the study – the content of this section, as written, is very difficult to understand and needs to be rewritten. The limitation raised in page 11, i.e. failure to access data on other healthcare services, e.g. within General Practice, as part of the data linkage process, should be included as a study limitation.	The section has been re-written to account for the reviewer's and editor's comments. The limitation mentioned by the reviewer has been added.
3. Introduction, paragraph 2: Need to explain the community pharmacy services being described in more detail, particularly for an international audience.	The text has been modified to account for the reviewer's suggestion.
4. Page 5, Outcome measures – these need to be stated much more clearly	The outcome measures have been reworded to the following: Primary: Rate of hospital readmission within 90 days for patients with and without a DMR Part 1 started Secondary: Strength of association of age decile, sex, deprivation decile, diagnostic grouping and DMR type (started or not started) with reduction in readmission within 90 days
5. There seems to be a conflict running throughout the paper as to what is the most important area of the research to emphasise within the text, the data linkage methodology or the outcomes (impact of DMR on rehospitalisation). To this reviewer	We thank the reviewer for their constructive comment. It was indeed our intention to provide equal focus to outcomes and data linkage (as both areas are novel for the UK, and we couldn't have achieved one without the other). However, we recognise that the technicalities around data linkage can be transferred to supplementary material. With this in mind, we have now simplified the text on data

the emphasis should be much more on the outcomes. With this in mind, I suggest that the data linkage piece on page 6 is simplified / inserted into the supplementary material.	linkage, especially the overview of steps, and are referring readers to the supplementary material.
6. The discussion section should have a greater focus on the impact of the new service on patient outcomes with comparison of current findings with other published post-discharge interventions designed to minimise rehospitalisation rates. Whereas the discussion on data linkage may be interesting regionally, it will be less interesting to international readers.	The section has been expanded to include more discussion on positive impact of the DMR with comparison to literature.
Reviewer: 2 Reviewer Name: Tamasine Grimes, Institution and Country: Trinity College Dublin, Ireland	
Thanks for the opportunity to review this manuscript addressing the association between activation of a DMR post-discharge and hospital readmission. The manuscript provides detail of service delivery and evaluation of the DMR, with evaluation supported by the linkage of multiple data sources. It provides important information to support further service development and delivery and the authors have clearly outlined opportunities and barriers to data linkage and analysis. Some considerations to support strengthening the manuscript:	
1. Does the data, as currently presented, support investigation of the impact or the effect of the DMR intervention? The authors acknowledge this themselves in the limitations, however, it may require the objectives and title of the study to be changed. Consider that the study describes an association between the intervention and readmission.	The research team has reflected on the point raised by the reviewer, and we agree that the wording needs to be amended throughout our paper to reflect this. We have changed the title and objectives of the study and have replaced the words “impact” or “effect” throughout the text with the word “association”.
2. Is the abstract accurate, balanced and complete? Suggest revise the title and edit the abstract to reflect that the study describes an association between the intervention and outcome measure, rather than the impact or effect of.	Complete, please see comment 1 above
3. The comparator group and the denominator are unclear. It would be helpful to state this explicitly. It seems the denominator was all inpatient referred for a DMR, the intervention group was those who activated part 1 of the DMR and the comparator was those referred for a DMR but who did not activate it. Is this correct? I am not familiar with the analysis approach chosen. I found myself unsure whether it was "confidence inference tree", "conditional inference tree" or something else. It would be helpful to provide a supporting reference and brief defence of this	The reviewer is correct and all definitions for denominator, intervention group and comparator have now been added to the methodology to improve clarity. We apologise for the spelling mistake, the approach taken was that of a conditional inference tree (CTree), which is a non-parametric class of regression trees embedding tree-structured regression models into a well-defined theory of conditional inference procedures. CTree uses a statistical theory (selection by permutation-based significance tests) in order to select variables instead of selecting the variable that maximizes an information measure (Gini coefficient or Information Gain) and thereby removes the potential bias in CART or similar decision trees. We have added the reference for this approach (Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: A conditional inference framework. Journal of Computational and Graphical Statistics. 2006;15(3):651–674)

approach. This limited my ability to critique the multivariate analysis, or have confidence in understanding the influence of independent variables on the outcome. Why were deaths excluded from the survival analysis?	We have also added two reference outlining its application in health sciences: (Hartney M, Liu Y, Velanovich V, Fabri P, Marcet J, Grieco M, Huang S, Zayas-Castro J. Bounceback branchpoints: Using conditional inference trees to analyze readmissions *Surgery* 2014;156(4):pp.842-848 https://doi.org/10.1016/j.surg.2014.07.020 Sardá-Espinosa A, Subbiah S, Bartz-Beielsteinb T Conditional inference trees for knowledge extraction from motor health condition data *Engineering Applications of Artificial Intelligence* 2017;62: pp.26-37 https://doi.org/10.1016/j.engappai.2017.03.008) Deaths are excluded because a patient death creates the inability for the same patient to be readmitted. Therefore, we have to exclude them from the survival analysis the same way people who leave a study would be excluded from traditional survival analysis, to try to avoid skewing the data so that it looks like less people were readmitted, where in reality they died and therefore could not be readmitted. This is in line with literature describing methodology on survival analysis, and we have now added references to two such published articles: Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. Br J Cancer. 2003;89(2):232–238. doi.10.1038/sj.bjc.6601118 and Singh R, Mukhopadhyay K. Survival analysis in clinical trials: Basics and must know areas. Perspect Clin Res. 2011;2(4):145–148. doi:10.4103/2229-3485.86872
4. The authors have presented a complex and what appears challenging data linkage. GDPR and health research regulations are topical at present. It would be helpful to provide supporting evidence of the legislation or policy that enables this work without consent or the oversight of a consent waiver process. This will be important for an international audience with varying degrees of regulation. The work "de-anonymization" is somewhat concerning, and perhaps should be re-phrased to reflect that pseudonymised data were made identifiable. The data controllers for each dataset could be outlined, and the relationship between these - for example, who is the controller of the community pharmacy data?	Thanks for allowing us the opportunity to explain this, it took a lot of our time at the start of the project to clarify whether ethical approval was explicitly required. We registered the project with the Research and Development office of Velindre University NHS Trust as the legal entity responsible for the conduct of studies within NHS Wales Informatics Service (NWIS), the organisation that holds all the data we required for this study. After reviewing our application, the office decided that the study does not require application to an NHS Research Ethics Committee but highlighted that the study should be conducted ensuring regulatory compliance in line with established NWIS policies and procedures. Throughout the study we liaised with the Head of Information Governance of NWIS to ensure this. We have clarified this in our amended section “Ethical considerations”. Data collection at the first instance was part of routine collection of information when the patient visits a healthcare setting. Patients provided informed consent when offered the DMR service as part of routine hospital and community pharmacy care. This consent covers the recording of data and any processing or pre-processing to a form (by NWIS), for the purpose of service activity, audit and evaluation, in an identifiable way. All data from community pharmacy DMR consultations are entered in *Choose Pharmacy*, and NWIS is the processor of that data.

	As an NWIS employee, the lead author worked with the NWIS Head of Information Governance of NHS Wales Informatics Service to ensure that the methodology for processing the information would ensure patient privacy was maintained in all circumstances. The model of processing was consistent with NWIS trusted third party responsibilities and is used in many circumstances to ensure confidentiality, integrity and availability of information. In particular, we paid attention to the following criteria set by the General Medical Council: • *The Information Commissioner's Office anonymisation code of practice (ICO code) considers data to be anonymised if it does not itself identify any individual, and if it is unlikely to allow any individual to be identified through its combination with other data. Simply removing the patient's name, age, address or other personal identifiers is unlikely to be enough to anonymise information to this standard* • *The ICO code also makes clear that different types of anonymised data pose different levels of re-identification risk. For example, data sets with small numbers may present a higher risk of re-identification than large data sets. The risk of re-identification will also vary according to the environment in which the information is held. For example, an anonymised data set disclosed into a secure and controlled environment could remain anonymous even though the same data set could not be made publicly available because of the likelihood of individuals being identified.* • *If a clinical audit is to be carried out, but not by the team that provided care or those working to support them, the information should be anonymised.* Indeed, in our secondary data analysis study patient anonymity was maintained at all stages of the research and there was no risk of de-identification at any point. We have clarified that data linkage involved pseudonymised data made identifiable rather than a simple "de-anonymisation", as the reviewer suggested.
5. It would be helpful to provide more detail of the conditional inference tree.	Complete – please see comment 3 above
6. The conclusions outline the effect of the DMR on readmission. This does not seem to be supported by the data presented. There appears to be an association, but as the authors acknowledge, the limitations of imbalance between groups (deprivation decile) and the analysis of part 1 of the DMR only, make it difficult to claim causation.	The text has been amended, please see response to comment 1 above
7. It would be worthwhile, through an implementation science lens, to investigate what supports or inhibits activation of part 1 of the DMR. The difference in deprivation decile likely	The reviewer raises an important point, and one which we have started investigated already. The research team has secured funding for a PhD studentship (started in Oct 2018), with a student exploring barriers and facilitators to

represents much more than "health consciousness".	the DMR service with the view of constructing a set of recommendations to policymakers. This point has been added to the discussion, supported by literature, and has been acknowledged as a limitation in the "strengths and weaknesses" of the study
Reviewer: 3 Reviewer Name: Richard Woodman, Institution and Country: Flinders University, Australia	
1. Whilst the study is original and potentially of interest there are a large potential for bias and the limitations of the study have not been adequately considered. In particular, multivariate analysis should be performed to better estimate the independent association between DMR use and readmission.	We thank the reviewer for raising this important point and allowing us to strengthen our study with additional statistical calculations. The reviewer is right in saying that we hadn't fully explored the association between DMR use and the other variables in a way that excludes influence from a combination of factors creating a false impression that DMR is the leading factor. i.e. that different demographics within the DMR group have a combined effect which makes DMR 'accidentally' look like the main contributing variable. We have considered the reviewer's comments carefully and have completed additional analysis, in the form of Cox regression survival analysis – please see below for details. The relevant methodology and results have been added to the main body of the paper and the STROBE statement has been updated accordingly.
2. Removal of patients that died from the analysis is likely to introduce bias rather than remove it. These patients should have their follow-up time recorded and this variable adjusted for in the analysis – in either a logistic regression or a Cox regression survival analysis.	We considered published literature on the methodology of survival analysis that informed removal of patients that dies from the analysis (please see response to reviewer 2, comment 3). Patients were followed as part of the censoring, with the follow up time is set at either readmission, death or 90 days. We have completed death rate calculations for the two subgroups in our analysis and have updated supplementary table 2 with the information (no DMR - 64/1235 = 5% vs DMR - 15/688 = 2%)
Whilst a strobe checklist has been completed there are many fields that have not been adequately addressed and simply state NA. Specifically: • Study size (a power calculation needs to be performed) • How were missing data addressed (how many patients were discharged but not linked to the DMR database, and how many patients that were linked with the DMR did not have information on readmission? What was done about theses missing data. Similarly did any of the patients have missing socioeconomic data and were they removed from the analysis). • How was loss to follow-up addressed? (was there missing data on readmissions for any patients?).	• A power calculation could not have been performed as this was a retrospective, pragmatic study, that looked at the complete dataset that was available to us. The sample size was not calculated using power analysis, but as per reviewer's suggestion we have now tried to estimate the effect size using hazard ratios in the survival analysis. • The DMR is a national service that can be triggered for any patient who fits one or more of the criteria described, upon discharge from hospital. The reviewer is right in that selection of patients is based on clinician judgement – as per the service's requirements. Once the patients are selected, all information is added on their hospital record, regardless of whether patients proceed to complete a DMR or not. Unfortunately, if for whatever reason patients who fit the criteria have not been selected, there is no record made on any national patient database, which means that there is no realistic way of identifying the numbers or extracting those patients for analysis. All patients who had been selected by a clinician get "flagged" in the database and were included in our analysis. Similarly, we

• There are no confounder adjusted estimates provided. The analysis needs to be adjusted for all other socio-demographic variables namely age, sex, SES, and diagnosis regardless of their significance with DMR. All are potential confounders of the association between DMR and readmission. • The limitations of the study are not adequately addressed. In particular, this is an observational cohort study, with enrolment with the DMR based on self-selection and/or clinician judgement. As such there is a large potential for bias. This bias should be addressed as far as possible with confounder adjusted analysis. The possibility of residual confounding should also be discussed. • The cumulative incidence curve for readmission suggests non-proportional hazards since the curves do not separate further after 30 days. A test for non-proportional hazards should be performed if Cox regression is used to adjust for the confounders. • Some adjustment for multiple comparisons should be performed with an appropriate Type 1 error rate used rather than $p<0.05$. The 3 main outcomes are all related to each other, and there are numerous categories of age considered separately for each outcome.	included in the analysis records for all patients who were readmitted. • There were very few cases where socio economic data was not available. These have still been included in the analysis, except where being analysed on this field alone (in cases where Survival analysis was done with stratification on these variables): ○ 36 people with blank diagnosis ○ 0 with missing sex ○ 1 with missing deprivation quintile ○ 0 with missing age ○ 0 with missing DMR status This information has now been added in the results. • As per the reviewer's advice, we completed a test for non-proportional hazards. In line with literature (Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6(7):121. doi:10.21037/atm.2018.02.12) Schoenfeld residuals test was used. The initial test run and showed non-proportionality. However, when the two sections were stratified at 40 days, then the assumption did not trigger this test. We based the follow-up time of 40 days based on plotting DMR using the aalen model (https://rviews.rstudio.com/2017/09/25/survival-analysis-with-r/) • We then completed Cox's survival analysis, using as confounders: Age, Sex, Diagnosis, Deprivation, and DMR. We employed a step function to explore the time-varying coefficient for stratification (Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6(7):121. doi:10.21037/atm.2018.02.12). The analysis works for stratification at 40 days. • We have added this additional test in our methodology and results. • We have looked at the hazard ratio confidence intervals to combat the possible issues with Type 1 error. • With this analysis, each variable had a hazard ratio with different confidence intervals which look at whether the readmission rate is affected by that variable. The only variable triggering the significance tests was the stratified DMR, with a hazard ratio of 0.59739 with a confidence interval underneath 1 (0.5043-0.7076). This suggests that readmission within 40 days is reduced by DMR.
It is concerning that ethics approval was not sought. Why is Cardiff University Ethics approval (senior author's affiliation) not required?	Thanks for allowing us the opportunity to explain this, it took a lot of our time at the start of the project to clarify whether ethical approval was explicitly required. We registered the project with the Research and Development office of Velindre University NHS Trust as the legal entity responsible for the conduct of studies within NHS Wales Informatics Service (NWIS), the organisation that holds all the data we required for this study. After reviewing our application, the office decided that the study does not require application to an NHS Research Ethics Committee

	but highlighted that the study should be conducted ensuring regulatory compliance in line with established NWIS policies and procedures. Throughout the study we liaised with the Head of Information Governance of NWIS to ensure this. We have clarified this in our amended section “Ethical considerations”. Data collection at the first instance was part of routine collection of information when the patient visits a healthcare setting. Patients provided informed consent when offered the DMR service as part of routine hospital and community pharmacy care. This consent covers the recording of data and any processing or pre-processing to a form (by NWIS), for the purpose of service activity, audit and evaluation, in an identifiable way. All data from community pharmacy DMR consultations are entered in *Choose Pharmacy*, and NWIS is the processor of that data. This study involved records-based research that did not involve people directly. The lead author (affiliated with Cardiff University and also with NWIS) worked with the NWIS Head of Information to ensure that the methodology for processing the information would ensure patient privacy was maintained in all circumstances. The model of processing was consistent with NWIS trusted third party responsibilities and is used in many circumstances to ensure confidentiality, integrity and availability of information. In particular, we paid attention to the following criteria set by the General Medical Council: • *The Information Commissioner’s Office anonymisation code of practice (ICO code) considers data to be anonymised if it does not itself identify any individual, and if it is unlikely to allow any individual to be identified through its combination with other data. Simply removing the patient’s name, age, address or other personal identifiers is unlikely to be enough to anonymise information to this standard* • *The ICO code also makes clear that different types of anonymised data pose different levels of re-identification risk. For example, data sets with small numbers may present a higher risk of re-identification than large data sets. The risk of re-identification will also vary according to the environment in which the information is held. For example, an anonymised data set disclosed into a secure and controlled environment could remain anonymous even though the same data set could not be made publicly available because of the likelihood of individuals being identified.* • *If a clinical audit is to be carried out, but not by the team that provided care or those working to support them, the information should be anonymised.* Indeed, in our secondary data analysis study patient anonymity was maintained at all stages of the research and there was no risk of de-identification at any point.

VERSION 2 – REVIEW

REVIEWER	Tamasine Grimes Trinity College Dublin, Ireland
REVIEW RETURNED	20-Jan-2020

GENERAL COMMENTS	Thanks for the invitation to review the revised manuscript. I am satisfied that the reviewers' comments have been addressed. Best wishes for your continued work investigation the implementation of the DMR.