PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prescribing trends over time by non-medical independent prescribers (NMIPs) in primary care settings across Wales (2011-2018): a secondary database analysis
AUTHORS	Alghamdi, Saeed; Hodson, Karen; Deslandes, Paul; Gillespie, David; Haines, kath; Hulme, Elliott; Courtenay, Molly; Deslandes, Rhian

VERSION 1 – REVIEW

REVIEWER	Jill Wilkinson Victoria University of Wellington, New Zealand
REVIEW RETURNED	29-Jan-2020

GENERAL COMMENTS	A well written an valuable article. I have only minor points to raise: The title, abstract and various places in the manuscript refer to 'prescribing trends' - a phrase I found was a little misleading as a reader because it suggested prescribing trends of particular medicines rather than the volume of prescriptions over time. I suggest re-visiting the use of this phrase and then using it consistently throughout. On page 8 line 39, the impact of patients not getting their prescription dispensed was 'likely to be small'. This is a significant problem in New Zealand due to the co-payment requirements for each prescription item. A few words of clarification on this point would be helpful here. Page 16 line 47 - suggest re-phrasing the sentence starting 'This is wasteful ...' Figure 1: I suggest reducing the unit size on the vertical y-axis to show the increase in number of prescription items more clearly (similar to figure 2).

REVIEWER	Emma Graham-Clarke University of Birmingham United Kingdom
REVIEW RETURNED	09-Feb-2020

GENERAL COMMENTS	Thank you for inviting me to review this interesting and timely study. It adds to the body of evidence concerning non-medical prescribing, highlighting changes in practice over time. I have a few comments to make regarding the paper and some minor typographical suggestions are listed at the end. The figures/graphs have not translated clearly into the proof document. They may need to be of a higher resolution or different format to make them clearer. I am not familiar with using ARIMA and this paper would benefit from being reviewed by someone with knowledge of the technique

	to ensure that the results are presented in the most appropriate manner. Page 3 – Strengths and limitations In the proof section, which I have reviewed, this follows on from the abstract. As such the reference numbering is out of sequence with the main paper. If this section is to be published at the beginning of the paper, then I would recommend changing the reference numbers. You comment that the system 'only captured prescriptions that were dispensed in the community pharmacies'. My understanding is that CASPA will capture only NHS prescriptions, and not any private prescription. This could be significant when discussing the lack of prescribing by optometrists, as they are private practitioners in general and therefore may have limited access to NHS budgets. I appreciate that some may be directly contracted to provide NHS work, but I am unclear if this is the situation in Wales. Introduction Page 4 line 46 – strictly speaking optometrists are not classed as Allied Health Professionals (they are regulated by the General Optical Council) Page 4 line 50 et seq – apart from nurses and pharmacists, the other non-medical prescribing professions are limited in what they can prescribe. For example, podiatrists are limited to prescribing for conditions associated with the foot, ankle and associated structures, whilst optometrists are limited to prescribing for conditions associated with the eye and surrounding areas. Page 5 line 38. Paramedics gained independent prescribing rights in Wales in February 2019. I appreciate that this is outside your research time period, but it is an indicator that non-medical prescribing will continue to expand. Results Page 11 line 37 et seq – please check your figures. I don't believe the figure for the period 2017-8 is correct. Page 14 table 2 – ARIMA is not a statistical technique that I have used, but papers that I have read that have used this technique present the results graphically. Instead you present the pre-intervention and post intervention slope figures, but it is unclear how is these are derived. I think this aspect of the results presentation requires a review to make it clearer for the reader. Page 15 table 3 – this nicely demonstrates the increasing uptake across the health boards at different time points. Figures 1 and 2 – these pair of graphs are striking and would probably benefit from being presented jointly. The numbers of NMIP prescriptions are probably too small to make a combined graph feasible but please investigate some other means of presentation. Discussion Page 16 line 33 et seq – you rightly comment that therapeutic radiographers are unlikely to prescribe in primary care. The other professions that you mention may be prescribing but for a variety of reasons the activity is not picked up in your study, for example, prescribing privately or prescribing for treatment at the point of care. This warrants further consideration and elaboration in your discussion. You discuss the varying geographical areas and numbers of GPs that each health board covers. Looking at table 1, I am struck that

	the PTHB, whilst it has the smallest percentage of prescribed items by NMIPs, actually has more prescribed items per 100,000 population than two of the other health boards. This also links to figure 4, where PTHB stands out quite dramatically in the increase in prescriptions and the number per 100,000 population. You don't comment at all in your discussion about this and I wondered what your views were. Typographical comments Page 1, line 7 – this would read easier with a comma after 'clusters'. Page 6 line 19 – I think this needs a comma after 'primary care services'. Page 8 line 30 – I would be inclined to add NHS to the comment 'Welsh prescriptions for use in primary care', to indicate that private prescriptions are excluded. Page 8 line 43 – would this be clearer if it read 'the number of items refers to each single item prescribed…'? Page 10 line 12 – should read 'Chief Pharmaceutical Officer' Reference 23, 24, 31 – the web links doesn't seem to work – please check your reference links

REVIEWER	Nolwenn LE MEUR EA 7449 REPERES (EHESP-Univ Rennes), France
REVIEW RETURNED	10-Mar-2020

GENERAL COMMENTS	Saeed S Alghamdi et al presents a paper "Prescribing trends over time by non-medical independent prescribers (NMIPs) in primary care settings across Wales (2011-2018): a secondary database analysis". The objectives of the study are to identify the number of NMIPs and their associated trend of prescribed items when primary care clusters came into practice. The paper is easy to read. The limits of the study a clearly stated. The output may be of interest for those working in the field of health system evolution and transformation. However, some improvements are needed: Major: The number of NMIPs and their volume of prescribing in primary care has increased, following the recommendations. However, as mentioned by the authors, it does not prove a better quality of care. Indeed, the numbers in Figure 1 and Figure 2 and paragraphs 1 and 2 of the results seem to show that dispensing of drugs by NMIPs increases but that dispensing of drugs by GPs do not decreases by the same amount. Do you observe an over-prescription mechanism or is it a response to long lasting absence of care (seeking)? In table 1, 1) the number of GPs, the number of NMIPs per health board, the number of NMIPs per 100,000 inhabitants per health board could be interesting to have in parallel to the number of items prescribed. 2) Is the number of prescribed items by NMIPs correlated with the number of NMIPs per health board? 3) Does the lack of GPs correlate with the % of the prescribed items by NMIPs in each BH?

	4) Could you calculate the % of the (same) prescribed items by GP? In table 2, If I am correct the 95%CI is the confidence interval for the difference? If so, it should be clearer in the table header or caption? I am questioning the ARIMA model for the PTHB data as looks strange in Table 3 and Figure 4 (see comments on Figure 4) Figure 3, 1) for comparison purposes between HB, more that the number of NMIPS it would be interesting to visualized the number of each NMIPs per 100,000 inhabitants in each HB or relative to the number of GPs. 2) Indeed, is there a relationship between the evolution of the number of NMIPS and the number of GPs in the different HB? Figure 4 the sharp increases in PTHB is strange. As the data been verified? If that is a true phenomenon, is there a rational explanation? In the discussion, 1) As suggested for the early adopters, could the time to adoption of the recommendations for late adopters be linked to the % of GPs in the HB? 2) It could also be discussed that the populations covered by the HB might differ in terms of pathologies and may not have same needs therefore may not seek the health care (professionals and prescriptions) Minor: 1) In the abstract, the acronym HB is being written in full letters 2) P11 line 42 it would be more readable to write 2017-2018 instead of 17-18 in the sentence "…while the largest increase was from the last quarter of 2015 to 17-18" 3) Reference 35 it shoud be Available and not "Avilable"

REVIEWER	Dr Kara Stevens University of Plymouth, UK
REVIEW RETURNED	17-Mar-2020

GENERAL COMMENTS	From reading, this manuscript this appears to be a policy evaluation using interrupted time series analysis (ITSA) on the number of prescriptions by NIMPs. Although, I think this is interesting research question on how clusters may affect the number of NIMPs prescriptions, the manuscript does not clearly communicate this. Below are comments on each component of the review checklist. 1. The objective implies that this is a description of the number of NIMPs prescriptions. However, with it appears to be an evaluation of an "intervention" (e.g. policy change). I think actual objective of the study was to compare the prescription patterns of NIMPs before and after the implementation of primary care clusters for Wales and each cluster. 2. In the abstract, I do not believe some of the text is in the correct sections. For example, it seems the objective is under the design. I would say the design was quasi-experimental, analysed using ITSA.

	3. Depending on what the actual research question is has implications on what sort of statistical methodology should be used to answer this question. If the aim was simply to describe NMIPs prescriptions then an ITSA would not be appropriate. 4. Information on what data was obtained appears to be thorough. However, some of the wording is a little confusing, e.g. "The number of items refers to a single item…" 6. I am not sure having outcomes reported per 100,000 is entirely appropriate all the way through. I would consider performing all the analysis and presenting most of the results in values closer to the actual data, then presenting in 100,000 during the discussion, if comparing with other studies. 7. The description for ITSA does not appear to be correct. The ARIMA component is used to describe the residuals of a regression model, plots of the ACF and partial ACF are probably best as part of supplementary material, but would demonstrate the rigor of statistical analysis and ideally included. The regression model should be fully specified, outlining the phase period, intercept, trend, interaction etc. I would urge the researchers to use appropriate statistical packages, e.g. R or STATA, and reference exactly what was used to perform the analysis for transparency. For an adequate estimate of change in trend, there should be 8 observations pre and 8 observations post intervention (not including any phase in period). 8. They should reference statistical software and methods used. 9. Firstly researchers need to plot the data, and it is often advised to add a vertical line identify the time point when the policy change was made. From the description of the data, it seems that researchers have monthly data, which should be used in this plot and probably in the analysis as well. These plots will help to identify seasonality, any potential phase in period and any other events that may be associated with the time series. A plot of the time series should always be presented, it will not only provide a good representation for the reader but also provide valuable insight into the appropriate model. I would suggest including a plot of each cluster and the combined data. Once the models have been fitted, plotting a line of the actual data and forecast data (without the intervention) may provide valuable insight into the impact of the clusters. 10. The results are very confusing. In the table 1, the column titled number appears to be superfluous, what the denominator was used to obtain the %. In table 2, again what is the use of the column titled number? The table includes a 95% CI, what is the 95% CI is for? Table 3 seems to indicate over testing. An appropriate plot may help to limit the possible effects of over testing. In the first figure, these are not particularly helpful because of the scale of the y-axis, the author should consider a more appropriate starting values, e.g. 200000 to 300000. 11. As I am not sure the statistical analysis is correct, I believe this would impact the results and the conclusions. Should the analysis be changed accordingly, these should all change as well.

REVIEWER	Jacob Simmering University of Iowa Carver College of Medicine, USA 20-Mar-2020
REVIEW RETURNED	20-Mar-2020

GENERAL COMMENTS	Alghamdi and co-authors present an interesting analysis of the effect of changes in the National Health Service (NHS) on

	prescribing rates by non-medical independent prescribers (NMIP), such as nurses and pharmacists, working in primary care settings. An intervention to increase prescribing by NMIP and reduce pressure on general practitioners (GPs) was performed during the window October 2015 to December 2015. The authors present an ARIMA model with an exogenous variable for whether the intervention is in effect to model the effect of adding NIMPs. Specifically, the primary outcome was the number of prescriptions per month filled each month based on prescriptions written by NIMPs. The authors also provide a descriptive overview of the types and quantity of NIMP in the various health boards in Wales. The authors found an unequal distribution of NIMP between the different health boards. Specifically, BCUHB had significantly more nurses and pharmacists as NMIPs than the other health boards. There was a significant increase in the number of RXs filled that were written by NMIP following the intervention. The authors also explored varying implementation lags of 3, 6, 9, 12, or 24 months following the start of the intervention. They found two health boards had a significant increase in RXs written by NMIP at 3 months, 1 at 9 months, and 2 at one year while the final two health boards had no significant increase even after two years. In general, this is an interesting analysis showing a response in provide behavior to policies encouraging RX writing by NMIP. Specific comments follow: Comments: It may be helpful to report the number of NMIP in the different health boards standardized by the population covered by that health board, especially in Figure 3. It may be helpful to report the percentage of prescriptions written by NMIP rather than the raw number of prescriptions due to differing sizes and RX volume between the health boards, especially in Figures 2 and 4 as well as in the main analysis. I am concerned by the extent to which the change in numbers in PTHB drives the results. While some of the other HBs in Figure 4 show an increase in the number of RXs written by NMIPs following 2015, it is unclear if that is simply noise as the effect disappears in 2017. Table and figure captions could be more informative. For instance, Tables 2 and 3 don't mention what the outcome variable of the model was (I believe number of RX filled that were written by NMIP by month). I wonder whether the time-at-which-the-intervention-is-significant analysis reported in Table 3 is really indicating time until adaptation? The different health boards are different sizes – does the effect being significant for BCUHB and HDUHB simply reflect larger size and greater power? Likewise, I'm concerned about the results from PTHB based on the plot shown in Figure 4. There are many abbreviations used throughout the paper which impair readability. Some of these are unavoidable, such as the abbreviations for the various health boards; however, some like AHP are only used a few times. It might be helpful to remove as

	many abbreviations as possible as the paper requires the somewhat cumbersome abbreviations for the health boards and the NMIP.

VERSION 1 – AUTHOR RESPONSE

Our response to Reviewer 1 (Jill Wilkinson) comments (- for the Reviewer comment; * our response to the comment):

- The title, abstract and various places in the manuscript refer to 'prescribing trends' - a phrase I found was a little misleading as a reader because it suggested prescribing trends of particular medicines rather than the volume of prescriptions over time. I suggest re-visiting the use of this phrase and then using it consistently throughout.

* We thank the reviewer for taking the time to suggest changing the term ‘trend’ to alternative options such as prescribing volume. We acknowledge that prescribing volume can be used here but, we believe that trend would be the right term for our study since we are describing the change in prescribing of medicines by NMIPs over time. Also, we follow a study that aimed to investigate nurses prescribing activities, over time, in English primary care settings, which has used the trend term. This study has also used a national primary care prescription database to do a secondary data analysis between 2006-2010. This study entitled ‘Trends over time in prescribing by English primary care nurses: a secondary analysis of a national prescription database’, which is available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3922985/

- On page 8 line 39, the impact of patients not getting their prescription dispensed was 'likely to be small'. This is a significant problem in New Zealand due to the co-payment requirements for each prescription item. A few words of clarification on this point would be helpful here.

* Thank you for this comment. A clarification for this comment is that the prescription charge for people in Wales was abolished in 2007 allowing all patients who were registered with their Welsh GPs to get their prescriptions dispensed from a pharmacy in Wales free of charge. As a result, the impact of non-dispensed items would have been reduced by this, which limiting the financial burden to patients. A reference of this was added to the study (reference number 22, which changed from “Deslandes, P. All Wales Therapeutics and Toxicology Centre (AWTTC) at CVUHB. 2018. Personal communication (conversation with Saeed Alghamdi), 16 May 2018” To “The Welsh Government. National Health Service (Free Prescriptions and Charges for Drugs and Appliances) (Wales) Regulations. [online] Legislation.gov.uk. 2007. Available at: http://www.legislation.gov.uk/wsi/2007/121/made (last accessed 24 April 2020).”

- Page 16 line 47 - suggest re-phrasing the sentence starting 'This is wasteful ...'

* Thank you for this suggestion. I can confirm that the sentence you mention has been amended to “If they were not using their prescribing qualification, this may suggest that HBs need to investigate the reasons for that in order to prevent wasting the time and expenses incurred for training and failure to deliver an improved service to patients.”

- Figure 1: I suggest reducing the unit size on the vertical y-axis to show the increase in number of prescription items more clearly (similar to figure 2).

* Thank you for this comment. If the unit size is reduced on the y axis, it may imply that the change in the number of prescription items was very large. This may mis-represent the data as the increase was only by 7.1%. We believe it would be more appropriate for the figure to remain as it was in order that we don’t give a false impression of how large the increase was. However, upon your kind request we have attached at the end of this document (page 16 and 17) the original figure without changing the scale (figure 1, page 16) and the second figure with the scale being changed as per your kind suggestion (figure 2, page 17) for your information. We would welcome your feedback and if you think that the figure with the scale being changed is the most appropriate to use in this paper, we would be very happy to replace the original one with the second one.

Our response to Reviewer 2 (Emma Graham-Clarke) Comments (- for the Reviewer comment; * our response to the comment):

- The figures/graphs have not translated clearly into the proof document. They may need to be of a higher resolution or different format to make them clearer.

* Thank you for pointing this out. The figures have been changed to a better quality to be clearer as per your kind request.

- I am not familiar with using ARIMA and this paper would benefit from being reviewed by someone with knowledge of the technique to ensure that the results are presented in the most appropriate manner.

* Thank you for your honest thoughts on the methodology. We have reviewed the ARIMA method that we used in our paper and to make sure that we are using the right test analysis for the data we have asked for advice from the right people, particularly an expert statistician, who helped to decide if the ARIMA analysis is the right method or not. According to the expert statistician advice, who have been added as an author for this study, a simpler analysis would be the best option to analyse this kind of data. This test is also another type of interrupted time series by using “the ordinary-least squares regression with Newey-West standard errors and a lag for the autocorrelation structure. The Cumby-Huizinga test for autocorrelation was examined to determine the appropriate autocorrelation structure to be accounted for in the model. The model included pre- and post-intervention trends, as well as a coefficient to examine a change in level immediately post-intervention. The parameter estimates are presented alongside 95% confidence intervals and p-values. The counterfactual trend (i.e. the trend in the absence of the intervention) was examined, and this was compared to the actual observed trend to calculate absolute and relative differences at the end of the observed period (March 2018). Analysis was performed using the itsa command in Stata V16.0” as stated in the methodology section.

- Page 3 – Strengths and limitations. In the proof section, which I have reviewed, this follows on from the abstract. As such the reference numbering is out of sequence with the main paper. If this section is to be published at the beginning of the paper, then I would recommend changing the reference numbers.

* Thank you for this comment. We have reviewed the sequence of all the references as per your kind request.

- You comment that the system ‘only captured prescriptions that were dispensed in the community pharmacies’. My understanding is that CASPA will capture only NHS prescriptions, and not any private prescription. This could be significant when discussing the lack of prescribing by optometrists, as they are private practitioners in general and therefore may have limited access to NHS budgets. I appreciate that some may be directly contracted to provide NHS work, but I am unclear if this is the situation in Wales.

* Thank you for your comment. We were looking at NHS prescriptions, and therefore any private prescriptions issued were not the focus of the study. This is a limitation with regards to private prescriptions written by optometrists for this study and we added it to the limitation section of this study.

Introduction

- Page 4 line 46 – strictly speaking optometrists are not classed as Allied Health Professionals (they are regulated by the General Optical Council)

* Thank you for this comment and this has been reviewed and changed to” Pharmacists, nurses, optometrists and Allied Health Professionals (AHPs) can qualify as non-medical prescribers after completing an advanced prescribing training programme”.

- Page 4 line 50 et seq – apart from nurses and pharmacists, the other non-medical prescribing professions are limited in what they can prescribe. For example, podiatrists are limited to prescribing for conditions associated with the foot, ankle and associated structures, whilst optometrists are limited to prescribing for conditions associated with the eye and surrounding areas.

* Thank you for this comment and this has been reviewed and changed to “This programme lawfully allows these healthcare professionals to prescribe within their area of competence. such as that pharmacists and nurses can prescribe medicines, appliances, and wound dressings as either independent or supplementary prescribers within their clinical area of practice. Some NMIPs are limited to prescribe certain medications within their clinical of speciality, such as optometrists who can only prescribe for eye conditions and surrounding tissues.” We couldn’t elaborate more since we are limited in terms of the word counts.

- Page 5 line 38. Paramedics gained independent prescribing rights in Wales in February 2019. I appreciate that this is outside your research time period, but it is an indicator that non-medical prescribing will continue to expand.

Thank you for this comment. This has been reviewed and this information was added as follows: “The recent healthcare professionals who gained the prescribing authority in Wales were paramedics in 2019.”

Results

- Page 11 line 37 et seq – please check your figures. I don’t believe the figure for the period 2017-8 is correct.

* Thank you for this comment. We apologise for this mistake and we have removed this finding with the new analysis for the data, although the correct number was 40,124 for the period 2017-8.

- Page 14 table 2 – ARIMA is not a statistical technique that I have used, but papers that I have read that have used this technique present the results graphically. Instead you present the pre-intervention and post intervention slope figures, but it is unclear how is these are derived. I think this aspect of the results presentation requires a review to make it clearer for the reader.

* Thank you for this comment. With the new analysis, we have removed the table and changed figure 4 to two figures (a and b) to show the differences between HBs over time with a vertical line at the time of the intervention (the introduction of primary care clusters at October 2015). We have also put the findings of the analysis and a figure for each Health Board as a supplementary material since we are limited in the number of figures (as per the journal instructions).

- Page 15 table 3 – this nicely demonstrates the increasing uptake across the health boards at different time points.

* Thank you for your kind comment. However, we have removed it and replaced it with the new analysis.

- Figures 1 and 2 – these pair of graphs are striking and would probably benefit from being presented jointly. The numbers of NMIP prescriptions are probably too small to make a combined graph feasible but please investigate some other means of presentation.

* Thank you for your comments. However, Figure 1 shows the prescribing by all prescribers in Wales, including doctors and NMIPs, whereas, Figure 2 shows the prescribing by NMIPs only and therefore, it is not appropriate to join both figures.

Discussion

- Page 16 line 33 et seq – you rightly comment that therapeutic radiographers are unlikely to prescribe in primary care. The other professions that you mention may be prescribing but for a variety of reasons the activity is not picked up in your study, for example, prescribing privately or prescribing for treatment at the point of care. This warrants further consideration and elaboration in your discussion.

* Thank you for your comments. This has been reviewed and changed to ”However, the other professions, such as chiropodists, podiatrists and optometrists, could potentially be working in primary care settings but do not appear to have issued NHS prescriptions as they could have been prescribing medications for their patients within private hospitals, at point of care or not using their prescribing qualification. If they were not using their prescribing qualification, this may suggest that HBs need to investigate the reasons for that in order to prevent wasting the time and expenses incurred for training and failure to deliver an improved service to patients.”

- You discuss the varying geographical areas and numbers of GPs that each health board covers. Looking at table 1, I am struck that the PTHB, whilst it has the smallest percentage of prescribed items by NMIPs, actually has more prescribed items per 100,000 population than two of the other

health boards. This also links to figure 4, where PTHB stands out quite dramatically in the increase in prescriptions and the number per 100,000 population. You don't comment at all in your discussion about this and I wondered what your views were.
* Thank you for pointing this out. A justification for this point was added to the discussion section (which is that: "Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales that has the lowest number of populations compared to other HBs. An equivalent increase in the number of prescribers and items would therefore produce a bigger percentage change than in a larger HB. However, the largest increase in the trend of the prescribing items in this HB over the last two years of the study period may be explained by the increase in the number of NMIPs. Moreover, PTHB only has primary care services, so whilst other HBs may have been training IPs in both primary and secondary care settings, the focus in PTHB would have been primary care only, which may have resulted in a greater change. However, due to the nature of the database used, it was not possible to investigate this further and this could be the focus of future work."
Typographical comments
- Page 1, line 7 – this would read easier with a comma after 'clusters'.
*Thank you for your comment. This has been reviewed and a comma was added as suggested.
- Page 6 line 19 – I think this needs a comma after 'primary care services'.
* Thank you for your comment. This has been reviewed and a comma was added as suggested.
- Page 8 line 30 – I would be inclined to add NHS to the comment 'Welsh prescriptions for use in primary care', to indicate that private prescriptions are excluded.
* Thank you for your comment. This has been reviewed and "NHS" was added as suggested.
- Page 8 line 43 – would this be clearer if it read 'the number of items refers to each single item prescribed…'?
* Thank you for your comment. This has been reviewed and changed as suggested to "The number of items refers to each single item prescribed by a prescriber on a prescription form ".
- Page 10 line 12 – should read 'Chief Pharmaceutical Officer'
* Thank you for your comment. This has been reviewed and changed to "Chief Pharmaceutical Officer".
- Reference 23, 24, 31 – the web links doesn't seem to work – please check your reference links
* Thank you for your comment. This has been reviewed and changed so that the reference links are working fine now.

Our response to Reviewer 3 (Nolwenn LE MEUR) Comments (- for the Reviewer comment; * our response to the comment):
- Major:
- The number of NMIPs and their volume of prescribing in primary care has increased, following the recommendations. However, as mentioned by the authors, it does not prove a better quality of care. Indeed, the numbers in Figure 1 and Figure 2 and paragraphs 1 and 2 of the results seem to show that dispensing of drugs by NMIPs increases but that dispensing of drugs by GPs do not decreases by the same amount. Do you observe an over-prescription mechanism or is it a response to long lasting absence of care (seeking)?
* Thank you for this comment. We acknowledge that the NMIPs' prescribing was added on to GP prescribing rather than replacing it, which we don't know the exact reason for this, and it is beyond the scope of the study and would form the basis of further work.
- In table 1,
1) the number of GPs, the number of NMIPs per health board, the number of NMIPs per 100,000 inhabitants per health board could be interesting to have in parallel to the number of items prescribed.
* Thank you for this insightful comment. Unfortunately, it is not possible for us to present this data as the number of GPs and NMIPs per HB, on a yearly basis, are not available to us.

2) Is the number of prescribed items by NMIPs correlated with the number of NMIPs per health board?
* Thank you for this insightful comment. Unfortunately, it is not possible for us to present this data as the number of NMIPs per HB, on a yearly basis, are not available to us in order to investigate this kind of correlation.
3) Does the lack of GPs correlate with the % of the prescribed items by NMIPs in each BH?
* Thank you for your comment. We didn't calculate it based on the number of GPs and we didn't look for the correlation between the number of GPs and the prescribing of items by NMIPs in each HB since the number of GPs were not available on yearly basis for us.
4) Could you calculate the % of the (same) prescribed items by GP?
* Thank you for your comment. We didn't calculate the % of the prescribed items by NMIPs by GP since the number of GPs were not available on yearly basis for us.
- In table 2,
1) If I am correct the 95%CI is the confidence interval for the difference? If so, it should be clearer in the table header or caption?
* Thank you for your comment. We have removed this table as we have reviewed the ARIMA method that we used in our paper. To make sure that we are using the right test analysis for the data we have asked for advice from the right people, particularly an expert statistician, who helped to decide if the ARIMA analysis is the right method or not. According to the expert statistician's advice, who have been added as an author for this study, a simpler analysis would be the best option to analyse this kind of data. This test is another type of interrupted time series by using "the ordinary-least squares regression with Newey-West standard errors and a lag for the autocorrelation structure. The Cumby-Huizinga test for autocorrelation was examined to determine the appropriate autocorrelation structure to be accounted for in the model. The model included pre- and post-intervention trends, as well as a coefficient to examine a change in level immediately post-intervention. The parameter estimates are presented alongside 95% confidence intervals and p-values. The counterfactual trend (i.e. the trend in the absence of the intervention) was examined, and this was compared to the actual observed trend to calculate absolute and relative differences at the end of the observed period (March 2018). Analysis was performed using the itsa command in Stata V16.0" as stated in the methodology section, and the ARIMA tables were replaced by tables of the new analysis.
2) I am questioning the ARIMA model for the PTHB data as looks strange in Table 3 and Figure 4 (see comments on Figure 4)
* Thank you for pointing this out. Although the ARIMA analysis was changed to the ordinary-least squares regression, we reviewed the data of the PTHB from the original source and it was correct. A justification for this strange finding was added to the discussion section (which is that: "Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales that has the lowest number of populations compared to other HBs. An equivalent increase in the number of prescribers and items would therefore produce a bigger percentage change than in a larger HB. However, the largest increase in the trend of the prescribing items in this HB over the last two years of the study period may be explained by the increase in the number of NMIPs. Moreover, PTHB only has primary care services, so whilst other HBs may have been training IPs in both primary and secondary care settings, the focus in PTHB would have been primary care only, which may have resulted in a greater change. However, due to the nature of the database used, it was not possible to investigate this further and this could be the focus of future work."
- Figure 3,
1) for comparison purposes between HB, more that the number of NMIPS it would be interesting to visualized the number of each NMIPs per 100,000 inhabitants in each HB or relative to the number of GPs.
* Thank you for this comment. Unfortunately, it is not possible for us to present this data as the number of NMIPs per HB on a yearly basis, as well as the number of GPs in each HBs, are not available to us in order to investigate this kind of correlation.

2) Indeed, is there a relationship between the evolution of the number of NMIPS and the number of GPs in the different HB?
* Thank you for this comment. Unfortunately, it is not possible for us to present this data as the number of NMIPs per HB on a yearly basis, as well as the number of GPs in each HBs, are not available to us in order to investigate this kind of correlation.
- Figure 4 the sharp increases in PTHB is strange. As the data been verified? If that is a true phenomenon, is there a rational explanation?
* Thank you for pointing this out. We have spoken to the health board and the data is correct, however investigating further was beyond the original scope of the study itself. A possible justification for this point was added to the discussion section (which is that: “Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales that has the lowest number of populations compared to other HBs. An equivalent increase in the number of prescribers and items would therefore produce a bigger percentage change than in a larger HB. However, the largest increase in the trend of the prescribing items in this HB over the last two years of the study period may be explained by the increase in the number of NMIPs. Moreover, PTHB only has primary care services, so whilst other HBs may have been training IPs in both primary and secondary care settings, the focus in PTHB would have been primary care only, which may have resulted in a greater change. However, due to the nature of the database used, it was not possible to investigate this further and this could be the focus of future work.”
- In the discussion,
1) As suggested for the early adopters, could the time to adoption of the recommendations for late adopters be linked to the % of GPs in the HB?
* Thank you for this insightful comment. Unfortunately, we couldn’t link it to the % of GPs in each HB since we don’t have the number of GPs per HB.
2) It could also be discussed that the populations covered by the HB might differ in terms of pathologies and may not have same needs therefore may not seek the health care (professionals and prescriptions)
* Thank you for suggesting this point. Unfortunately, we don’t have the evidence to discuss that as well as it is beyond the aim of this paper.
- Minor:
1) In the abstract, the acronym HB is being written in full letters
* Thank you for this comment. This has been reviewed and the acronym HBs was added after the full letters of the term (Health Boards).
2) P11 line 42 it would be more readable to write 2017-2018 instead of 17-18 in the sentence “…while the largest increase was from the last quarter of 2015 to 17-18”
* Thank you for this comment. This has been reviewed and with the new analysis, this sentence has been removed.
3) Reference 35 it should be Available and not “Avilable”
* Thank you for this comment. This has been reviewed and Avilable was changes to Available as requested.

Our response to Reviewer 4 (Dr Kara Stevens) Comments (- for the Reviewer comment; * our response to the comment):
1. The objective implies that this is a description of the number of NIMPs prescriptions. However, with it appears to be an evaluation of an “intervention” (e.g. policy change). I think actual objective of the study was to compare the prescription patterns of NIMPs before and after the implementation of primary care clusters for Wales and each cluster.
* Thank you for this comment. The exact objective of this study has been reviewed and changed to “This research aimed to identify the number of non-medical independent prescribers (NMIPs) in primary care in Wales and describe their prescribing trend of items between 2011 and 2018, in order to compare their prescribing pattern before and after the implementation of primary care clusters for

Wales.”. However, it is not to compare prescribing trends between clusters, but to compare the prescribing trends between the seven Health Boards in Wales before and after the implementation of the primary care clusters.
2. In the abstract, I do not believe some of the text is in the correct sections. For example, it seems the objective is under the design. I would say the design was quasi-experimental, analysed using ITSA.
* Thank you for pointing this out. We have reviewed this and changed the sequence of the abstract so that the objective is under the design of this study as per your suggestion. The design of the study was also reviewed and changes to “Retrospective secondary data analysis and Interrupted Time Series (ITS) analysis in order to compare prescribing by NMIPs pre and post-implementation of primary care clusters across Wales” as per your kind suggestion.
3. Depending on what the actual research question is has implications on what sort of statistical methodology should be used to answer this question. If the aim was simply to describe NMIPs prescriptions then an ITSA would not be appropriate.
* Thank you for providing this point. The ARIMA analyses was used to compare between the seven Health Boards before and after the implementation of the primary care clusters in order to show the difference in slope between the pre and post-intervention (pre and post-implementation of primary care clusters) changes in the trend of prescribing by NMIPs. This was to understand whether the changes in prescribing over time occurred at a gradual or abrupt onset, step changes were significant or not. However, We have reviewed the ARIMA method that we used in our paper and to make sure that we are using the right test analysis for the data we have asked for advice from the right people, particularly an expert statistician, who helped to decide if the ARIMA analysis is the right method or not. According to the expert statistician advice, who have been added as an author for this study, a simpler analysis would be the best option to analyse this kind of data. This test is also another type of interrupted time series by using “the ordinary-least squares regression with Newey-West standard errors and a lag for the autocorrelation structure. The Cumby-Huizinga test for autocorrelation was examined to determine the appropriate autocorrelation structure to be accounted for in the model. The model included pre- and post-intervention trends, as well as a coefficient to examine a change in level immediately post-intervention. The parameter estimates are presented alongside 95% confidence intervals and p-values. The counterfactual trend (i.e. the trend in the absence of the intervention) was examined, and this was compared to the actual observed trend to calculate absolute and relative differences at the end of the observed period (March 2018). Analysis was performed using the itsa command in Stata V16.0” as stated in the methodology section.
4. Information on what data was obtained appears to be thorough. However, some of the wording is a little confusing, e.g. “The number of items refers to a single item…”
* Thank you for kind comment about the information of the data. The number of items refers to each single item prescribed by a prescriber on a prescription form for a patient as obtained for the reference.
6. I am not sure having outcomes reported per 100,000 is entirely appropriate all the way through. I would consider performing all the analysis and presenting most of the results in values closer to the actual data, then presenting in 100,000 during the discussion, if comparing with other studies.
* Thank you for your comment. We used the actual data of the number of items for the new analysis using “the ordinary-least squares regression for all HBs. Whereas, the number of items per 100,000 population was only used to present the data in figures 1 and 4a and 4b in order to compare the trends of prescribing items between HBs and in all Wales in order to take the population in consideration as some Health Boards such as BCUHB has the largest number of populations compared to other Health Boards, which showed a high increase in the number of items prescribed by NMIPs compared to other HBs. Therefore, it was better to use the 100, 000 population, which has also been advised by the statistical team in the University. The number of populations for each health board was obtained on yearly basis (from 2011 to 2018) from the StatsWales website (https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Local-Health-Boards/populationestimates-by-lhb-age).

7. The description for ITSA does not appear to be correct. The ARIMA component is used to describe the residuals of a regression model, plots of the ACF and partial ACF are probably best as part of supplementary material, but would demonstrate the rigor of statistical analysis and ideally included. The regression model should be fully specified, outlining the phase period, intercept, trend, interaction etc. I would urge the researchers to use appropriate statistical packages, e.g. R or STATA, and reference exactly what was used to perform the analysis for transparency. For an adequate estimate of change in trend, there should be 8 observations pre and 8 observations post intervention (not including any phase in period).

* Thank you for pointing this out. We have reviewed the ARIMA method that we used in our paper and to make sure that we are using the right test analysis for the data we have asked for advice from the right people, particularly an expert statistician, who helped to decide if the ARIMA analysis is the right method or not. According to the expert statistician advice, who have been added as an author for this study, a simpler analysis would be the best option to analyse this kind of data. This test is also another type of interrupted time series by using “the ordinary-least squares regression with Newey-West standard errors and a lag for the autocorrelation structure. The Cumby-Huizinga test for autocorrelation was examined to determine the appropriate autocorrelation structure to be accounted for in the model. The model included pre- and post-intervention trends, as well as a coefficient to examine a change in level immediately post-intervention. The parameter estimates are presented alongside 95% confidence intervals and p-values. The counterfactual trend (i.e. the trend in the absence of the intervention) was examined, and this was compared to the actual observed trend to calculate absolute and relative differences at the end of the observed period (March 2018). Analysis was performed using the itsa command in Stata V16.0” as stated in the methodology section.

8. They should reference statistical software and methods used.

* Thank you for your comment. The new statistical analysis was by using the ordinary-least squares regression with Newey-West standard errors and a lag for the autocorrelation structure. The Cumby-Huizinga test for autocorrelation was examined to determine the appropriate autocorrelation structure to be accounted for in the model. Analysis was performed using the itsa command in Stata V16.0. The following reference was used as a guidance to conduct the analysis: Linden A. Conducting interrupted time-series analysis for single-and multiple-group comparisons. The Stata Journal. 2015 Jun;15(2):480-500.

9. Firstly researchers need to plot the data, and it is often advised to add a vertical line identify the time point when the policy change was made. From the description of the data, it seems that researchers have monthly data, which should be used in this plot and probably in the analysis as well. These plots will help to identify seasonality, any potential phase in period and any other events that may be associated with the time series. A plot of the time series should always be presented, it will not only provide a good representation for the reader but also provide valuable insight into the appropriate model. I would suggest including a plot of each cluster and the combined data. Once the models have been fitted, plotting a line of the actual data and forecast data (without the intervention) may provide valuable insight into the impact of the clusters.

* Thank you for pointing this out. With the new analysis, we have changed figure 2 and figure 4 (figure 4a and figure 4b) to show the differences between HBs over time with a vertical line at the time of the intervention (the introduction of primary care clusters at October 2015). We have also put the findings of the analysis and a figure for each Health Board as a supplementary material since we are limited in the number of figures as per the journal instructions).

10. The results are very confusing. In the table 1, the column titled number appears to be superfluous, what the denominator was used to obtain the %. In table 2, again what is the use of the column titled number? The table includes a 95% CI, what is the 95% CI is for? Table 3 seems to indicate over testing. An appropriate plot may help to limit the possible effects of over testing. In the first figure, these are not particularly helpful because of the scale of the y-axis, the author should consider a more appropriate starting value, e.g. 200000 to 300000.

*Thank you for your comments. Table one was changed to table 2 and the column titled number was taken out as per your kind suggestion. A clarification of the % of items prescribed by NMIPs in each

HB was added to the table, which was that “The percentage of the prescribed items by NMIPs in each HB was calculated based on the total number of items prescribed by NMIPs in all Wales”.
Regarding Table 2 and Table 3 (that has been submitted in the first submission) have now been removed since the analysis has been changed and its findings were removed from the study
In Figure 1: Thank you for this comment. If the unit size is reduced on the y axis, it may imply that the change in the number of prescription items was very large. This may mis-represent the data as the increase was only by 7.1%. We believe it would be more appropriate for the figure to remain as it was in order that we don’t give a false impression of how large the increase was. However, upon your kind request we have attached at the end of this document (page 16 and 17) the original figure without changing the scale (figure 1, page 16) and the second figure with the scale being changed as per your kind suggestion (figure 2, page 17) for your information. We would welcome your feedback and if you think that the figure with the scale being changed is the most appropriate to use in this paper, we would be very happy to replace the original one with the second one.
11. As I am not sure the statistical analysis is correct, I believe this would impact the results and the conclusions. Should the analysis be changed accordingly, these should all change as well.
* Thank you for pointing this out. As stated above, We have reviewed the ARIMA method that we used in our paper and to make sure that we are using the right test analysis for the data we have asked for advice from the right people, particularly an expert statistician, who helped to decide if the ARIMA analysis is the right method or not. According to the expert statistician advice, who have been added as an author for this study, a simpler analysis would be the best option to analyse this kind of data. This test is also another type of interrupted time series by using “the ordinary-least squares regression with Newey-West standard errors and a lag for the autocorrelation structure. The Cumby-Huizinga test for autocorrelation was examined to determine the appropriate autocorrelation structure to be accounted for in the model. The model included pre- and post-intervention trends, as well as a coefficient to examine a change in level immediately post-intervention. The parameter estimates are presented alongside 95% confidence intervals and p-values. The counterfactual trend (i.e. the trend in the absence of the intervention) was examined, and this was compared to the actual observed trend to calculate absolute and relative differences at the end of the observed period (March 2018). Analysis was performed using the itsa command in Stata V16.0” as stated in the methodology section. The discussion and conclusion sections were adjusted according to that.

Our response to Reviewer 5 (Jacob Simmering) Comments (- for the Reviewer comment; * our response to the comment):
- It may be helpful to report the number of NMIP in the different health boards standardized by the population covered by that health board, especially in Figure 3.
* Thank you for your comments. We didn’t calculate the number of NMIPs per 100,000 inhabitants per health board as we only have the total number of NMIPs in each HB over the last seven years from the source of the data, but not on yearly basis.
* It may be helpful to report the percentage of prescriptions written by NMIP rather than the raw number of prescriptions due to differing sizes and RX volume between the health boards, especially in Figures 2 and 4 as well as in the main analysis.
* Thank you for your insightful comment. We have calculated some of the findings using the percentages and reported together with the raw data in the main text body. We have reviewed the ARIMA method that we used in our paper and to make sure that we are using the right test analysis for the data we have asked for advice from the right people, particularly an expert statistician, who helped to decide if the ARIMA analysis is the right method or not. According to the expert statistician advice, who have been added as an author for this study, a simpler analysis would be the best option to analyse this kind of data. This test is also another type of interrupted time series by using “the ordinary-least squares regression with Newey-West standard errors and a lag for the autocorrelation structure. The Cumby-Huizinga test for autocorrelation was examined to determine the appropriate

autocorrelation structure to be accounted for in the model. The model included pre- and post-intervention trends, as well as a coefficient to examine a change in level immediately post-intervention. The parameter estimates are presented alongside 95% confidence intervals and p-values. The counterfactual trend (i.e. the trend in the absence of the intervention) was examined, and this was compared to the actual observed trend to calculate absolute and relative differences at the end of the observed period (March 2018). Analysis was performed using the itsa command in Stata V16.0" as stated in the methodology section. With the new analysis, we have changed figure 2 and figure 4 (figure 4a and figure 4b) to show the differences between HBs over time with a vertical line at the time of the intervention (the introduction of primary care clusters at October 2015). We have also put the findings of the analysis and a figure for each Health Board as a supplementary material since we are limited in the number of figures as per the journal instructions).

- I am concerned by the extent to which the change in numbers in PTHB drives the results. While some of the other HBs in Figure 4 show an increase in the number of RXs written by NMIPs following 2015, it is unclear if that is simply noise as the effect disappears in 2017.

* Thank you for pointing this out. A justification for this point was added to the discussion section (which is that: "Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales that has the lowest number of populations compared to other HBs. An equivalent increase in the number of prescribers and items would therefore produce a bigger percentage change than in a larger HB. However, the largest increase in the trend of the prescribing items in this HB over the last two years of the study period may be explained by the increase in the number of NMIPs. Moreover, PTHB only has primary care services, so whilst other HBs may have been training IPs in both primary and secondary care settings, the focus in PTHB would have been primary care only, which may have resulted in a greater change. However, due to the nature of the database used, it was not possible to investigate this further and this could be the focus of future work."

- Table and figure captions could be more informative. For instance, Tables 2 and 3 don't mention what the outcome variable of the model was (I believe number of RX filled that were written by NMIP by month).

* Thank you for your comment. With the new analysis, we have removed both tables and replaced it by Table 1 and Table 2 that have different findings, and we have checked its caption details to ensure it has enough information for the reader.

- I wonder whether the time-at-which-the-intervention-is-significant analysis reported in Table 3 is really indicating time until adaptation? The different health boards are different sizes – does the effect being significant for BCUHB and HDUHB simply reflect larger size and greater power? Likewise, I'm concerned about the results from PTHB based on the plot shown in Figure 4.

* Thank you for your comment. With the new analysis, we have removed this table. However, we have reviewed the data and are happy that they are correct. As stated in the third point, a justification for this point was added to the discussion section (which is that: "Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales that has the lowest number of populations compared to other HBs. An equivalent increase in the number of prescribers and items would therefore produce a bigger percentage change than in a larger HB. However, the largest increase in the trend of the prescribing items in this HB over the last two years of the study period may be explained by the increase in the number of NMIPs. Moreover, PTHB only has primary care services, so whilst other HBs may have been training IPs in both primary and secondary care settings, the focus in PTHB would have been primary care only, which may have resulted in a greater change. However, due to the nature of the database used, it was not possible to investigate this further and this could be the focus of future work."

- There are many abbreviations used throughout the paper which impair readability. Some of these are unavoidable, such as the abbreviations for the various health boards; however, some like AHP are only used a few times. It might be helpful to remove as many abbreviations as possible as the paper requires the somewhat cumbersome abbreviations for the health boards and the NMIP.

* Thank for your comment and we have reviewed it and removed unnecessary abbreviations such as "AHPs" as per your kind request.

VERSION 2 – REVIEW

REVIEWER	Emma Graham-Clarke Sandwell and West Birmingham NHS Trust United Kingdom
REVIEW RETURNED	18-Jun-2020

GENERAL COMMENTS	Thank you for inviting me to review this paper. I note the changes that you have made in response to previous reviewers' comments. Thank you for seeking statistical advice regarding which statistical test is most appropriate to use. The page numbers on the manuscript are inconsistent so I have taken the PDF page numbers as a guide. Abstract. Page 3, line 7 et seq The first bullet point may read better as: This is the first study' using a secondary database analysis, which has … Please check when abbreviations are defined, and if they are needed. For example, you use NMIPs in the design section of the abstract but define it later on. You also define independent prescribers as IP, but then don't use that abbreviation again in the abstract. Methods. Page 10? Line 13 et seq This sentence reads a little awkwardly 'They agreed the intervention phase should be after six months of the provided funding by the Government to HBs, which means the October 2015, to allow ….'. my interpretation is that you mean: 'They agreed the intervention phase began six months after the provided funding by the Government to HBs, meaning October 2015, to allow for an appropriate time for each HB to train NMIPs.' Is this correct? please amend your wording so that it is clear what you mean. Results. Page 12? The total no of NMIPs. I am confused with this paragraph. At the beginning you state that there are 21 physiotherapist prescribers, but in your final sentence you state that the numbers increased to 17 across the boards. The accompanying graph shows 21 physiotherapists. Please check your figures and clarify any discrepancy. Discussion. Page 18? Line 8 et seq This sentence is also a little awkward; 'Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales that has the lowest number of populations compared to other HBs.' I think you meant: 'Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales with the lowest population compared to other HBs.' Please check the interpretation and amend your sentence to clarify your point. Likewise this sentence is difficult to understand: 'However, the largest increase in the trend of the prescribing items in this HB over the last two years of the study period may be explained by

	the increase in the number of NMIPs.' Do you mean 'large' instead of 'largest'? Page 18? Line 54 et seq Please amend the grammar of the sentence starting: 'However, these studies are outdated…' Figure 1 Although you prefer the figure with the axis starting from 0, I believe the change in prescribing is better illustrated by your alternative figure. Figure 2 The predicted line and the actual figures only differ at the end of the study period. They do not appear to support the finding of a 60% increase in prescribing with the advent of NMP. Please review.

REVIEWER	Nolwenn Le Meur Ecole des Hautes Etudes en Sante Publique
REVIEW RETURNED	15-Jun-2020

GENERAL COMMENTS	As written by the authors "The aim of this study was to identify the number of NMIPs in Wales and describe their prescribing volume (from April 2011 to March 2018) as a whole, as well as within the seven HBs, before and after the implementation of primary care clusters." 1) Identify the number of NMIPs in Wales If I understood correctly, in Figure 3 the number of NMIPs identified is the number of NMIPS who prescribed at least one item between April 2011 in March 2018? This does not mean that in 2018 in BCUHB the number of NMIPs nurses is 204? It could be lower? 2) Describe their prescribing volume As answered by the authors, I understand that the authors do to have all the data in hands to compute the proposed indicators. However, I am worried that the description of the prescribing trends over time by NIMPs using solely the absolute total number of items is misleading. I am concerned that the positive trend estimated by the evolution of the total number of items prescribed by NMIPs is over-estimated. The authors should express the evolution in rates as the proportion of items prescribed by NMIPs out of all the prescriptions prescribed by all prescribers as written lines 37-38 p 12. This might adjust for the potential overall increase of prescriptions over the years due to demographic changes (in population and in health care providers). In fact, is the current ITS model adjusted for the variation in the number of prescribers and the covered population before and after the intervention? If not, the observed increase is probably over-estimated. It should be discussed in the discussion. In addition, the extreme numbers in PTHB probably drive the results. The authors should try to redo the model without PTHB data to assess that effect. 3) Within the seven HBs, before and after the implementation of primary care clusters

	To be comparable, the HB should be described not only on the overall population they covered but also in terms of their number of clusters and the evolution of their number of prescribers (NMIPS and medical prescribers) over the 7-year period or before and after the intervention. Otherwise it is difficult to disentangle if the observed increases in prescribing (if any) and the observed variations between HB are due to the evolution of prescribers, clusters or population. Overall, the question that remain is whether NMIPs are complementary to medical prescribers or prescribe potentially more? The latest would explain part of the observed increase in the absolute number of prescribed items.

REVIEWER	Jacob Simmering University of Iowa, USA
REVIEW RETURNED	19-Jun-2020

GENERAL COMMENTS	The revisions and responses to my comments on the prior version seem adequate. I prefer the OLS approach for ITS analysis reported in this version to the ARIMA approach previously used. The analytical framework and model is clearer and, as a result, the results more interpretable relative to using ARIMA and the use of robust standard errors/auto-correlation lag structure is sufficient to address any concerns about the errors being properly estimated. I would echo reviewer 1's comments about Figure 1 not having the intended impact due to the relatively large range on the y-axis. The authors state that a alternative version was included but I was unable to find the alternative figure.

VERSION 2 – AUTHOR RESPONSE

Our response to Reviewer 2 (Emma Graham-Clarke) Comments (- for the Reviewer comment; * our response to the comment):

- Abstract. Page 3, line 7 et seq: The first bullet point may read better as: This is the first study' using a secondary database analysis, which has …

* Our response: Thank you for suggesting this point. We have changed this sentence as per your kind suggestion to "This is the first study using a secondary database analysis, which has provided insights and empirical findings on the prescribing pattern of medicines by non-medical independent prescribers (NMIPs) over time in primary care in Wales."

- Please check when abbreviations are defined, and if they are needed. For example, you use NMIPs in the design section of the abstract but define it later on. You also define independent prescribers as IP, but then don't use that abbreviation again in the abstract.

* Our response: Thank you for pointing this out. We have reviewed the abbreviations and amended it as per your kind request. Regarding the IP abbreviation in the abstract section, we have used it in the introduction and results part of the abstract, therefore we kept it.

- Methods. Page 10? Line 13 et seq: This sentence reads a little awkwardly ‘They agreed the intervention phase should be after six months of the provided funding by the Government to HBs, which means the October 2015, to allow ….’. my interpretation is that you mean: ‘They agreed the intervention phase began six months after the provided funding by the Government to HBs, meaning October 2015, to allow for an appropriate time for each HB to train NMIPs.’ Is this correct? please amend your wording so that it is clear what you mean.

* Our response: Thank you for providing your comment and suggestion for this point. Your interpretation is right, and we have changed it as per your kind suggestion to “They agreed the intervention phase began six months after the provided funding by the Government to HBs, meaning October 2015, to allow for an appropriate time for each HB to train NMIPs.”

- Results. Page 12? The total no of NMIPs. I am confused with this paragraph. At the beginning you state that there are 21 physiotherapist prescribers, but in your final sentence you state that the numbers increased to 17 across the boards. The accompanying graph shows 21 physiotherapists. Please check your figures and clarify any discrepancy.

* Our response: Thank you for point this out. The 21 number of physiotherapist prescribers is representing the total number of physiotherapist prescribers who prescribed at least one item over time from April 2011 to March 2018. We have calculated the total number based on their prescriber numbers and we have excluded any repeated prescriber number over time. Whereas, 17 is the number of physiotherapist prescribers who prescribed items only in March 2018 (not over all the study period, but only on one month which is the last month of the study “March 2018”).

- Discussion. Page 18? Line 8 et seq: This sentence is also a little awkward; ‘Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales that has the lowest number of populations compared to other HBs.’ I think you meant: ‘Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales with the lowest population compared to other HBs.’ Please check the interpretation and amend your sentence to clarify your point. Likewise this sentence is difficult to understand: ‘However, the largest increase in the trend of the prescribing items in this HB over the last two years of the study period may be explained by the increase in the number of NMIPs.’ Do you mean ‘large’ instead of ‘largest’?

* Our response: Thank you for providing your comment and suggestion for this point. We have changed as you have suggested to “Although PTHB showed the lowest number of items prescribed by NMIPs over the study period, it is the smallest geographical area in Wales with the lowest population compared to other HBs”. Also, we changed “largest” to “large” as it was a typo mistake.

- Page 18? Line 54 et seq: Please amend the grammar of the sentence starting: ‘However, these studies are outdated…’

* Our response: Thank you for providing this comment. As per your kind request, we have reviewed the grammar of this sentence “However, these studies are outdated given the pace of change as well as not been conducted in Wales in particular, which may not reflect recent practice and policies.” and changed to “However, these studies are outdated given the pace of change. Moreover, it has not been conducted in Wales in particular, which may not reflect recent practice and policies in this country.”

- Figure 1: Although you prefer the figure with the axis starting from 0, I believe the change in prescribing is better illustrated by your alternative figure.

* Our response: Thank you for suggesting this point. We have changed figure 1 to the alternative figure as per your recommendation.

- Figure 2: The predicted line and the actual figures only differ at the end of the study period. They do not appear to support the finding of a 60% increase in prescribing with the advent of NMP. Please review.

* Our response: Thank you for pointing this out. The 60% figure compares the predicted observation point in March 2018 (based on the dashed line following in implementation of primary care clusters) with the counterfactual predicted observation point in March 2018 had the pre-implementation trend continued. The observed total number of dispensed prescriptions by NMIPs in March 2018 is higher than the predicted line, so the 60% increase appears to be a conservative estimate.

Our response to Reviewer 3 (Nolwenn LE MEUR) Comments (- for the Reviewer comment; * our response to the comment):

1) Identify the number of NMIPs in Wales: If I understood correctly, in Figure 3 the number of NMIPs identified is the number of NMIPS who prescribed at least one item between April 2011 in March 2018? This does not mean that in 2018 in BCUHB the number of NMIPs nurses is 204? It could be lower?

* Our response: Thank you for pointing this out. Figure 3 illustrates the total number of NMIPs (pharmacists, nurses and physiotherapists) who prescribed at least one item from April 2011 to March 2018 in primary care in Wales in different HBs. It shows the total number of NMIPs over the study period (not only in 2018) based on their prescriber numbers and we have excluded any repeated prescriber number over time. For example, 204 is representing the total number of nurses who each one of them prescribed at least one item over the study period. Also, the number of NMIPs could in fact be greater than 204 as there could be other NMIPs who are qualified but haven’t used their qualification.

2) Describe their prescribing volume: As answered by the authors, I understand that the authors do to have all the data in hands to compute the proposed indicators. However, I am worried that the description of the prescribing trends over time by NIMPs using solely the absolute total number of items is misleading. I am concerned that the positive trend estimated by the evolution of the total number of items prescribed by NMIPs is over-estimated. The authors should express the evolution in rates as the proportion of items prescribed by NMIPs out of all the prescriptions prescribed by all prescribers as written lines 37-38 p 12. This might adjust for the potential overall increase of prescriptions over the years due to demographic changes (in population and in health care providers). In fact, is the current ITS model adjusted for the variation in the number of prescribers and the covered population before and after the intervention? If not, the observed increase is probably over-estimated. It should be discussed in the discussion. In addition, the extreme numbers in PTHB probably drive the results. The authors should try to redo the model without PTHB data to assess that effect.

* Our response: Thank you for providing this comment. The aim of this study was to describe the prescribing trend of items by NMIPs between 2011 and 2018, in order to compare their prescribing pattern before and after the implementation of primary care clusters for Wales. Therefore, the aim was not to compare prescribing trends by NMIPs with other or all prescribers, but to review the evolution of NMIPs as a discrete entity. Also, we have conducted two sensitivity analyses 1: excluding PTHB (Table S3 and Figure S8) and 2: excluding PTHB and the final two months of observations (Table S4 and Figure S9) as illustrated in the supplementary file. These two analyses show that our findings are robust, and our overarching conclusions are unaffected by these sensitivity analyses. There was a change in dispensed prescriptions by NMIPs following the implementation of primary care clusters. After excluding Powys, there was evidence of both a step and slope change.

3) Within the seven HBs, before and after the implementation of primary care clusters

To be comparable, the HB should be described not only on the overall population they covered but also in terms of their number of clusters and the evolution of their number of prescribers (NMIPS and medical prescribers) over the 7-year period or before and after the intervention. Otherwise it is difficult to disentangle if the observed increases in prescribing (if any) and the observed variations between HB are due to the evolution of prescribers, clusters or population.

* Our response: Thank you for this insightful comment. The objective of this study was to describe the prescribing trend of items by NMIPs between 2011 and 2018, in order to compare their prescribing pattern before and after the implementation of primary care clusters for Wales. Therefore, the objective is not to compare prescribing trends between clusters, but to compare the prescribing trends between the seven Health Boards in Wales before and after the implementation of the primary care clusters. Moreover, it is not possible for us to compare prescribing of items by NMIPs between clusters since we don't have this kind of data as we only have the data of HBs.

- Overall, the question that remain is whether NMIPs are complementary to medical prescribers or prescribe potentially more? The latest would explain part of the observed increase in the absolute number of prescribed items.

* Our response: Thank you for this comment. Since the aim of this study was to describe the prescribing trend of items by NMIPs in primary care in Wales before and after the implementation of primary care clusters, we cannot determine if the NMIPs' prescribing was added on to GP prescribing or replacing it. Therefore, we don't know the exact reason for this as it is beyond the scope of the study and this will form the basis for further work.

Our response to Reviewer 5 (Jacob Simmering) Comments (- for the Reviewer comment; * our response to the comment):

- The revisions and responses to my comments on the prior version seem adequate.

* Our response: Thank you very much and we are glad that we have managed to address your concerns.

- I prefer the OLS approach for ITS analysis reported in this version to the ARIMA approach previously used. The analytical framework and model is clearer and, as a result, the results more interpretable relative to using ARIMA and the use of robust standard errors/auto-correlation lag structure is sufficient to address any concerns about the errors being properly estimated.

* Our response: Thank you for your kind comment on the methodology. We have reviewed the method that we used in our paper to make sure that we are using the right test analysis for the data.

- I would echo reviewer 1's comments about Figure 1 not having the intended impact due to the relatively large range on the y-axis. The authors state that a alternative version was included but I was unable to find the alternative figure.

* Our response: We are sorry that you couldn't have access to the alternative figure for figure 1. However, it has been changed to the alternative figure as requested by reviewer 1 as well as the editorial team. It is also now attached in the figure files as (Figure 1).

VERSION 3 – REVIEW

REVIEWER	Emma Graham-Clarke Sandwell and West Birmingham NHS Trust United Kingdom
REVIEW RETURNED	04-Sep-2020

GENERAL COMMENTS	Thank you for addressing my comments. The manuscript reads much better now.

REVIEWER	Nolwenn Le Meur Ecole des Hautes Etudes en Sante Publique
REVIEW RETURNED	24-Aug-2020

GENERAL COMMENTS	I thank the authors for answering my comments. I have no further comment.