PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	OpenPrescribing: Normalised Data and Software Tool to Research Trends in English NHS Primary Care Prescribing 1998-2016
AUTHORS	Curtis, Helen; Goldacre, Ben

VERSION 1 – REVIEW

REVIEWER	Earn Gan Institute of Genetic Medicine, Newcastle University United Kingdom
REVIEW RETURNED	29-Oct-2017

GENERAL COMMENTS	I would like to congratulate the authors for undertaking this excellent piece of work, allowing easy access to the longitudinal prescribing trend of various medications in England. The freely accessible interactive analysis tool is very useful and valuable for monitoring prescribing trend in a timely fashion. The paper is well written, the method and results are well described. I only have a few minor comments: 1. Please describe how and by whom the online interactive analysis tool will be maintained? How frequent will the online tool be updated? 2. Normalisation of the PCA data was focus on the 7 most prescribed chapters(1-6 and 10). However, some medications appear in more than 1 chapters (e.g methotrexate is included in chapter 10 and 13, as treatment for musculoskeletal and skin conditions). Have the authors taken this into consideration and incorporate the data on Methotrexate from both chapters? 3.Figure 1- I think the words in green and yellow were difficult to read, the authors might want to consider another colours. 4. Have authors ever consider incorporating other useful clinical data into the interactive analysis tool (e.g combined data from MHRA interactive drug analysis profile to monitor both the prescribing trend and the number of reported adverse reactions related to individual medications)

REVIEWER	Samantha Hollingworth School of Pharmacy The University of Queensland Brisbane, Australia
REVIEW RETURNED	01-Nov-2017

GENERAL COMMENTS	This is an innovative and very useful development and of great interest to many, especially clinicians, policymakers, and pharmacopedemiologists. General Please consider revising with an international audience. It is not always clear for a non-UK person. 'Data' is a plural word so please make sure your verbs match. Pages as per top left or right hand of pdf. Abstract P1 Line 31 'together' is likely redundant after compile. Introduction. This is an exciting development but a little hard to understand for someone not familiar with the UK system and the BNF. You can be sure that there will be researchers and clinicians from outside the UK who will be interested to use these data for comparative studies about the use of medicines. Some further examples about the terminology will aid interpretation by non-UK audiences e.g. SQU etc. Please consider adding some examples to Box 1 and make it consistent with Box 2. Please clarify if the 'presentation' variable is the only one that will provide information the dose and formulation. Methods P4 line 7 please confirm the data are for each calendar year. P5 line 42 please clarify what 'pseudo-chapters' are P6 line 34. Please clarify that you provide the costs in each year but have ALSO adjusted those values for inflation to 20176 (Table 1) How have you managed combination products? Please make a statement about whether the BNF contains both prescription products and or other over the counter products (e.g. paracetamol) and complementary and alternative medicines (e.g. herbs, vitamins, etc.). Are there any co-payments made by patients or is the total cost borne by the NHS? If the former are there any data on patient payments? I am not able to comment on the software programs or statistical code (but well done for providing it in the interests of transparency). Results P8 line 8 Not sure what you mean by this phrase – please clarify "the reduction caused by aggregation over SQU" P8 lines 17-20. Consider giving average annual increase in % for items, costs, etc. Table 1 – you refer to 'drug name'. What does this correspond to in the BNF (Box 2) – chemical name? Presentation? Consistent terminology will aid non-UK readers. Table 1 please include a note that you have adjusted costs to 2016 for inflation corrected costs. Table 1 Are the costs equivalent to the sum of the drug tariff prices x number of items in the each calendar year? Table 2 please give units in row header e.g. n or %. Consider a descriptor of each chapter code e.g. respiratory (also Table 3). Fig 1 Please consider using darker colours for text e.g. the yellow text is hard to read.

	Figures – consider modifying figures so that they are legible in black and white (i.e. white, grey, stippled, black, etc.). Please confirm if users are able to download the data into excel files? The BMF matching process would have been a challenge so well done for sorting out those issues. Discussion I think this tool is a fantastic advance but I strongly suggest you consider adding further functionality by having the medicines coded by ATC (Anatomical, Therapeutic Chemical classification system (https://www.whocc.no/atc_ddd_index/) It is widely used in Europe and Asia, etc. If this is too difficult then please provide direction to any sources or a file that maps BNF medicines to ATC codes. P13 lien 12 You mention the issue of the DDDs and why you are not able to incorporate this aspect (yet!). The use metric of DDD/1,000 population/day is widely used in other countries. P13 line 15. Please clarify what you mean here: “However, users can download our BNF-normalised dataset in order to apply these calculations to a subset of drugs for a more accurate analysis of trends.” Please comment on the sustainability of the tool. Is your group able to update the tool each year as data become available? (I hope so!) P13 line 14 you refer to other publications – please give the citations. P14 line 23 ditto – please cite, say, two examples References #13 ‘Author’ is “Patient” Please check.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Earn Gan
Institution and Country: Institute of Genetic Medicine, Newcastle University, United Kingdom
Please state any competing interests: None declared

Please leave your comments for the authors below
I would like to congratulate the authors for undertaking this excellent piece of work, allowing easy access to the longitudinal prescribing trend of various medications in England. The freely accessible interactive analysis tool is very useful and valuable for monitoring prescribing trend in a timely fashion. The paper is well written, the method and results are well described.
> Thank you

I only have a few minor comments:

1. Please describe how and by whom the online interactive analysis tool will be maintained? How frequent will the online tool be updated?

> Added to the manuscript: “We will update the tool annually, dependent upon continuing funds for the OpenPrescribing project”

2. Normalisation of the PCA data was focus on the 7 most prescribed chapters(1-6 and 10). However, some medications appear in more than 1 chapters (e.g methotrexate is included in chapter 10 and 13, as treatment for musculoskeletal and skin conditions). Have the authors taken this into consideration and incorporate the data on Methotrexate from both chapters?
> Drugs have kept their original classification where appropriate, so those legitimately in multiple chapters have remained so. There are examples - such as methotrexate - where drugs are listed several times in the BNF, but without multiple codes. Therefore, methotrexate prescribed for a skin condition (as listed in Chapter 13) would still be prescribed and dispensed as if it were in Chapter 10. The data contains no detail on indication for us to distinguish these further.

3.Figure 1- I think the words in green and yellow were difficult to read, the authors might want to consider another colours.
> This has been modified to use darker colours.

4. Have authors ever consider incorporating other useful clinical data into the interactive analysis tool (e.g combined data from MHRA interactive drug analysis profile to monitor both the prescribing trend and the number of reported adverse reactions related to individual medications)
> Good suggestion! We have been attempting to obtain a dataset of all MHRA adverse reaction reports so hopefully in the future this will be added as a feature.

Reviewer: 2
Reviewer Name: Samantha Hollingworth
Institution and Country: School of Pharmacy, The University of Queensland, Brisbane, Australia
Please state any competing interests: None declared.

Please leave your comments for the authors below
This is an innovative and very useful development and of great interest to many, especially clinicians, policymakers, and pharmacopedemiologists.
>Thank you, we hope it will save lots of people time and provide useful information!

General
Please consider revising with an international audience. It is not always clear for a non-UK person.
‘Data’ is a plural word so please make sure your verbs match.
> Changed several occurrences of mismatched verbs

Pages as per top left or right hand of pdf.

Abstract
P1 Line 31 ‘together’ is likely redundant after compile.
> Removed
Introduction.
This is an exciting development but a little hard to understand for someone not familiar with the UK system and the BNF. You can be sure that there will be researchers and clinicians from outside the UK who will be interested to use these data for comparative studies about the use of medicines. Some further examples about the terminology will aid interpretation by non-UK audiences e.g. SQU etc. Please consider adding some examples to Box 1 and make it consistent with Box 2. Please clarify if the ‘presentation’ variable is the only one that will provide information the dose and formulation.

> We have added an example to Box 1, rearranged the explanatory text and the relevant paragraphs. Removed references to SQU.

Methods
P4 line 7 please confirm the data are for each calendar year.
> This has been clarified in the text
P5 line 42 please clarify what 'pseudo-chapters' are
> Removed reference to pseudo-chapters

P6 line 34. Please clarify that you provide the costs in each year but have ALSO adjusted those values for inflation to 20176 (Table 1)
> A sentence has been added to reflect this.

How have you managed combination products?
> Combination products are classified as such by their Chemical Name in the BNF. So, for example, drugs with two active ingredients are assigned a Chemical name accordingly, such as "Paracetamol & Caffeine". We therefore did not need to handle these products differently. We have added a line in Box 1 to clarify this ("[The Chemical Name]... is not always an individual chemical: examples include "Paracetamol Combined Preparations" and "Paracetamol & Caffeine".)

Please make a statement about whether the BNF contains both prescription products and or other over the counter products (e.g. paracetamol) and complementary and alternative medicines (e.g. herbs, vitamins, etc.).
> Added to Box 2 "The BNF contains an entry for every product available to be prescribed in Britain. This includes medicinal products, dietary supplements, complementary therapies and physical appliances such as bandages"

Are there any co-payments made by patients or is the total cost borne by the NHS?
If the former are there any data on patient payments?

> In England some patients pay a prescription charge (currently £8.60 per item), which is not related to the cost of the medicine, This payment is not reflected in the PCA data. The number of prescription charges can be found on the NHS PD1 report (https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/pd1-reports).
We have added a line to Box 1 to clarify this: "Patients who are eligible contribute a fixed fee towards each prescription charge, but this only applies to a minority of items and it is not possible to identify which items in this dataset".

I am not able to comment on the software programs or statistical code (but well done for providing it in the interests of transparency).

Results
P8 line 8 Not sure what you mean by this phrase – please clarify "the reduction caused by aggregation over SQU"
> Rephrased to "the reduction caused by aggregation of a small number of drugs available in multiple formulations despite having identical names"

P8 lines 17-20. Consider giving average annual increase in % for items, costs, etc.
> % changes have been added to two columns.

Table 1 – you refer to 'drug name'. What does this correspond to in the BNF (Box 2) – chemical name? Presentation? Consistent terminology will aid non-UK readers.

> The terminology is now better explained in the methods section and we have added the following to the table legend: "'Drug Name' is the field describing the presentation of each drug, i.e. its formulation, dose and product name."

Table 1 please include a note that you have adjusted costs to 2016 for inflation corrected costs.
> We have made this more explicit by adding "(2016 £)" to the relevant headers in the table.

Table 1 Are the costs equivalent to the sum of the drug tariff prices x number of items in the each calendar year?
> Costs are Net Ingredient Cost (NIC) as supplied in the PCA data and described in Box 1. This has been clarified in the Table legend.

Table 2 please give units in row header e.g. n or %. Consider a descriptor of each chapter code e.g. respiratory (also Table 3).
> We have added "n" and "%" as appropriate and added Chapter names to Table 2. As some of the names are long it is difficult to fit them into Table 3, but we have referred readers to Table 2 for this information.

Fig 1 Please consider using darker colours for text e.g. the yellow text is hard to read.
> This has been modified to use darker colours.
Figures – consider modifying figures so that they are legible in black and white (i.e. white, grey, stippled, black, etc.).
> We realise that these will be difficult to see on a black and white print-out but the figures are screenshots from the tool; it is not practical to change the tool to use textures as well as colours when (often) many different and rather small areas are shown. The main purpose of the figures is to demonstrate the appearance and usefulness of the tool, which we think they achieve even in monochrome. Users should tend to use the tool for their own analysis rather than the paper, such that they see the most up-to-date figures.

Please confirm if users are able to download the data into excel files?
> Users can access the .csv files on Figshare, the link to which is available through the FAQ page linked from the dashboard.

The BMF matching process would have been a challenge so well done for sorting out those issues.
> Indeed it was, thank you!

Discussion
I think this tool is a fantastic advance but I strongly suggest you consider adding further functionality by having the medicines coded by ATC (Anatomical, Therapeutic Chemical classification system (https://www.whocc.no/atc_ddd_index/) It is widely used in Europe and Asia, etc. If this is too difficult then please provide direction to any sources or a file that maps BNF medicines to ATC codes.
> We would be interested to add this functionality but we are not aware of any file which allows direct conversion of all BNF codes to ATC codes at chemical level. There is a file (available here https://isd.digital.nhs.uk/trud3/user/guest/group/0/pack/6) which maps at sub-paragraph level (i.e. only by drug class, not chemical) or by virtual product identifier (VPID); so, for accurate matching, all BNF codes would first need to be mapped to VPID, which is likely to leave many gaps. Alternatively, the dataset could be mapped to ATC codes via chemical name. An initial attempt matches only 43% of chemicals in our processed dataset to their ATC code (853 of 1,998 distinct chemicals). A substantial amount of work would therefore be required to overcome the differences in abbreviation or classification of each of the remaining chemicals in order to identify their ATC code (e.g. "calcitonin" could be matched to one of three ATC codes at level 5). Linking the data to ATC codes would inevitably leave gaps and inconsistencies in the data where the level 5 code cannot be found.

P13 lien 12 You mention the issue of the DDDs and why you are not able to incorporate this aspect (yet!). The use metric of DDD/1,000 population/day is widely used in other countries.
> We have found that conversion to ADQs or DDDs is feasible for subsets of drugs, but the linkage datasets available for BNF codes to DDDs or ADQs are not complete. Given that and the fact that we imputed BNF codes for most drugs but some remain unknown, linking the data to DDDs or ADQs would inevitably leave gaps in the data where the conversion rate is not known. Therefore we suggest that users download the complete data and calculate DDDs themselves for their subset of drugs of interest.

P13 line 15. Please clarify what you mean here: “However, users can download our BNF-normalised dataset in order to apply these calculations to a subset of drugs for a more accurate analysis of trends.”
> We have clarified this statement in the text.

Please comment on the sustainability of the tool. Is your group able to update the tool each year as data become available? (I hope so!)
> Added “We will update the tool annually, dependent upon continuing funds for the OpenPrescribing project”

P13 line 14 you refer to other publications – please give the citations.
P14 line 23 ditto – please cite, say, two examples
> Added citations for both.

References
#13 ‘Author’ is “Patient” Please check.
> Changed to Colin Tidy.

VERSION 2 – REVIEW

REVIEWER	Earn Gan Newcastle University United Kingdom
REVIEW RETURNED	08-Dec-2017

GENERAL COMMENTS	I am happy with the amendments made by the authors. Please consider adding in a brief legend for table 1 explaining the trend of the annual changes in percentage for the prescribed items and costs. Readers might be puzzled by the inverse relationship between prescribed items and costs in a number of years (might be good to explain the potential reasons behind these changes).

REVIEWER	Samantha Hollingworth School of Pharmacy, The University of Queensland, Australia
REVIEW RETURNED	04-Dec-2017

GENERAL COMMENTS	The authors have comprehensively addressed the comments. Well done.