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Dr Rubin Minhas

The BMJ

25th April 2016

Dear Dr Minhas

Manuscript ID BMJ.2016.032072 "Is it safe to reduce antibiotic prescribing for self-limiting respiratory tract infections in primary care? Cohort study using electronic health records"

Thank you for your communication dated 11th April 2016 and for sending the Editor's and Reviewers' very helpful comments on our paper. We agree that these comments have raised some important issues.

We have now addressed each comment in detail, making a number of substantial changes to the paper. We now enclose a revised version of the manuscript, together with a point-by-point response to the comments, shown on the following pages.

In responding to the review comments, we have added new material to the paper, increasing its length. We would be prepared to consider some material as supplementary if necessary.

The research maybe be included in our end of project report to the NIHR HTA programme. This is not expected to be published until 2018. We expect that the results and conclusions will be consistent with this paper.

Thank you for considering this revised paper for possible publication in *The BMJ.*

With best wishes

Yours sincerely

Martin Gulliford

Professor of Public Health

EDITORIAL COMMENTS

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Thank you, please see detailed responses below.

STATS REPORT

The software hglm is an R package and needs citing.

Thank you, the R packages used have now been cited.

Coefficients in Table 2 per 10 units, inconsistent as RTI per 1000 and AB per 100.

Thank you for commenting on this. We have now clarified this by adding column headings in Table 2 that read 'for 10 per 1,000 increase' or 'for 10% increase'.

[We do not think that the three metrics can be made completely consistent. The proportion of consultations with antibiotics prescribed is a proportion expressed as a percent. The RTI consultation rate, and the antibiotic prescribing rate for RTI, are rates in relation to the registered general practice population. The GP population is measured in thousands, so rates are expressed as rates per thousand. This is consistent with our previous reports (e.g. references 6 and 22). We do not think the results can be communicated more effectively, or made more consistent, by presenting rates per 100, or by expressing changes as for a 100 per 1,000 change in prescribing. Suppose we present the AB prescribing rate as being ~15 per 100, then a 10 unit change to 5 per 100 represents a much greater decrement than a 10 unit change in prescribing proportion.]

Forest plots need ref (IRR=1) included perhaps as an open blob to show the linear trend.

Thank you, the reference category has now been added as a point in the Forest plots.

The groups within each diagnosis as currently listed are the wrong way round, with the smallest at the top and largest at the bottom. They need reversing.

Thank you, the categories have now been reversed so that the highest is at the top.

P values need only 2 decimal places if P >= 0.01, or 3 if P < 0.01 (modified AMA recommendations). Rates in Table 1 and Figure 1 need 2-3 significant digits, not 2 decimal places.

These changes have now been implemented.

PLEASE REMOVE TRACES OF CAUSAL INFERENCE AS THIS IS A GP PRACTICE LEVEL ANALYSIS

Thank you, the text has been reworded so as not to suggest any causal inferences.

PLEASE REMOVE THE REFERENCES TO A CLINICAL TRIAL

Thank you, we now say (page 8); 'The research was conducted to inform a study funded by the NIHR Health Technology Assessment programme. The outcomes were selected from a wider range of safety outcomes proposed for the study because they were identified as being potentially associated with RTI.'

PLEASE RE-DO THE ANALYSIS, USING MENINGITIS AS THE PREFERRED CLINICAL OUTCOME RATHER THAN CELLULITIS

Thank you, cellulitis has now been omitted and bacterial meningitis has been included as an outcome as discussed below.

Reviewer: 1

The use of large datasets of electronic medical records have the drawback of their accuracy – mainly for the diagnostic codes – and, particularly in this paper, this aspect is even more relevant since you considered the diagnosis of different complications. For instance, were pneumonias confirmed radiographically? You should more clearly describe if some of these complications, mainly those attended in the secondary sector such as pneumonia, could have been missed in this cohort study.

Thank you, we now explain (page 5): 'Infective complications of respiratory tract infections were defined using Read codes recorded in participants' electronic health records (EHRs). EHR data include diagnoses recorded at primary care consultations and home visits. In addition, the CPRD referral file includes coded data for hospital referrals and hospital discharges.'

We also say (page 6): 'Codes for 'pneumonia' were drawn from section H2 of the Read code classification, which includes codes for 'Pneumonia and Influenza'. Codes were included if they indicated the presence of pneumonia without a viral aetiology.'

Linked to the previous query, it's not clear to me if you also considered the pneumonias admitted to the hospital.

Thank you please see response given above. We also comment (page 15): 'Future studies might also make use of linked hospital episode data, which are available for selected CPRD practices in England in more recent years, in order to evaluate hospitalised cases in more detail.'

About 20% of pneumonias are expected to be managed in the hospital setting, and some of them will have a poor outcome. We all know that the chances of detecting differences in the number of very infrequent complications such as Lemierre's syndrome or intracranial abscess across the different groups are slim, even with the use of large databases. However, the presence of complicated pneumonia, bacteraemia, and death in these diagnoses are not as infrequent as the previous complications. You do not describe the severity of these complications, mainly because the methodology used is not appropriate for that, but did you find any difference in terms of mortality between the highest and the lowest antibiotic prescribing practice groups?

Thank you. This study was designed to evaluate the occurrence rather than the outcomes of the complications reported. We now say (page 15): 'We evaluated changes in infective complications at the level of the general practice population, the research did not show whether or not individual patients who experienced complications received antibiotics, nor did we evaluate the outcomes of individual patients who were diagnosed with complications in this study. Further research is required to evaluate the severity of complications such as pneumonia and their outcomes including mortality.'

In the Introduction section you mention that Petersen et al observed that the estimated number of patients who would have to be treated with antibiotics to avoid one episode of pneumonia after an upper respiratory tract infection, one quinsy after sore throat and one mastoiditis after otitis media was higher than 4,000. However, you do not mention that the risk of pneumonia in the month after the diagnosis of acute bronchitis in Petersen's study was high and substantially reduced by antibiotic prescription, with this protective effect being greatest in people aged 65 and over (with a NNT of 39 in this group age).

Thank you, we now add (page 4): 'However, pneumonia was more frequent and in people aged 65 and over it was estimated that there might be one case for every 39 antibiotic prescriptions avoided.'

When it comes to the number of pneumonias, your results differed considerably from the findings of Petersen et al, since you found that only one extra case of pneumonia would be seen if GPs reduced the antibiotics prescribed by 10%. I miss a clearer discussion about these differences. You standardised the incidence rates of pneumonia by sex and age. However, could you identify the number of extra pneumonias among elderly patients that could have been observed if GPs had reduced the antibiotic prescribing by 10%?

Thank you, we now add (page 12): 'In additional analyses, we found that the incidence rate ratio associating the antibiotic prescribing proportion with pneumonia was similar for the population under 65 years (IRR 0.88) and 65 years or older (IRR 0.88).'

We also say (page 15): 'Further research is needed to evaluate whether the present results will be confirmed when sub-groups who may be at higher risk are analysed, including older adults.'

The BMJ is an international journal and from this perspective the lowest quartile of antibiotic prescribing, with a median of 38% of antibiotics prescribed for the respiratory tract infections,

might be even higher than the mean antibiotic prescription rate observed in some other countries in Europe such as Sweden or Netherlands (the latter country with 22.5% of antibiotics prescribed for these infections as you mention in reference 8). One might also wonder why you considered quartiles instead of breaking down the different practices into more groups, such as quintiles, sextiles or even deciles. It would permit having groups of practices with really very low antibiotic prescribing rates and some complications might have been more clearly observed in these very low antibiotic prescription practices. Despite the fact that the overall prescription of antibiotics has not dramatically changed over the last years, nowadays there is an increasing number of GPs who are very aware of the threat of the antimicrobial resistance and prescribe very few antibiotics for these self-limiting respiratory tract infections, and these GPs would not be reflected in the lowest quartiles but could have been reflected in the lowest deciles, for instance. You should discuss this point.

Thank you, we acknowledge this point by adding (page 16): 'Antibiotic prescribing in the UK is high compared with some international comparators, and we cannot be sure that the associations reported here would also hold at very low antibiotic prescribing levels.'

However, we did not repeat the analysis using a variety of cut-points, as this might increase the risk of statistical error.

You used a cohort of individuals followed up from 2005 to 2014. It would be interesting to have some information about the trend of how the number of consultations for respiratory tract infections and antibiotic prescription for these conditions have changed over this 10-year period in the UK.

Thank you, we have now added the new Figure 1, which presents trends in RTI consultations and antibiotic prescribing between 2005 and 2014.

We now comment in the text (page 9): 'Figure 1 presents data for RTI consultations and associated antibiotic prescribing between 2005 and 2014. The RTI consultation rate per 100,000 continued a long-term decline[6] during the period, reducing in from 256 to 220 per 100,000 in men and from 351 to 307 per 100,000 in women. The antibiotic prescribing rate for RTI declined from 128 to 106 per 100,000 in men and from 184 to 155 per 100,000 in women. The proportion of RTI consultations with antibiotics prescribed declined from 53.9% to 50.5% in men, and from 54.5% to 51.5% in women.'

Linked to the previous query, you should also describe whether the use of rapid tests (CRP for instance) and the rate of delayed prescribing of antibiotics have significantly changed in this period. It is not clear to me if you were able to identify the percentage of antibiotics not immediately prescribed (delayed). If not, you should make it clearer in the paper. Since some studies have not observed any increase of the number of complications of sore throat when a delayed prescribing of antibiotics was carried out compared to treated patients, provided you have this information, you could specify if the use of the delayed prescribing of antibiotics varied across the different antibiotic prescribing quartiles.

Thank you, we now discuss as a limitation (page 15): 'some general practices may use delayed antibiotic prescribing strategies[3] but these were not distinguished in the analysis of prescriptions issued.'

We also comment (page 15): ‘It is also possible that use of near-patient testing may have contributed to better diagnosis during the period.’

Some tweaks:

You should describe all the acronyms used in the tables and figures. Having to go to the text every time you come across some of them that are not explained as footnotes is really cumbersome.

Thank you, footnotes have been added to explain all abbreviations.

The vertical line depicting the lack of statistical significance (in number 1) in figures is missing and is crucial for visual impact.

Vertical lines are now included in the Forest plots.

Reviewer: 2

1 The choice of all the 5 respiratory secondary infections that could be ‘missed’ are uncontroversial.

However the inclusion of cellulitis is interesting, and may be something that most GPs would not have thought of, or worried about, since it appears to be unrelated to respiratory infections. Indeed of the 2 references cited to support its inclusion by the Authors, the Zwart 2003 described only one case of impetigo!

Thank you for this feedback. While we believe (based on the present results as well as reference 3) that skin infections may be associated with RTI, we accept that this might not be viewed as a safety concern in the context of deciding whether to prescribe antibiotics. Cellulitis has therefore been omitted.

This begs the question of what else might have been included as credible, commonly worried-about, infections that might have been avoided by antibiotic use. And they might include meningitis . . .

Thank you for this suggestion. Bacterial meningitis has now been included: ‘‘Bacterial meningitis’ included codes for meningococcal meningitis, meningococcal septicaemia, pneumococcal meningitis and haemophilus meningitis, as well as unspecified bacterial meningitis.’ (page 6)

2 The data for these analyses are highly dependent on GPs’ coding (through Read codes) correctly. Coding always has an element of subjectivity (especially with ARIs, which all sit on a variety of spectra). These analyses must assume that GPs who are high antibiotic prescribers code the same away as those who are not. Actually there is some evidence from 45 years ago this is not true in Scotland, and there is nothing to suggest that it might be better today. [Howie JG, Richardson IM, Gill G, Durno D. Respiratory illness and antibiotic

use in general practice. J R Coll Gen Pract. 1971;21:657-63.; and also Howie J. Diagnosis--the Achilles heel? JR Coll Gen Pract. 1972;22:310-5.] These data suggest that GP who use antibiotics are more likely to use diagnostic labels of 'antibiotic-justified diagnoses'.

So there should be some speculation about how differences in coding ARIs might have affected the results. This might affect the data about ARI consulting rates, and then secondarily the antibiotic prescribing rates.

Unfortunately we can't see any way to check if this is a problem, unless the organisation holding the electronic medical record database has previously undertaken validity testing of the diagnostic codes independently.

Thank you, we now comment (page 15): 'Diagnostic coding has a subjective element[35] and bias might arise if low-prescribing practices are more likely than high-prescribing practices to code 'pneumonia' in order to justify the prescription of an antibiotic.'

3 Primary Outcome.

The Methods describes "For each CPRD general practice, we estimated the rate of RTI consultations per 1,000 registered patients; the antibiotic prescribing rate for RTI per 1,000 registered patients; and the proportion (%) of RTI consultations with antibiotics prescribed".

The higher the rate of ARI consultations the higher the incidence of infective complications. This is perhaps what would be expected, and therefore is unsurprising.

Also the higher the proportion (percentage) of antibiotics prescribed, also the lower the incidence suppurative complications, supporting the hypothesis that the liberal use of antibiotics suppresses a rage of downstream infections. However we know from past work of Little's that high antibiotic prescribers also are associated with high 'returns' with new subsequent RTIs. So the proportion of antibiotics prescribed has to be adjusted for higher consulting rates (working in the opposite direction).

Instead we are provided with the actual rates of antibiotic prescribing, although unfortunately relegated to supplementary information, (as Suppl Fig 1), although reported in Results (p10 li48), but not really explored further.

We actually think this is the least biased data: as the actual rate of antibiotics prescribed per thousand patients, it is free of the consultation rate bias. It shows only one of the potentially downstream infections (pneumonia) is associated with increased antibiotic activity, and this is a very important result.

Thank you for these comments. In the present study, antibiotic prescribing is not an outcome, so the reviewers may intend to refer to the 'primary analysis'. When antibiotic prescribing is an outcome measure, as in a trial, total antibiotic prescribing will be determined by the number of consultations and the proportion of consultations with antibiotics prescribed. We agree that the antibiotic prescribing rate will be the appropriate outcome measure for a trial.

Here antibiotic prescribing is an exposure rather than an outcome. It may be less clear which measure of antibiotic prescribing should be regarded as the primary measure. The antibiotic prescribing rate is partly determined by the RTI consultation rate, while the proportion of consultations with antibiotics prescribed is not especially dependent on the RTI consultation

rate, as we note by presenting correlation coefficients. This tends to favour the antibiotic prescribing proportion as the primary analysis.

Drawing conclusions with respect to the proportion of consultations with antibiotics prescribed also has greater relevance to prescribers than the antibiotic prescribing rate.

We also note that analyses for each measure of antibiotic prescribing were adjusted for the RTI consultation rate so conclusions should not differ greatly for the two measures, which turns out to be the case.

We have responded to the reviewer comments by moving the Table showing estimated associations with the antibiotic prescribing rate from the supplement to the main body of the paper. We have also added associations of outcomes with the antibiotic prescribing rate in the revised Table 2. Presentation of these results now makes clear that findings for the two measures of antibiotic prescribing are generally consistent.

Reviewer: 3

On the negative side, when one uses a large dataset, it is relatively easy to see statistically significant findings that have little clinical relevance or importance for the individual practice or patient (1-2 cases a year for cellulitis and pneumonia, 1 case of abscess a decade).

Thank you, we now add (page 16): 'We also caution that, in the analysis of large datasets, 'significant' results must be judged in relation to their clinical importance.'

In the Introduction, the authors note an earlier study found the overall risk of complications was low and the "number of patients who would have to be treated to avoid one complication was estimated in excess of 4,000." They did not use a similar way to describe their own data, but it would have been of great interest and would put in perspective for the clinician how to interpret this data.

Thank you, we estimated the absolute measures of effect shown in Table 3. These are not directly comparable to those of Petersen et al. because theirs was an individual-level analysis, while the present study was at general practice level.

2. They emphasize the significant findings and mention this minimal increased risk is likely offset by the risks of antibiotic treatments that are unnecessary. Some data regarding this would have been very informative, even if just by literature review.

Thank you, we now add (page 13): 'Benefits to individual patients from avoiding antibiotics include reductions in common adverse reactions to antibiotics including rashes, vomiting and diarrhoea which may affect 10% of patients,[5] as well as less common side-effects such as anaphylaxis. Benefits to general practices may include a demedicalisation of RTI followed by a decline in the consultation rate, since previous observational studies show higher prescribing general practices attract more consultations for RTI.[25] '

3. There is no breakdown of how individual RTIs were treated, and whether the cases of pneumonia/cellulitis/peritonsillar abscess had any association with patients that actually had

an RTI and did or did not get an antibiotic (discussed by the authors, appropriately, as a weakness). If they occurred in a completely different population, can the association be explained by RTI antibiotic treatments? If the excess cases could not be linked to patients with RTIs who were not treated with antibiotics, how should the results be interpreted?

Thank you, we now comment (page 15): 'we evaluated changes in infective complications at the level of the general practice population, the research did not show whether or not individual patients who experienced complications received antibiotics. Conclusions might differ if individual analyses showed that complications arise in patients who were treated with antibiotics.'

4. The results of infective complications according to quartile of proportion of RTI consultations with antibiotics prescribed, as well as infective complications according to rate of RTI consultations are emphasized and relevant tables/figures included. In contrast, the association between prescribing rate - which takes into account RTI consultation rate and proportion of RTI consultations with antibiotics prescribed - is included only as a supplementary figure, but it seems that this interaction is very important. As discussed, practices with high proportion of antibiotic treatments for RTI consultations encourage more RTI visits than other practices. Perhaps those practices are more experienced with RTI consultations and less likely to miss other diagnoses, or other hypotheses are possible. In any event, this analysis showed only a significant association with pneumonia - less striking results.

Thank you, please see our response to reviewer 2.

5. How does this study help clinicians? It is difficult to see how this information can be practically helpful. Its main benefit is reassurance – reducing antibiotic treatment of RTIs does not have collateral damaging impact. The way the paper is framed, it just doesn't get this across as the major point.

Thank you, we intended to cover this point in the Box on 'What this paper adds' where it reads 'Even a substantial reduction in antibiotic prescribing was predicted to be associated with only a small increase in numbers of cases observed, and this would be expected to reduce the risks of antibiotic resistance, the side effects of antibiotics and, the medicalisation of largely self- limiting illnesses.'

Reviewer: 4

a) May be good to define Primary Care since in a number of countries this is 'ambulatory care' - so avoid confusion.

Thank you, we now say (page 3): 'primary care, including first-point-of-contact ambulatory care'

b) Page 3 line 10. Other references for consideration include: (I) Laxminarayan R, Matsoso P et al. Access to effective antimicrobials: a worldwide challenge. Lancet.

2016;387(10014):168-75 - as this gives figures for the appreciable increase in antibiotic use worldwide during recent years and the implications; (ii) taken forward in LMICs by Mendelson M, Rottingen JA et al. Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. Lancet. 2016;387(10014):188-98

Thank you, we now add (page 3): 'Reducing inappropriate use of antibiotics, as well as ensuring that antibiotics can be used when they are needed, represent important components of a strategy to control infectious diseases.[2]'

c) Line 20 page 3 - negligible benefits to whom?

Thank you, we now say (page 3): 'Antibiotic treatment of RTIs offers negligible benefit to affected patients[4]'

d) Page 3 Lines 38 - 47. Good also to say that interventions are also being targeted at patients to reduce antibiotic prescribing as do mention this on page 13 (lines 42/ 43) and in the French study quoted. Other publications discussing this include Rezal RS, Hassali MA et al. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature. Expert review of anti-infective therapy. 2015;13(5):665-80. This is because patients themselves are often a source of over use of antibiotics in ambulatory care as mentioned on page 13). This is recognised by typically multicomponent strategies among authorities to reduce inappropriate antibiotic use, e.g. (i) Huttner B et al. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. The Lancet infectious diseases. 2010;10(1):17-31; (ii) Dyar OJ, Beovic B et al. How can we improve antibiotic prescribing in primary care? Expert review of anti-infective therapy. 2016;14(4):403-13; (iii) Furst J, Cizman M et al. The influence of a sustained multifaceted approach to improve antibiotic prescribing in Slovenia during the past decade: findings and implications. Expert review of anti-infective therapy. 2015;13(2):279-89

Thank you, we now add (page 17): 'The safety outcomes of no antibiotic prescribing strategies for RTI are an important aspect for communication to patients and the public in the context of wider communication strategies to support antimicrobial stewardship.[39]'

e) Page 5 line 38. Not sure every reader outside the UK will be familiar with Read codes as opposed to ICD 10 codes - so a brief explanation may be needed

Thank you, we now explain (page 5): 'The Read code classification represents a terminology used to code primary care electronic health records in the UK.[20]'

f) Page 5 lines 50 - 57 - may be good to say why broke the cohorts down into the age groups discussed and not other potential age groups

We used 10 year age groups, except at the extremes of age, which we think is acceptable practice.

Reviewer: 5

1. Are diagnoses for hospital admittance part of the complication diagnoses recorded? If complications with severe courses are not included, the safety of low prescribing rates may still be questioned. On the other hand, there would probably be serious side effects from antibiotic use, demanding hospital admittance.

Thank you, please see response to Reviewer 1.

2. Antibiotic prescribing proportion of 65% in the highest quartile and of 38% in the lowest quartile, with an overall median of 51%, is still high concerning mainly self- limiting infections. Moving from the highest quartile to the level of the lowest would still probably give a prescribing proportion for RTIs that is rather high. In the perspective of antibiotics as limited resources, it would be of a greater interest to know how a 15% or 20% proportion for RTI would affect the complication rate.

Thank you, we now explain (page 13): 'Changes will be proportionately greater for larger reductions in antibiotic prescribing.'

3. In a Norwegian study we found that the proportion of broad spectrum antibiotics varied even more than the proportion of treated RTIs. Have the authors looked into the association between narrow-spectrum antibiotics and the rate of complications?

Thank you, we now add (page 15): 'The risk of complications associated with different classes of antibiotics also merits study.'

4. The assessment of the consequences of a 10% reduced prescribing proportion of antibiotics is not unproblematic. The individual GP that takes the decision of prescribing while facing the patient, has individual attitudes and experiences that may affect the way the patient is treated and information given. It is not obvious that a shift in prescribing proportion from high to low will give the same complication outcome as the observed association found in this study. Only a randomised, controlled intervention study will be able to verify that assumption.

Thank you, we now comment (page 13): 'These estimates represent averages across general practice populations, but complications might be fewer than expected if general practitioners are able to effectively stratify antibiotic prescribing according to level of risk.'

Reviewer: 6

1. Can the reader be sure that all complications in the cohort have been registered? The authors state that data are gathered from the electronic patient records. But I assume that a number of these complications have been detected outside the practices, such as direct contact with the emergency rooms, out of hours services or direct contact with the

hospital. Are the authors sure that all these contacts have been registered in the patient records? If so, are there any quality measurements that this is fullfilled?

Thank you, we explain on page 5 that 'CPRD data are considered to be representative of the UK population and the high quality of CPRD data have been confirmed in many previous studies.[19]' We also comment (page 6) that 'EHR data include diagnoses recorded at primary care consultations and home visits. In addition, the CPRD referral file includes coded data for hospital referrals and hospital discharges.' We also comment (page 16) 'general practice populations may vary in their use of out-of-hours and emergency services, whose generally higher antibiotic prescribing may not be captured in CPRD.'

2. Why are not doctor factors included in the analysis, such as gender, age, years of practice, degree of work load? Other studies like our own demonstrated that docor factors can be predictors for antibiotic prescribing. We found that being a specialist and a busy doctor, were significant predictors (ref gjelstad x 2).

Thank you, we now add (page 15): 'The research did not address variation in prescribing at the level of the individual physician.'

3. I miss a more comprehensive discussion on the choice of relevant complications? Why is not necrotising fasciitis included in the complications? It is rare, but I assume still more frequent than Lemierre's syndrom. Furthermore meningitis as a result of otitis media, sinusitis, and orbital cellulitis as a complication to sinusitis. Of course there may be a discussion about the relationship between an RTI and a subsequent complication, but this will be the same as with cellulitis.

Thank you, as noted above 'cellulitis' has now been omitted and 'bacterial meningitis' has been included.

4. Is the cohort representative of UK general practice? Can the fact that these practices probably are more academic run, lead to a different cohort of patients? What data are available to clarify this? What about proportion of immigrants on the lists in addition to the deprivation scale?

Thank you, we note on page 5: 'CPRD data are considered to be representative of the UK population and the high quality of CPRD data have been confirmed in many previous studies.[19]' We did not have any data for analysis on migration and ethnicity.

5. Why did you have to draw a sample from each practice, what were the reasons from the ethical committee. I assume that all data were anonymized or pseudonymized?

Thank you, we have added on page 5 that the data were fully anonymised (technically pseudonymised).

We say on page 7 of the paper that 'These measures were estimated on a sample of CPRD data because it was not feasible, and our licence did not allow us, to perform the analysis on the entire CPRD database.' There were more than 800,000 participants who had RTI consultations in 2014 alone, so over a 10 year period there would have been several million.

Under the terms of our licence we are not able to download data for more than a million patients, so we took a sample.

1. *What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)*

Included (page 20).

2. *Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)*

Included (page 9).

3. *Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).*

Not applicable.

4. *Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)*

Enclosed.

5. *Contributorship statement+ guarantor (see http://resources.bmj.com/bmj/authors/article-submission/authorship-contributorship)*

Included (page 18).

6. *Transparency statement: (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/transparency-policy)*

Included (page 18).

7. *Copyright statement/licence for publication (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)*

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8. *Data sharing statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research)*

Included (page 18).

9. *Funding statement and statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).*

Included (page 18)

10. *Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).*

Included (page 9).

11. Please ensure the paper complies with The BMJ's style, as detailed below:

Thank you, we believe that all of the BMJ style points have been addressed.