PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Electronically delivered, multi-component intervention to reduce unnecessary antibiotic prescribing for respiratory infections in primary care. A cluster randomised trial using electronic health records. REDUCE Trial study original protocol.
AUTHORS	Juszczyk, Dorota; Charlton, Judith; McDermott, Lisa; Soames, Jamie; Sultana, Kirin; Ashworth, Mark; Fox, Robin; Hay, Alastair; Little, Paul; Moore, Michael; Yardley, Lucy; Prevost, A.; Gulliford, Martin

VERSION 1 - REVIEW

REVIEWER	Mariam de la Poza, Pablo Alonso-Coello Institut Català de la Salut Iberoamerican Cochrane Center
REVIEW RETURNED	27-Jan-2016

GENERAL COMMENTS	This is a very well design protocol for a very rellevant question. No specific comments except that it might benefit from an statistical review. We have revised the protocol using the SPIRIT checklist.

REVIEWER	Sigurd Høye Department of General Practice, University of Oslo, Norway
REVIEW RETURNED	27-Jan-2016

GENERAL COMMENTS	Thank you for the opportunity to read this interesting protocol. I completely agree that “The challenge now is to take the components of intervention that have been shown to be effective and to find methods to deploy these efficiently into routine practice settings.” This study seems to meet this challenge. However, I find that the protocoll does not give sufficient information on some important issues. Overall: I find it a bit hard to understand what is new in this study. How does it differ from the eCRT study? I find that possible obstacles (recruitment, adherence to the electronic prompts etc) are not adequately discussed. Possibly they should be mentioned in the “Limitations”-list. Abstract: “Upper respiratory tract infections (uRTIs) account for about 60 % of antibiotics…” I guess you mean “Respiratory tract infections (RTIs)”

	Background: I would have appreciated a rewrite of the background section. Both language and content could be improved. P3 L47: “A majority of these infections are self-limiting” Please be more specific. “A majority” could be 51% - then a 50% prescription rate would be quite appropriate. Explaining and proving the existence of over-prescribing is a crucial point. P4 L15: “Recent evidence (7)” This is not very recent anymore. P5 L44: «identifies ways to increase engagement in the intervention and increase effect sizes (19). This research is at a later stage of translation than previous trials” I do not fully understand this. Which “ways to increase engagement” are you referring to, and what does “This research” and “previous trials” refer to? Study setting and target population P6 L57 I would have appreciated to know how UK general practices were recruited to the CPRD. I do not find it sufficient that you state that “The registered population is generally representative of the UK general population” P7 L27 “The 120 practices…» Where does this number come from? How many eligible practices are there? How many of them do you think will consent to participate? Sample size calculations Why do you start with a number of practices and calculate the power, instead of the opposite? Intervention development and implementation P8 L38 What kind of development was done for this study? It seems that both the main elements have been used in earlier studies. Also, it would have been interesting to know what kind of adjustments the qualitative research resulted in. P9 L24 Again: Upper RTI. Do you define cough/bronchitis as an URTI? P9 L56 What are the practices to do with the monthly feedback? How do you make sure that these are read and discussed? Outcome evaluation P10 L26 Why do you mention smoking, alcohol, hospital data etc? I guess you neither will use, nor have permission to use, this information?

REVIEWER	Annette Diener Institute of General Practice University Medical Center Rostock, Germany
REVIEW RETURNED	27-Jan-2016

GENERAL COMMENTS	This study protocol describes a RCT aiming at GPs using electronic

	health records and electronically delivered information as an intervention to reduce inappropriate antibiotic prescriptions for self-limiting respiratory tract infections. The trial is highly relevant and might offer a simple and cost-effective way to optimise antibiotic prescribing. Major comments: 1. Abstract: − In the introduction (page 2 line 6) one or two more sentences would be helpful to underline and explain the problem-field of antibiotic prescription rates of about 60 % in the UK. − The methods and analysis part of the study would benefit from more detailed information about how many practices are being recruited and how many patients with relevant symptoms are expected to be involved during the intervention time. 2. Strengths: − Page 3 line 8: Readers outside the UK might benefit from information about electronic health records as to be used, what data are recorded, by whom they are used, etc. In consequence it is not clear, why the use of EHR is a strength of the study. − One would expect statements about the feasibility and the high number of collectable data. 3. Limitations: − In this section I would expect a broader discussion about potential biases. − The problem about the complexity of an intervention including all identified factors (page 3 line 22-26) should be addressed more clearly: Which factors were identified, which were included in the intervention design, which were not and why. 4. Background: On page 4 line 23 the author writes, “The management of acute respiratory tract infections offers an opportunity to make a major impact on unnecessary antibiotic prescribing.“ This sentence needs more explanation. 5. Methods / Design: Study setting and target population: − In this paragraph (page 6 line 53) the authors describe the participating practices and population. For better understanding a total number of general practices in the UK and the number of their patients should be given. − Page 7 line 3: Even if the quality of electronic health data in the CPRD is well described the study protocol would benefit from a short overview about “up-to-standard” data. − On page 7 line 8 the authors describe eligible practices which will be invited to participate. Information about the total number of eligible GP practices, expected numbers of participating GPs (and their patients) and the mode of recruitment should be given here (invitation by letter, for instance). Also expected drop out-rates would be helpful (e. g. shown in a flow-cart). 6. Allocation: On page 8 the allocation process needs be described in more detail. As the study is performed at the King’s College London it does not become clear how the involved scientists are blinded allocating the practices to control and intervention arm. Minor comments 7. On page 2 line 5 is written “Upper respiratory tract infections (uRTIs) account for about 60% of antibiotics prescribed in primary care.“ whereas on page 3 line 46 the author mentions “…but approximately 50% of patients who present with an upper respiratory tract infection are prescribed an antibiotic.“ The numbers should be consistent.

	8. References: References 3 and 6 are identical.

REVIEWER	Daniella Meeker University of Southern California, Los Angeles CA, United States
REVIEW RETURNED	17-Mar-2016

GENERAL COMMENTS	The proposed study has a strong experimental design. The intervention design is informed by past work and a pilot study is expected to refine feasibility and acceptability. Investigators might consider step-wedge experimental design given the complexity of the intervention. Economic evaluations are also proposed - In addition to the quantitative evaluation, a process evaluation is proposed which is likely to produce high value information for future work. Indroduction (2) For related interventions using electronic medical records, consider citing Meeker et al. Meeker, D., J. A. Linder, C. R. Fox and et al. (2016). "Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: A randomized clinical trial." JAMA 315(6): 562-570. or Gerber, J. S., P. A. Prasad, A. G. Fiks and et al. (2013). "Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: A randomized trial." JAMA 309(22): 2345-2352. (3) For complex intervention design, consider reviewing Lau, R., F. Stevenson, B. N. Ong, K. Dziedzic, S. Treweek, S. Eldridge, H. Everitt, A. Kennedy, N. Qureshi, A. Rogers, R. Peacock and E. Murray (2015). "Achieving change in primary care-effectiveness of strategies for improving implementation of complex interventions: systematic review of reviews." BMJ Open 5(12): e009993. Authors site the limitation "Initiatives to influence antibiotic prescribing both locally and nationally could influence the results of the current trial", normally this would not be the case in an RCT - an additional line of exposition would be helpful (e.g. performance improvement may have peaked due to concommittant interventions). p5 line 23 - missing comma. p5 line 33 "This simple intervention showed a near 2% reduction in antibiotic prescribing" do the authors mean "2 percentage points"? Methods Consider secondary outcomes that measure the prescribing rates by diagnosis. Given stated concerns over other influences or trends in antibiotic prescribing, statistical methods used in Gerber et al. may be of interest either as sensitivity analyses or main analysis. Qualitative approach is valuable - it is not stated, but follow-up interviews aimed at sampling feedback from providers representing a range of effectiveness would be of interest.

VERSION 1 – AUTHOR RESPONSE

REVIEWER COMMENT	RESPONSE	Changes in the manuscript (changes highlighted in yellow)
REVIEWER 1 Mariam de la Poza, Pablo Alonso-Coello Institution and Country, Institut Català de la Salut Iberoamerican Cochrane Center		
This is a very well design protocol for a very relevant question. No specific comments except that it might benefit from an statistical review.	Thank you for your review and comments. We have reviewed the paper to clarify some statistical points.	*Since many parts of the methods section have been rewritten, please see the revised manuscript. All changes made are highlighted in yellow.*
REVIEWER: 2 Sigurd Høye Institution and Country Department of General Practice, University of Oslo, Norway		
Thank you for the opportunity to read this interesting protocol. I completely agree that "The challenge now is to take the components of intervention that have been shown to be effective and to find methods to deploy these efficiently into routine practice settings." This study seems to meet this challenge. However, I find that the protocol does not give sufficient information on some important issues.	Thank you for your comments. We have revised the protocol to provide more details on the intervention development and intervention content to improve the quality of this protocol paper.	*Since many parts of the protocol have been rewritten, please see the revised manuscript. All changes made are highlighted in yellow.*
Overall: I find it a bit hard to understand what is new in this study. How does it differ from the eCRT study?	This has now been addressed. Two major novel components of the current study are: practice-level feedback on antibiotic prescribing and recruitment of a GP champion for each practice.	The development of the intervention was informed by existing health records, behaviour-change theory, systematic review evidence, clinical guidelines, qualitative research with non-trial practices (31 GPs and 3 nurse prescribers interviewed), as well as process evaluation data from the previous proof of concept trial [1]. Main elements used in the previous eCRT study were refined and new elements were added. Two novel major components are the provision of practice-level feedback on antibiotic prescribing and recruitment of a GP champion for each practice since facilitation plays an important role affecting the context in which change

		occurs [2]. A large part of the intervention refinement focused on the investigation of factors influencing implementation and selection of modifications of the tools in order to achieve maximum benefits of the intervention. (Pages 9 – 10)
I find that possible obstacles (recruitment, adherence to the electronic prompts etc) are not adequately discussed. Possibly they should be mentioned in the "Limitations"-list.	Thank you for this comment. We agree that adherence to the intervention might affect the intervention effectiveness and this has been added as a possible limitation to the limitations list.	**Limitations** • Although behavioural theory and qualitative research were used to enhance the effectiveness of intervention design, it was not possible to include all identified factors without creating an intervention which would be too complex and difficult to use. • It is possible that the intervention will have a smaller effect than expected as possible problems with implementation might be encountered (e.g. low adherence to electronic prompts). This will be examined during process evaluation. • Initiatives to influence antibiotic prescribing both locally and nationally could influence the results of the current trial (Page 3)
Abstract: "Upper respiratory tract infections (uRTIs) account for about 60 % of antibiotics…" I guess you mean "Respiratory tract infections (RTIs)"	Yes, we agree. This has now been addressed.	Respiratory tract infections (RTIs) account for about 60% of antibiotics prescribed in primary care. (Page 2)
Background: I would have appreciated a rewrite of the background section. Both language and content could be improved	Thank you for your comment. The background section has been re-written to provide more background information and to improve language.	*Since many parts of the introduction section have been rewritten, please see the revised manuscript. All changes made are highlighted in yellow.*
Background P3 L47: "A majority of these infections are self-limiting" Please be more specific. "A majority" could be 51% - then a 50% prescription rate would be quite appropriate. Explaining and proving the existence of over-prescribing is a crucial point.	This comment has been address and more detailed statistics on current prescribing practices and guidelines have been presented.	Respiratory tract infections, including cough, acute bronchitis, common colds, otitis media, sinusitis and sore throat (including laryngitis, pharyngitis and tonsillitis) are among most common presentations in primary care [3 4]. A majority of these infections are self-limiting [5-7] and the UK guidance recommends no

		antibiotic strategy or a delayed antibiotic prescription for otherwise healthy adults [4], but approximately 50% of patients who present with a respiratory tract infection are prescribed an antibiotic [8]... Recent analyses of data from CPRD suggest an overall prescribing proportion of between 50% and 60% for these conditions, with 70% of episodes of otitis media and 90% of episodes of sinusitis resulting in antibiotic prescription [3 8]. (Pages 3 – 4)
Background P4 L15: “Recent evidence (7)” This is not very recent anymore.	This comment has been addressed.	Added (Page 4) Research evidence suggests that patients prescribed antibiotics for respiratory or urinary tract infection in primary care might develop bacterial resistance for up to 12 months [9].
Background P5 L44: «identifies ways to increase engagement in the intervention and increase effect sizes (19). This research is at a later stage of translation than previous trials” I do not fully understand this. Which “ways to increase engagement” are you referring to, and what does “This research” and “previous trials” refer to?	This point has been clarified and we hope our response is adequate.	Added (Page 6) Process evaluation undertaken as a part of the eCRT study suggested that although the intervention resulted in a significant reduction of antibiotic prescriptions among intervention practices, the intervention tools have been underutilised by many participating GPs. For example, some GPs were not aware of the implementation of the system into their practice (16.) These findings together with evidence from the systematic review, recent trials and systematic reviews of the wider implementation science literature [10 11], identify ways to increase engagement in the intervention and increase effect sizes [12]. This research is at a later stage of translation than previous randomised trials evaluating strategies to reduce antibiotic prescribing.
Study setting and target population P6 L57 I would have appreciated to know how UK general practices were recruited to the CPRD. I do not find it sufficient that you state that “The registered population is generally representative of the UK general population”	Comments addressed in response to Reviewer’s 3 comment.	Added (Page 7) The study will be conducted in the Clinical Practice Research Datalink (CPRD). The CPRD is the largest primary care databases of longitudinal medical records worldwide and includes about 7% (coverage of over 11.3 million patients) of UK general practices [13]. The CPRD data is generated via GP computer systems and special software collects data from practice servers

		on a monthly basis. The UK CPRD data collects anonymised data on clinical diagnosis, laboratory tests, issued prescriptions, clinical referrals and hospital admissions. To record healthcare, GPs can use a combination of coded and free text data [13]. The registered population is generally representative of the UK general population in terms of sex, age and ethnicity; and the quality of electronic health records data in the CPRD is well described [14]. General practices in England, Scotland, Wales and Northern Ireland that presently contribute up-to-standard data to the Clinical Practice Research Datalink (CPRD) will be eligible for the study.
Study setting and target population P7 L27 "The 120 practices…» Where does this number come from? How many eligible practices are there? How many of them do you think will consent to participate?	Thank you for your comment. We have clarified in the paper why we estimated 120 practices to be a feasible number.	Added (Page 8) At the trial start in January 2015, there were 427 general practices active in CPRD. Based on previous experience [eCRT reference], we estimated that it would be feasible to recruit a maximum of 120 CPRD general practices.
Sample size calculations Why do you start with a number of practices and calculate the power, instead of the opposite?	Thank you for your comment. We have provided a justification as to why we have calculated the power starting with the number of practices.	Added (page 8) In order to obtain as precise a result as possible, we aimed to achieve the maximum feasible sample size.
Intervention development and implementation P8 L38 What kind of development was done for this study? It seems that both the main elements have been used in earlier studies. Also, it would have been interesting to know what kind of adjustments the qualitative research resulted in.	Thank you for this comment. We have provided additional details on development work that has been undertaken for this study.	Added (Page 9 – 10) The development of the intervention was informed by existing health records, behaviour-change theory, systematic review evidence, clinical guidelines, qualitative research with non-trial practices (31 GPs and 3 nurse prescribers interviewed), as well as process evaluation data from the previous proof of concept trial [1]. Main elements used in the previous eCRT study were refined and new elements were added. Two novel major components are the provision of practice-level feedback on antibiotic prescribing and recruitment of a GP champion for each practice since facilitation plays an important role affecting the context in which change occurs [2]. A large part of the intervention refinement focused on

		the investigation of factors influencing implementation and selection of modifications of the tools in order to achieve maximum benefits of the intervention.
Intervention development and implementation P9 L24 Again: Upper RTI. Do you define cough/bronchitis as an URTI?	This point has been clarified and we have removed the word 'upper' throughout the paper.	
Intervention development and implementation P9 L56 What are the practices to do with the monthly feedback? How do you make sure that these are read and discussed?	This comments has been addressed and more detailed description of the intervention has been provided.	Added (Page 11) Each practice in the intervention arm will also receive monthly feedback on their antibiotic prescribing in the preceding month from CPRD analysis. The reports would present the prescribing rates in a table format and would also include evidence for safe best practice in respiratory tract infections management. Practices will be encouraged to review the monthly feedback received as part of the trial during monthly practice meetings where all practice staff are present. GP champion for each practice will be encouraged to circulate the feedback prior to the meeting and ensure that the discussion of the feedback is on the meeting agenda.
Outcome evaluation P10 L26 Why do you mention smoking, alcohol, hospital data etc? I guess you neither will use, nor have permission to use, this information?	This has been addressed. We removed these outcomes as they are not relevant for current analyses.	
REVIEWER 3: Annette Diener Institution and Country Institute of General Practice University Medical Center Rostock, Germany		
This study protocol describes a RCT aiming at GPs using electronic health records and electronically delivered information as an intervention to reduce inappropriate antibiotic prescriptions for self-limiting respiratory tract infections. The trial is highly relevant and might offer a simple and cost-effective way to optimise antibiotic prescribing.		

Major comments: − In the introduction (page 2 line 6) one or two more sentences would be helpful to underline and explain the problem-field of antibiotic prescription rates of about 60 % in the UK	Thank you for your comment. In the background section of the paper we have provided more evidence proving the existence of over-prescribing.	Added (Page 8) Over-utilisation of antibiotics in primary care also contributes to the emergence of antimicrobial drug resistance, increasing the risk of infections that may be very difficult to treat both in the local community as well as for individual patients. Recent evidence suggests that patients prescribed antibiotics for respiratory or urinary tract infection in primary care might develop bacterial resistance for up to 12 months [9]. Recent analyses of data from CPRD suggest an overall prescribing proportion of between 50% and 60% for these conditions, with 70% of episodes of otitis media and 90% of episodes of sinusitis resulting in antibiotic prescription [3 8]. Such rates of prescribing suggest that nearly all general practices are currently prescribing antibiotics at rates that are 'way off the mark' [15] in the context of good practice recommendations, which advise that most RTIs can be managed without the prescription of antibiotics [4]. Although there are no available guidelines on safe level of antibiotic prescribing for RTIs, the results of an analysis of Dutch primary healthcare records demonstrates a significantly lower prescribing rate compared with the UK, with approximately 22.5% patients consulting with a RTI episode, being issued a prescription [16]. Since majority of antibiotic prescribing takes place in primary care, the management of these infections offers an opportunity to make a major impact on unnecessary antibiotic prescribing. The Department of Health as a part of the UK Antimicrobial Resistance Strategy identified education and training as a key measure to reduce inappropriate and unnecessary antibiotic prescribing [17]. (Page 4)
Major comments: − The methods and analysis part of the study would benefit from more detailed information about how many practices are being recruited and how many patients with	Thank you, this comment has been addressed.	The mean practice list size was 8,537, and 120 general practices will include some 1.02 million registered patients, with about 224,000 RTI consultations over 12 months.

relevant symptoms are expected to be involved during the intervention time.		
Strengths: Page 3 line 8: Readers outside the UK might benefit from information about electronic health records as to be used, what data are recorded, by whom they are used, etc. In consequence it is not clear, why the use of EHR is a strength of the study.	This comment has been addressed. We have provided a more detailed description of the Clinical Practice Research Datalink which provides anonymised primary care records for public health research.	Added (Page 7) The study will be conducted in the Clinical Practice Research Datalink (CPRD). The CPRD is the largest primary care databases of longitudinal medical records worldwide and includes about 7% (coverage of over 11.3 million patients) of UK general practices [13]. The CPRD data is generated via GP computer systems and special software collects data from practice servers on a monthly basis. The UK CPRD data collects anonymised data on clinical diagnosis, laboratory tests, issued prescriptions, clinical referrals and hospital admissions. To record healthcare, GPs can use a combination of coded and free text data [13]. The registered population is generally representative of the UK general population in terms of sex, age and ethnicity; and the quality of electronic health records data in the CPRD is well described [14]. General practices in England, Scotland, Wales and Northern Ireland that presently contribute up-to-standard data to the Clinical Practice Research Datalink (CPRD) will be eligible for the study.
Strengths: − One would expect statements about the feasibility and the high number of collectable data.	Thank you for this suggestion. These are important strengths of the current study. We have highlighted these in the main text.	
2Strengths: − The problem about the complexity of an intervention including all identified factors (page 3 line 22-26) should be addressed more clearly: Which factors were identified, which were included in the intervention design, which were not and why	Thank you for your comment. We agree however this is beyond the scope of the current paper. We are currently working on a different paper intervention development and intervention content.	
Limitations: – In this section I would expect a broader discussion about potential biases.	Thank you for your comments. We have extended the section covering the limitations of the current study. We also expect to have a broader discussion of the study limitation in other	Added (Page 3) **Limitations** • Although behavioural theory and qualitative research were used to enhance the effectiveness of intervention design, it was not possible to

	publications related to this study: description of the intervention development and intervention content; main findings of the trial; findings of a mixed-methods evaluation of trial procedures.	include all identified factors without creating an intervention which would be too complex and difficult to use. • Due to the complexity of the intervention (i.e. different elements), our data cannot isolate which elements would be responsible for change in antibiotic prescribing (if achieved) • Initiatives to influence antibiotic prescribing both locally and nationally could influence the results of the current trial
Background: On page 4 line 23 the author writes, "The management of acute respiratory tract infections offers an opportunity to make a major impact on unnecessary antibiotic prescribing." This sentence needs more explanation.	Thank you for your comment. In the background section of the paper we have provided more evidence proving the existence of over-prescribing in primary care.	Added **(Page 4)** Over-utilisation of antibiotics in primary care also contributes to the emergence of antimicrobial drug resistance, increasing the risk of infections that may be very difficult to treat both in the local community as well as for individual patients. Recent evidence suggests that patients prescribed antibiotics for respiratory or urinary tract infection in primary care might develop bacterial resistance for up to 12 months [9]. Recent analyses of data from CPRD suggest an overall prescribing proportion of between 50% and 60% for these conditions, with 70% of episodes of otitis media and 90% of episodes of sinusitis resulting in antibiotic prescription [3 8]. Such rates of prescribing suggest that nearly all general practices are currently prescribing antibiotics at rates that are 'way off the mark' [15] in the context of good practice recommendations, which advise that most RTIs can be managed without the prescription of antibiotics [4]. Although there are no available guidelines on safe level of antibiotic prescribing for RITs, the results of an analysis of Dutch primary healthcare records demonstrates a significantly lower prescribing rate compared with the UK, with approximately 22.5% patients consulting with a RTI episode, being issued a prescription [16]. Since majority of antibiotic prescribing takes place in primary care, the management

		of these infections offers an opportunity to make a major impact on unnecessary antibiotic prescribing. The Department of Health as a part of the UK Antimicrobial Resistance Strategy identified education and training as a key measure to reduce inappropriate and unnecessary antibiotic prescribing [17].
Methods / Design: Study setting and target population: − In this paragraph (page 6 line 53) the authors describe the participating practices and population. For better understanding a total number of general practices in the UK and the number of their patients should be given.	This comment has been addressed. We have provided a more detailed description of the Clinical Practice Research Datalink which provides anonymised primary care records for public health research.	Added (Page 7) The study will be conducted in the Clinical Practice Research Datalink (CPRD). The CPRD is the largest primary care databases of longitudinal medical records worldwide and includes about 7% (coverage of over 11.3 million patients) of UK general practices [13]. The CPRD data is generated via GP computer systems and special software collects data from practice servers on a monthly basis. The UK CPRD data collects anonymised data on clinical diagnosis, laboratory tests, issued prescriptions, clinical referrals and hospital admissions. To record healthcare, GPs can use a combination of coded and free text data [13]. The registered population is generally representative of the UK general population in terms of sex, age and ethnicity; and the quality of electronic health records data in the CPRD is well described [14]. General practices in England, Scotland, Wales and Northern Ireland that presently contribute up-to-standard data to the Clinical Practice Research Datalink (CPRD) will be eligible for the study.
Page 7 line 3: Even if the quality of electronic health data in the CPRD is well described the study protocol would benefit from a short overview about “up-to-standard” data.		[changed to ‘research quality’]
On page 7 line 8 the authors describe eligible practices which will be invited to participate. Information about the total number of eligible GP practices, expected numbers of participating GPs (and their patients) and the mode of recruitment should be given here (invitation by letter, for	This comment has been addressed. We have provided a more detailed description of the Clinical Practice Research Datalink which provides anonymised primary care records for public health research.	At the trial start in January 2015, there were 427 general practices active in CPRD. Based on previous experience (18), we estimated that it would be feasible to recruit a maximum 120 CPRD general practices. The mean practice list size was 8,537, and 120 general practices will include some 1.02 million registered

instance). Also expected drop out-rates would be helpful (e. g. shown in a flow-cart).		patients, with about 224,000 RTI consultations over 12 months (Page 8)
Allocation: On page 8 the allocation process needs be described in more detail. As the study is performed at the King's College London it does not become clear how the involved scientists are blinded allocating the practices to control and intervention arm.	We agree and the allocation process has been described in more detail.	Added (page 9) 'The research team are at all times blind to the identity of trial practices, which is only known to CPRD staff.'
Minor comments On page 2 line 5 is written "Upper respiratory tract infections (uRTIs) account for about 60% of antibiotics prescribed in primary care." whereas on page 3 line 46 the author mentions "…but approximately 50% of patients who present with an upper respiratory tract infection are prescribed an antibiotic." The numbers should be consistent.	Thank you for your comment. These percentages refer to two different phenomena. "Upper respiratory tract infections (uRTIs) account for about 60% of antibiotics prescribed in primary care."- this means that of all antibiotic prescribed within primary are, 60% are prescribed for URTIs. "…but approximately 50% of patients who present with an upper respiratory tract infection are prescribed an antibiotic."- this means that approximately 50% of patients who present with a URTI in primary care, are prescribed an antibiotic.	
References: References 3 and 6 are identical.	Thank you for pointing this out. This has now been addressed.	
REVIEWER 4: Daniella Meeker Institution and Country University of Southern California, Los Angeles CA, United States		
The proposed study has a strong experimental design. The intervention design is informed by past work and a pilot study is expected to refine feasibility and acceptability. Investigators might consider step-wedge experimental design given the complexity of the intervention. Economic evaluations are also proposed - In addition to the quantitative evaluation, a process evaluation is proposed which is likely to produce high value information for future work.	Martin	A step-wedge design might be considered in evaluating the future roll-out of apparently successful interventions. (page 16) see Trials journal reference.
Introduction (2) For related interventions	Thank you for suggesting these references. We are	

using electronic medical records, consider citing Meeker et al. Meeker, D., J. A. Linder, C. R. Fox and et al. (2016). "Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: A randomized clinical trial." JAMA 315(6): 562-570. or Gerber, J. S., P. A. Prasad, A. G. Fiks and et al. (2013). "Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: A randomized trial." JAMA 309(22): 2345-2352. (3) For complex intervention design, consider reviewing Lau, R., F. Stevenson, B. N. Ong, K. Dziedzic, S. Treweek, S. Eldridge, H. Everitt, A. Kennedy, N. Qureshi, A. Rogers, R. Peacock and E. Murray (2015). "Achieving change in primary care-effectiveness of strategies for improving implementation of complex interventions: systematic review of reviews." BMJ Open 5(12): e009993.	aware of these studies and we have included these in the systematic review conducted as a part of intervention development. However we feel that the description of these studies in the introduction section is beyond the scope of this paper.	
Authors site the limitation "Initiatives to influence antibiotic prescribing both locally and nationally could influence the results of the current trial", normally this would not be the case in an RCT - an additional line of exposition would be helpful (e.g. performance improvement may have peaked due to concommittant interventions).	Martin	"Initiatives to influence antibiotic prescribing both locally and nationally could influence the results of the current trial, if these external influences contributed to optimal performance improvement across both trial arms.'
p5 line 23 - missing comma.	This has been addressed.	
p5 line 33 "This simple intervention showed a near 2% reduction in antibiotic prescribing" do the authors mean "2 percentage points"?	Martin	Changed to '2 percentage point'
Methods Consider secondary outcomes that measure the prescribing rates by diagnosis.	Martin	Page 12 secondary outcomes include 'different categories of respiratory infections, including colds, sore throat, cough and bronchitis, otitis media and rhino-sinusitis;'
Given stated concerns over other influences or trends in antibiotic prescribing, statistical	Thank you for this suggestion. These are interesting methods. For this	

methods used in Gerber et al. may be of interest either as sensitivity analyses or main analysis.	study, we consider that an effect of clinical and public health importance should be detectable using the standard methods described.	
Qualitative approach is valuable - it is not stated, but follow-up interviews aimed at sampling feedback from providers representing a range of effectiveness would be of interest	Thank you for this comment. Process evaluation will include qualitative interviews with providers representing a range of effectiveness. However, this information might have not been clear in the original paper, so this has been clarified.	A process evaluation will be conducted to evaluate the barriers and facilitators to implementation and the use of the intervention using a mixed methods approach. Participants in the process evaluation will primarily include general practitioners, but staff involved with intervention implementation will also be included, aiming pragmatically for the maximum achievable sample. We will aim to recruit practitioners with a range of experiences of the intervention to explore their unique or important perspective. A questionnaire and an interview guide will be developed guided by criteria suggested by Linnan and Steckler [18] for the process evaluation of public health interventions and research and will explore participants' experiences of using the intervention materials and experiences of the study implementation. Inductive thematic analysis will be used to analyse qualitative data. As a part of process evaluation, contextual information on initiatives to influence antibiotic prescribing which might be implemented both locally and nationally, will be collected. This will include periodic surveys of documentary sources, primarily those accessible on the internet. It will also include specific questionnaire items concerning participating practices' exposure to other influences, such as interaction with local NHS prescribing advisers. As a part of process evaluation, compliance with the intervention protocol will be assessed. This will be done by evaluating the total number of times the intervention tools (including the practice prescribing reports, the decision support tools and webinars) are accessed over the intervention period.

References:

1. McDermott L, Yardley L, Little P, et al. Process evaluation of a point-of-care cluster randomised trial using a computer-delivered intervention to reduce antibiotic prescribing in primary care. BMC Health Serv Res 2014;**14**:594.
2. Rycroft-Malone J. The PARIHS Framework—A Framework for Guiding the Implementation of Evidence-based Practice. Journal of nursing care quality 2004;**19**(4):297-304.
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VERSION 2 – REVIEW

REVIEWER	Mariam de la Poza, Pablo Alonso-Coello Institution and Country, Institut Català de la Salut Iberoamerican Cochrane Center
REVIEW RETURNED	18-May-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Sigurd Høye Department of General Practice, University of Oslo, Norway
REVIEW RETURNED	04-May-2016

GENERAL COMMENTS	Thank you for the opportunity to read the revised version of the protocol. I find that all my comments are addressed in a satisfactory manner. I wish the authors the best of luck with the trial.

REVIEWER	Annette Diener Institute of General Practice University Medical Center Rostock, Germany
REVIEW RETURNED	06-May-2016

GENERAL COMMENTS	Thank you very much for your detailed response. All comments were adequately addressed. I don't have any further comments.

REVIEWER	Daniella Meeker University of Southern California United States
REVIEW RETURNED	22-May-2016

GENERAL COMMENTS	All prior comments have been addressed.