Author's response to reviews

Title: Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care: study protocol for a randomised controlled trial and baseline characteristics of participating general practitioners [ISRCTN73182671]

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Author's response to reviews: see over
Dear Editor

We would like to thank you for reviewing our manuscript and for reconsidering a revised version for publication in BMC Family Practice. We carefully addressed all the points raised by the reviewers in the point by point reply and thank them for their work. All contributors have approved this revised version of the manuscript and fulfil criteria for authorship.

We hope that this revision meets your and the reviewers’ expectations and that it can be accepted for publication in the present form. We are looking forward to your reply.

Yours sincerely

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First revision: Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care: study protocol for a randomised controlled trial and baseline characteristics of participating general practitioners [ISRCTN73182671]

Comments from Reviewer #1 Michael S Niederman

1.) In the introduction and throughout the manuscript, the authors state that they recruited general practitioners who are representative of all eligible general practitioners. There are absolutely no data presented to justify this statement. In fact, it is clear that they tried to recruit a number of general practitioners who did not accept recruitment. There may indeed be something very different about individuals who are willing to do the research versus those who weren’t. This raises a key credibility question about the study, namely is it feasible to use this type of approach in a primary care practice.

Reply:
We collected data on baseline characteristics of participating and all eligible general practitioners in Basel and its environment (Methods, page 9, paragraph 2, revised manuscript). These characteristics are presented in Table 1 (page 23). When compared, baseline characteristics of the participating GPs are similar to those of all eligible GPs. Therefore we say in the Abstract (page 3, paragraph 2) and the Methods section (page 9, paragraph 2) that these data suggest that participating GPs are representative of all eligible GPs with respect to presented characteristics. We also point out in the Discussion section (page 14, paragraph 2) that we are aware of the fact that we probably recruited highly motivated primary care physicians who are interested in the research question. This bias is probably unavoidable when one invites GPs to participate in a trial. However, we don’t think that this invalidates the results of our trial: motivated, interested GPs may already be more reluctant to prescribe antibiotics for ARTI than disinterested GPs. Motivated GPs might recruit patients for antibiotic treatment who are on average sicker than patients recruited by less motivated GPs. If true, this would make it harder to show a 20% reduction in antibiotic use for the ProCT group. And therefore the potential bias will be conservative.

To further clarify this important point raised by the reviewer, we rephrased the relevant sentences of paragraph 2, page 14, Discussion:

Second, we expect to have recruited highly motivated primary care physicians, interested in the research question and able to provide high quality data. Motivated, interested GPs might be more reluctant to prescribe antibiotics for ARTI; thus they might consider patients for antibiotic treatment which are on average sicker than patients considered by disinterested GPs. However, we believe that ProCT-guided ARTI management will lead to a reduced antibiotic use even in such a setting of motivated GPs and the potential bias will be conservative.

2.) I am still very confused about the protocol as it is designed. The authors suggest that the use of the protocol could lead to less antibiotic usage, but I am not clear about their concern of a
Hawthorne effect. The Hawthorne effect implies that if patients are managed according to the protocol, then the control group might over time have different management. For this protocol to be relevant and valuable, it needs to be organised in the following fashion. The investigators need to determine first that based on clinical criteria, they will treat with antibiotics. Then, the PCT measurement is done. If indeed this is the protocol, then the decision to treat the controls has already been made, and the use of PCT data should not change the enrollment in that only patients in whom they have decided to treat with antibiotics will be considered controls. This is a critically important methodological point which I do not feel is adequately addressed.

Reply:
We agree with these ideas on patient recruitment, and this is indeed exactly what we describe in our protocol (Methods, page 7, paragraph 2; and Figure 1).

To clarify this further we added information and rephrased paragraph 3, page 9 of the Methods section:

When a participating GP intends to give antibiotic treatment to an eligible patient based on clinical criteria and the patient gives written informed consent, the GP calls the study centre and the patient is randomly allocated to one treatment group or the other. The GP then takes a blood sample from the patient and sends it by courier service to the laboratory of clinical chemistry at the University Hospital Basel. This laboratory measures ProCT in all patients. Additionally, the GP documents patient baseline data on signs and symptoms, diagnostic procedures, diagnosis, co-morbidity and prescribed medication.

We also rephrased parts of paragraph 2, page 14, Discussion:

See point 1.

3.) A more clear explanation of the evidence-based guidelines for antibiotic usage should be provided.

Reply:
We now give a link to our institute’s web-site where a PDF of the evidence-based guidelines can be viewed (www.bice.ch/publications/reports). Additionally, we rephrased the relevant paragraph and now say in paragraph 2, page 8 of the revised manuscript:

HCB and MB developed guidelines for the management of ARTI based on evidence-based US-position papers which were endorsed by the Centers for Disease Control and Prevention, the American Academy of Family Medicine, the American College of Physicians, and the Infectious Disease Society of America [37-42]. We systematically searched MEDLINE and the Cochrane Library to update this evidence with recent controlled clinical trials. A panel of local primary care providers, infectious disease experts, and clinical epidemiologists reviewed the guidelines and made suggestions for adaptation to local conditions. We distributed the guidelines as a booklet (see www.bice.ch/publications/reports) and presented them in a 2-hour seminar to all participating GPs.
4.) The authors never discuss the fact that even if their intervention does lead to less antibiotic usage it is a very labour intensive and potentially expensive approach. It seems unrealistic to believe that patients will agree to have a blood test, wait for the results of the blood test to decide if they will get an antibiotic prescription and then return frequently for a follow-up blood test to decide when to stop the antibiotic therapy. The practicality of this approach in primary care seems doubtful and this issue is not discussed by the authors.

Reply:
The concept of our trial is as a “proof in principle” of the benefit and safety of ProCT-guided antibiotic use for ARTI in primary care with respect to patient relevant outcomes. Therefore, as an additional safety margin, the clinical and laboratory follow-up examination at day 1 was included in the study protocol. We agree that a centrally measured ProCT is not ideal for GPs and patients. However, in Switzerland, similar to other countries, GP’s often send blood samples to external laboratories for analysis of white blood cell count and C-reactive protein among others. Furthermore, if the results of our study show that antibiotic usage can be reduced by ProCT guidance, this will push the availability of a sensitive near-patient ProCT test. Such an assay is currently being developed (Brahms, personal communication).

We also added the following to our Discussion (page 14, paragraph 2):

Third, while measurement of ProCT at a central laboratory is not ideal for routine primary care, there are still a considerable number of general practices that send blood samples daily to a laboratory for analysis of C-reactive protein or leucocytes. Therefore this should also be feasible for ProCT until a near-patient test, which is currently being developed, becomes widely available.

5.) The authors state that follow-up of patients will be done in a blinded fashion by telephone. It seems impossible that the follow-up could be blinded since the interviewers could determine which patients had multiple blood tests and, therefore, which patients were enrolled in the procalcitonin monitoring group.

Reply:
We employed medical students from the University of Basel to conduct standardised telephone interviews. The students were informed and trained to interview patients with ARTI about their treatment, symptoms, degree of discomfort etc. They do not know about the intervention, nor the goals of the trial, nor other details. We also cannot think of any motivation for these students to manipulate the data collected.

6.) The authors have not listed antibiotic usage as a primary end point. Without this being a primary end point, I believe there is no point in doing the study. To simply say that the two management approaches, used in a low risk population, do not have different outcomes is a very un-ambitious study. This study will only have value if it leads to less antibiotic usage and as such, antibiotic usage deserves to be a primary end point.
Reply:
We agree with the reviewer, and the overall aim of this trial (Methods, page 6, paragraph 1) is to see if a ProCT-guided diagnostic and therapeutic strategy leads to similar patient outcomes but with lower total antibiotic use relative to a standard approach using current guidelines. We are more precise in our study hypothesis (Methods, page 11, paragraph 3): clinical outcomes for patients with ARTI will be no worse under ProCT-guided treatment, but patients with ProCT-guided treatment will have lower total antibiotic use; specifically a 20% lower antibiotic prescription rate and a 20% shorter antibiotic duration compared to patients treated under the standard approach.

The design of our trial is such that all recruited patients receive antibiotics by default (eligible patients are in need of antibiotics as judged by the GP). The only decision the GP can then make is whether to withhold antibiotics for a patient in the ProCT guided arm, on the basis of the ProCT test results GPs are given for these patients. Therefore antibiotic use will almost certainly be lower in the ProCT guided arm. The questions of interest are not whether antibiotic use is lower in this arm, but how much lower, and are patient outcomes adversely affected? We believe that if patient outcomes are affected, a ProCT strategy will not be acceptable. Therefore a patient outcome is our primary endpoint. We then have to show that this primary endpoint is no different under either strategy (this is then a non-inferiority trial), and this requires a much larger sample than an equivalent superiority trial. We then will have a large enough sample to answer both questions adequately: is the patient outcome adversely affected and what is the size of the reduction in antibiotic use?

To better reflect the reviewer’s point in our revised manuscript we have added a sentence to our sample size considerations (Methods, page 12, paragraph 1):

*This sample size will allow us to estimate the reduction in antibiotic use between the two arms to within ±6%.*
Point by point reply:

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Comments from Reviewer #2 (Chris Del Mar)

1.) Do patients provide consent? I would have thought this is mandatory, but I think will be a problem because GPs hate obtaining consent from patients during a clinic, and in this case the benefits for the patient may not be obvious (having antibiotics withheld is not hugely attractive), and they have to undergo two extra visits, and to provide blood (otherwise not normal I imagine) on two occasions.

Reply:
All recruited patients have to provide written informed consent. We note this in the Methods section (page 6, paragraph 3 and page 7, paragraph 2). Patients who are unable to give written informed consent are excluded from the trial (Abstract, page 2, paragraph 4 and Methods, page 7 paragraph 2).

We tried to keep the extra time and effort for the participating GPs to a minimum by designing study forms which are easy to fill in (we tested the forms several times with GPs and steadily improved them) and by providing patient consent forms which the eligible patients can read while their GP sees another patient. We realise that due to necessary logistics patients and GP’s have to make an extra effort for this trial. However in a previous trial in primary care [ISRCTN57824788], we found that patients are motivated to participate in a trial and make extra efforts when they know that they can help to improve medical care for future patients.

2.) How long will it take to communicate the results to the GP? I am not clear how this is operating: will the GP take a blood sample, and then defer the decision of the antibiotic until the result is conveyed back from the lab (presumably the next day – or any rate until after the patient has left?), and then the antibiotic prescribed? Perhaps a ‘delayed’ prescription will be used?

Reply:
After a blood sample is drawn it takes 2-4 hours until the results are communicated to the GP. This happens only if the patient is part of the ProCT group. The GP then informs the patient about antibiotic treatment by phone. If the ProCT level is high, the patient uses a ‘delayed’ prescription or comes back to the GP to pick up the antibiotic; if ProCT is low, the patient is asked to come back the next day for a safety check.

We added this information to the revised manuscript (Methods, page 9, paragraph 4):

Where patients are randomised to the ProCT-arm, GPs will be informed about ProCT results and given recommendations about appropriate antibiotic therapy within 2-4 h after the blood is taken
depending on the location of the practice. A cut-off ProCT level of 0.1 µg/l is used to rule out a bacterial respiratory tract infection. This value is identical to the cut-off used for the evaluation of patients in the emergency department of the University Hospital Basel [30]. In patients with a ProCT level below 0.1 µg/l, the diagnosis of a bacterial respiratory tract infection is considered highly unlikely, and the GP is encouraged to look for viral or alternative causes. Accordingly, the use of antibiotics is discouraged. In patients with a ProCT level above 0.25 µg/l, a bacterial respiratory tract infection is considered the most likely diagnosis and the use of antibiotics is recommended. For ProCT levels from 0.1 to 0.25 µg/l, a bacterial infection is unlikely and antibiotic treatment is not advocated.

The GP then informs the patient about antibiotic treatment by phone. Patients in whom antibiotics are given will be asked to use a delayed prescription or to come back to the practice to pick up the antibiotic there. For patients in whom antibiotics are withheld based on ProCT levels of 0.25 µg/l or below, a follow-up measurement of ProCT within 24 hours is mandatory.

See also changes made for point 4.

3.) It is a pity that patients for whom antibiotics are not contemplated are not included. As a GP I am interested to know how often a doctor was prompted to use antibiotics because of an unexpected high PCT. This would be all part of getting the right drug to the right patient.

Reply:
We considered this when planning the trial, but finally decided to exclude these patients. Our experience suggests that the scenario of a GP being prompted by an unexpected high ProCT to prescribe antibiotics would be extremely rare. On the other hand, the workload for participating GPs and the sample size of the trial would be much higher, probably rendering this “proof in principle” trial unfeasible.

4.) I am worried that the PCT was designed for ‘severe sepsis or bacterial infection’ (see BRAHMS website). This may be rare in primary care, even though there is evidence of benefit for many bacterial ARI infections, even if modest.

Reply:
It is true that the commercially available two-site assay (LUMItest® PCT, Brahms), which measures both ProCT and the conjoined CT:CCP I by means of a luminometer, is only useful to detect markedly elevated ProCT levels in severe, systemic bacterial infections, i.e. in sepsis. However, this manual assay has the disadvantage of being relative insensitive, with an accurate detection limit of ~0.3 to 0.5 µg/L. Thus; the LUMItest® assay is not sensitive enough to detect mildly or moderately elevated ProCT levels, which limits the diagnostic use in conditions other than overt sepsis. Accordingly, ProCT was first approved and marketed as a sepsis marker and limited to intensive care units.

We recently evaluated a newly developed ProCT assay for the guidance of antimicrobial therapy also for less serious infections, i.e. lower respiratory tract infections (Christ-Crain et al., Lancet 2004;363:600-7). This commercially available assay takes advantage of a time-resolved amplified
cryptate emission (TRACE) technology (Kryptor® PCT, Brahms, Hennigsdorf, Germany). It is based on a sheep polyclonal anti-calcitonin antibody and a monoclonal anti-katacalcin antibody, which bind to the calcitonin and katacalcin sequence of calcitonin precursor molecules. The assay has a functional assay sensitivity of 0.06 μg/L, i.e. 3 to 10-fold above normal mean values, which makes it suitable to detect minimally or moderately elevated ProCT levels.

Since the benefit from antibiotics is only modest for most patients with ARTI, we believe that it is important to find a way to better identify those patients who actually do benefit from antibiotics.

We added information about the ProCT assay and say now on page 8, paragraph 3 of the revised manuscript:

We measure ProCT by using a newly developed time-resolved amplified cryptate emission (TRACE) technology assay (Kryptor PCT, Brahms, Hennigsdorf, Germany). This assay is based on a sheep polyclonal antibody against calcitonin and a monoclonal antibody against katacalcin, which bind to the calcitonin and katacalcin sequence of calcitonin precursor molecules. The assay has an improved functional assay sensitivity of 0.06 μg/L – i.e., three to ten fold above normal mean values. Assay time is 19 min with 20-50 μl of plasma or serum. The test is performed at the central laboratory of the University Hospital Basel, and results can be communicated to participating GPs within 2-4 h depending on the location of the practice.

5.) Two references citations incorrectly present my name as ‘Mar’ rather than ‘Del Mar’.

Reply:
We apologise for this mistake and have corrected it in the revised version.

Additional comment from the authors:

We recently got a positive reply from the Swiss National Science Foundation to fund the trial. Therefore we changed the relevant sentence in the Acknowledgements section:

This study is funded by the University Hospital Basel and the Swiss National Science Foundation (project number 3300C0-107772/1).