Author's response to reviews

Title: The QICKd study protocol: a cluster randomised trial to compare quality improvement interventions to lower systolic blood pressure in chronic kidney disease (CKD) in primary care [ISRCTN56023731]

Authors:

Simon de Lusignan (slusigna@sgul.ac.uk)
Hugh Gallagher (Hugh.Gallagher@epsom-sthelier.nhs.uk)
Tom Chan (tchan@sgul.ac.uk)
Nicki Thomas (N.M.Thomas@city.ac.uk)
Jeremy van Vlymen (jvanvlym@sgul.ac.uk)
Michael Nation (michaelnation@kidneyresearchuk.org)
Neerja Jain (NeerjaJain@kidneyresearchuk.org)
Aumran Tahir (mtahir@nhs.net)
Elizabeth du Bois (Elizabeth.Dubois@wpct.nhs.uk)
Iain Crinson (icrinson@sgul.ac.uk)
Nigel Hague (njhmg@hotmail.co.uk)
Fiona Reid (freid@sgul.ac.uk)
Kevin Harris (Kevin.Harris@uhl-tr.nhs.uk)

Version: 2 Date: 31 March 2009

Author's response to reviews: see over
Dear Editor,

Title: The QICKd study protocol: a cluster randomised trial to compare quality improvement interventions to lower systolic blood pressure in chronic kidney disease (CKD) in primary care [ISRCTN56023731]

Comments on reviews and actions taken

Thanks for the careful reviews you have supplied. I think that by responding to these we have improved the paper.

I have pasted the reviewers’ comments into this document and responded to each comment. The responses are marked: **Author response>> And, they are in italics for clarity.**

We are delighted that both reviewers thought this an important protocol worthy of publication.

The revised paper has been circulated to the authors and been approved accordingly. I hope that this protocol is now considered up to standard for publication. Please let me know if you require any further changes.

Best wishes,

Simon de Lusignan, on behalf of the authors.

Reviewer’s report No 1:

With the present protocol the authors face one of the most relevant health care problems of the next decade: the optimal management of CKD in primary care. The study-protocol is very complex and well designed, however, there are few

Minor Essential Revisions:

1. It is not clearly stated how the study will be funded, the cost analysis of the study is lacking and it is not clear whether the physicians will receive incentives.

**Author response>>** The first paragraph of the acknowledgements (at the end of the paper just before the references; page 22) states the source of funding for the project. There are two funding sources – the Health Foundation and Edith Murhpy charitable foundation. Both of these awards were obtained as the result of national competitions and a process of peer review.

Concerning practitioner payments: we have added two sentences to the section on participants to clarify this.

2. The primary outcome of the study is the reduction of systolic blood pressure. The study is powered to detect a mean 3 mmHg difference in systolic blood pressure between the practice groups. The authors should clarify how this difference is related to the improvement of the quality of CKD management in primary care, how promotes the implementation of best practice and/or what links this primary outcome (surrogate)with the list of objectives of the study.

**Author response>>** This could have been clearer in the background section. This information was in earlier versions but removed when we cut down the size of the paper. We have expanded on the first paragraph of the background; we have cited the recent (September 2008) review by the National collaborating centre for chronic conditions and Royal College of Physicians, which has carefully reviewed this evidence.

3. The authors state in the objective N°5 that it will be possible to characterise the natural history of CKD, with longitudinal data registered prior to the study. In fact, they plan to retrieve data for the CKD patients up to 10 years before the start of the study. To this purpose the authors should report the prevalence of creatinine measurement (to estimate GFR)or of albuminuria, registered in CKD patients in the past 10 years, in a small sample of practices participating in the protocol, in order to show the feasibility of this objective.

**Author response>>** This is a good point. The 2008 NICE guidance defines progressive disease as decline of >5ml/min in 1 year or >10ml/min in 5 years. For reasons set out below there will be a lot more data for people with decline over 5 years; and we have changed the protocol accordingly.
The feasibility of looking at this data is based on two factors. (1) Has the practice "Lab-links" – electronic links to send laboratory results direct to the practice; and (2) What is the turnover of the practice. For example my practice was in the pilot of "Lab-links" in the mid 1990s and has a small turnover (<4%) per year; giving good continuity of data. Nearly all practices had lab-links installed prior to the 2004 new contract for general practice – as the financially incentivised chronic disease management indicators (e.g. renal function tests in hypertension) rely on well recorded pathology data recorded annually. However, a practice in areas of southwest London where much of the accommodation is small single occupancy "bed-sit-land" may have a turnover of 25% per year – though it's older population turnover less. We have added a line to the quality of GP computer data – Connection to hospital laboratories to note that we anticipate good data since 2004; and to the biomedical data section to say we may be restricted in the number of practices with 10 years data and need to look over a shorter period.

Reviewer's report No 2:

1. The plan is to conduct a two-year study but the authors state their experience is that ABE is more effective in its second and third years. Can they justify running a large study for two years that may show no significant effect because it didn't run for a third year?  
Author response>> An error occurred in the editing of the protocol submitted for publication which we wish to correct. Our observation of change in practices undertaking audit-based education found that there was a greater change between the second and third data collections. i.e. the change between the end of year one and year two were greater than the change between base-line (first) and the second data collections. We can only apologise for the lack of precision and that this got lost in translation. The text has been amended to reflect this.

2. The themes given for the interventions are largely clinical measures and the appropriate clinical response. Process of delivering care is mentioned and it may be that this is a more fruitful area of education to explore. We would advocate including advice on adherence, effective call/recall of patients and adverse drug effects and interactions if this is possible. 
Author response>> The process evaluation arm (4 practices) is attempting to explore these issues from a qualitative perspective – and we can specifically include these issues. Although not strictly adherence we can calculate a proxy for medicines possession ratio based on the number of prescriptions collected for ACE-I and ARB – probably the most important therapeutic interventions. We have added an additional point to Box 2 (new point 9) to reflect this. We have also added a sentence into the unexpected consequences paragraph. We were already looking at collecting data on falls with ACE-I and ARB on the advice of our advisory board.

3. It is difficult for the reader to get a strong sense of the interventions that are being tested and this is vital for learning lessons at the end of the study (whether outcomes are positive or negative). For example, what sort of size of document will the guidelines and prompts guidance be and in what format? How long is an ABE workshop likely to last, how many participants are likely to be at one session and what training is the local GP to have received? If the authors could explicitly point readers to specific examples they aim to emulate or provide more detail this would be of great use. 
Author response>> We have added to the sections which describe the interventions adding the detail requested by the reviewer.

4. Practices are to be recruited to the study and all of their population with CKD are to be the subjects. However, the primary research participants are to be general practitioners. Are the general practitioners to be consented individually or is the consent of the practice as a whole enough to include them. In other words, are all GPs in a practice to be participants or may they choose to abstain and if so how does that affect the sampling of all patients in a practice. It also appears that practice managers and nurses are to participate in the interventions, but they are not named as participants. Furthermore, I presume patients are not to be consented but if this was stated it would offer clarity. 
Author response>> Yes, GPs are the primary research participants. We expect to only recruit practices where all GPs consent to participate. We have included an explanation to this effect and that patients are not directly consented within the "Participants" section.

5. The study will define CKD in the subjects by two or more measures of eGFR < 60 at least 3 months apart. There doesn't seem to be a planned analysis of the
impact of the interventions on the measuring and recording of eGFR or of the difference between practices at baseline. As this is likely to impact upon the proportion of subjects defined by the study as having CKD, serious consideration should be given to the effect on analyses. If however the subjects will only be included if both measures of eGFR occurred prior to baseline this should be stated.

**Author response>>** We have qualified this statement by saying that we also plan to look at the effect on prevalence of also including people with a single reading. In the “clinical and laboratory markers” section we have also added a section on case definition. We will include cases since 1st April 2006 the point at which creatinine recording was standardised.

6. In paragraph 3 in the ‘Epidemiology of Chronic Kidney Disease’ section, the authors state “Studies have demonstrated a need to improve both information and training available with the aim of closing the gap in the quality of care currently provided.7”, yet they cite only one study which appears to demonstrate that targets are frequently unmet and documented hypertension was often untreated, but not the reasons for this. The authors do not state to whom the information and training should be made available (patients or practitioners).

**Author response>>** We have amended the protocol to make it clear we mean practitioners.

**Author response>>** Although not part of this study the grants we have received are also funding a study of the empowering patients through a peer educator programme.

7. The protocol does not include a rationale for the use of a cluster randomised trial.

**Author response>>** A brief section on the rationally for the CRT has also been added at the start of the method.

8. The four practices to be used for the in-depth process evaluation are to be purposively selected but the authors don’t state the type of purposive selection, the criteria to be considered, or how or why these practices will be selected.

**Author response>>** We selected these practices for their different types of location – north or south; city or suburban. We also looked for practices with each of the different brands of GP computer system. This is added to the text.

9. Practices will be randomly allocated to the three arms in blocks of nine. This will leave three practices to be allocated in each group (75-72 and 30-27) to reach the sample sizes required. Will these be allocated via a block of three at the end or will the study accept uneven sample sizes. Additionally, the authors do not state in what order practices will be allocated to groups (e.g. upon agreement or alphabetically).

**Author response>>** Yes, this is correct. We end up with a final small block of practices at the end. We randomise as each block of 9 is recruited; i.e. upon agreement.

10. Both of the final points in the boxes describing the intervention themes seem to relate to the process evaluation (rather than the intervention). If not, how is the information (e.g. how the intervention can be improved) to be fed back to the researchers and analysed?

**Author response>>** At least three of the study team are at each workshop. They complete feedback forms and report back through the operational team meetings; additionally a semi-structured interview is being undertaken after round 1 to ensure we capture any lessons from the baseline workshops. All delegates at these meetings also give feedback, which is also fed back to the study team. I have added a brief explanation of this to the end of the description of the intervention.

11. The precise primary outcome measure is unclear and the reason for choosing systolic blood pressure is not given. Hypertension is not defined nor when the measurement was taken: is it an SBP >=130mmHg or >=140mmHg at baseline for example? Is the desired outcome a change in mean SBP over the two years of -3mmHg in the ABC arm or a difference between arms in change over the two years of >3mmHg or a difference between arms in mean SBP >3mmHg at the 2 year point or something else?

**Author response>>** We have strengthened the background in response to the earlier comments to make it clearer that reduction in blood pressure is the most effective evidence-based intervention to slow the progression of CKD. As this can be influenced within general practice – it is our primary outcome measure.
We have added the reference to the NICE 2008 targets and stated the systolic targets: <140mmHg for low risk and <130mmHg for high risk. We are looking for a between arms change over the two years of >3mmHg; which is stated in the power calculation section.

12. The use of a mean value to measure impact has the potential to hide a multitude of possible scenarios. The authors should consider including a secondary measure of, for example, percentage of patients hypertensive at baseline whose SBP fell by (say) 5mmHg. If a significant difference is found this will provide stronger evidence of the impact of the intervention to patients’ health.

Author response >> this is a helpful suggestion which we have included.

13. The authors have chosen to include patients with CKD stages 4 and 5 in their analysis when many of these patients will (or should) be substantially managed by a renal consultant. Can the authors justify this inclusion? It is quite possible this will reduce the apparent effectiveness of the intervention. The authors could state upfront an intention to perform secondary analyses of their primary outcome measure across these different patient groups, hypothesising that the intervention would have less effect in CKD 4 and 5 because of specialist management.

Author response >> Again this is as sensible suggestion. Though stage 4 and 5 disease combined represent only around 3% of people with CKD.

14. There is no age cut-off in the analysis, which I believe is justifiable as there will hopefully be an effect across the patient cohort. Again, secondary analyses could compare the intervention between young, typical and very old age groups.

Author response >> We feel that CKD although more common in the elderly should still be treated.

15. There is no stated analysis of, or adjustment for, the impact of deaths on outcomes. Will dead patients be included or excluded? About 4000 patients (12%) will die in 2 years and those most likely to die are those with the highest BPs. This could reduce the power of the study because the high BP people in the control arm are likely to die and leave those with the lowest BP still in the project. This is really difficult.

Author response >> This is something we will explore. We have written to the ethics committee about including death in our dataset. The problems are that it is incompletely coded. However, we will try as far as possible to document and adjust for this.

16. The comparative analyses described include multiple regression analyses to examine the "relations between independent variables (e.g. known demographics and risk factors such as smoking status, level of cholesterol, obesity, anaemia, alcohol consumption etc) and dependent variables (e.g. CKD stage 3-5 and diabetes)." The 'independent' variables are likely to be highly correlated and this needs to be taken into consideration as part of the analysis. Including anaemia as an independent variable in a regression to explain CKD is problematic as causality is probably bi-directional.

Author response >> This is something we concur with and will need to take into account.

17. On page 16 the focus groups and their analysis are described. Will any particular approach be taken in conducting the analysis? In addition, is it IC (rather than IS) who will conduct the qualitative analysis?

Author response >> Apologies – this should be IC – I fear this was auto-correction! The analysis will utilise the 'Framework' approach developed at the National Centre for Social Research and now a widely used method for analysis within the field of health and social care research. This involves an initial phase of data management in which the transcripts of the group discussions will be checked for accuracy, and then re-read to gain familiarity with the data set. A conceptual or thematic framework will then be constructed. This will involve an indexing or labelling of the transcript data identifying initial themes or concepts. This process will then be applied to the entire dataset while undergoing a process of constant refinement, which included the identification of deviant cases. A set of thematic charts will then be constructed in order to sort the transcript data with similar subject matter into a hierarchy of main and sub-themes so that the data can be more easily synthesised prior to interpretative analysis. The first sentence and a reference have been added to this section of the protocol.
19. The study’s control relies on limited contact between general practices and renal units. In some parts of the country, renal units are engaging with general practices, both through education sessions and shared management of patients. Do the investigators know the extent of this in the areas they will be operating in or are they able to record this, for example through their questionnaire? 

**Author response>>** We collect information about local guidance as part of the process of creation of the “Guidelines and prompts.”

20. On page 8 the authors state “We will be able to compare questionnaire and non-questionnaire practices in each arm at the end of the study”. However, they don’t acknowledge the differing impacts the interventions (and control) could have on the results of the questionnaire itself. As well as genuinely increasing confidence, the interventions in the context of a study could lead to over-reporting of confidence or similarly under-reporting among the control group. The questionnaire may be useful and should be retained but this potential bias could be acknowledged. 

**Author response>>** We are primarily collecting the questionnaire data to compare the arms of the study. However, we will also compare questionnaire vs. non questionnaire in each arm. We have made small changes in the text to make this clear.

Minor essential revisions - Clarity and readability
1. It may help the readers if the aims and objectives are moved up to the start of the methods section. 

**Author response>>** We have done this as we agree it will aid clarity.

2. I found the protocol felt slightly disjointed at times and thought it could benefit from a stronger single narrative. 

**Author response>>** We have tried to improve this without making major content changes.

3. When talking about the QOF with reference to quality of GP data the authors suggest uncritically that the QOF has improved diagnosis recording, yet they appeared to suggest that data could be less reliable because of the QOF on the previous page. The authors should clarify this.

**Author response>>** We have tried to improved this.

4. The protocol contains a large number of spelling mistakes and the punctuation could be improved. For example, “presence of absence of”, “enbale” and on page 6, “…their own practices’…” should be “…their own practice’s…”.

**Author response>>** We have set out to correct these.

5. The use of abbreviations is inconsistent throughout the text and they are not always introduced. The list of abbreviations is also incomplete. For example in paragraph 2, in the ‘Epidemiology of Chronic Kidney Disease’ section, ‘rate’ is missing from the text ‘estimated glomerular filtration rate (eGFR)’. Later, GFR is used in place of eGFR and estimated glomerular filtration rate continues to be used.

**Author response>>** We have corrected these.

6. In paragraph 3 in the ‘Epidemiology of Chronic Kidney Disease’ section, “a threshold for intervention of 140/90 is recommended”; the authors should indicate this refers to BP and the units, mmHg.

**Author response>>** We have changed this.

7. When introducing the parallel study (page 7) the authors label its parts a) and b), but when they describe it they reverse the order and label its parts (1) and (2). To add to the confusion, the participant groups in figure 2 are labelled (1), (2) and (3), where (2) and (3) in the figure refer to (2) and (1) respectively in the text. This should be clarified.

**Author response>>** We have re-ordered these and labelled the interventions “(a),” “(b)” and “(c)” and the elements of the study (1) and (2). I hope this makes it easier to follow the protocol.

8. On page 7, the sentence “They will validate our questionnaire to assess confidence; during the study proper report on the intervention exposure (...) and
programme fidelity (...)" could be made clearer to the reader by changing it to "They will validate our questionnaire to assess confidence and, during the study proper, report on the intervention exposure (...) and programme fidelity (...)".

**Author response>>** We have made this change. Thanks – it reads better.

9. On page 4, paragraph 1, sentence 3 it could be made clearer that the models under review are of practice improvement interventions.

**Author response>>** We have improved this sentence.

10. In paragraph 3 in the 'Epidemiology of Chronic Kidney Disease' section, "with a target for optimal management of a systolic BP of between 130 and 139" could be rearranged as "with a target systolic BP of between 130 and 139 for optimal management".

**Author response>>** We have made this change – we agree it reads better.

11. In paragraph 6 in the 'Epidemiology of Chronic Kidney Disease' section, the fourth sentence (on over-aggressive guidance) should be rewritten and can be supported by citation.

**Author response>>** We have toned down and qualified this assertion; as we can’t find literature to support it. Indeed our rationale for collecting 10 years creatinine is to study this phenomena in more depth. The original statement very much concurs with our personal clinical experience and CKD data we have been involved with over the last 6 years.

12. It isn’t always clear which parts of the study are being referred to, for example, in “The study will use a model developed by the Primary Care Data Quality project” study means ABE and in “The content and focus of the guidelines and prompts arms of the study will be the same.” this again means as the ABE.

**Author response>>** We have corrected these – and given the whole paper a careful read through to try to improve the clarity of the paper.

13. There is a citation in the discussion to reference 57, but the reference list stops at 45. Similarly, there is a missing citation (Error! Bookmark not defined) in the discussion.

**Author response>>** We have removed this erroneous reference number and apologies that this reference was missing and a cross reference link got lost and became an error message. The intended reference is now properly numbered and the references now end at 52.

**Level of interest:** An article of importance in its field