Author’s response to reviews

Title: Renal transplant patients' preference for the supply and delivery of immunosuppressants in Wales: A discrete choice experiment.

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Author’s response to reviews:

Dear Editor

We thank you for the opportunity to respond to the reviewers' comments and concerns. We have listed below a point-by-point response to each concern, and include a fully revised manuscript (both as a 'clean' version, and including the tracked changes).

Yours sincerely

Dyfrig Hughes

Anne Holbrook (Reviewer 1): This is a manuscript on the preferences of renal transplant patients for receiving their immunosuppressant drugs, in one region of Wales.

Detailed comments are provided as bubble comments in the pdf itself.

The article is well written and organized.

***We thank for the reviewer for her careful reading and useful comments on our paper

Several areas should be improved (see details in manuscript comments):

1. Accuracy of the article title:
a. “The title is misleading as the preferences do not deal with the broad issues of immunosuppressant prescribing (really nothing to do with prescribing); this is about receipt of the drugs themselves”

***The article title has been changed from “Renal transplant patients’ preference for immunosuppressant prescribing in secondary care: A discrete choice experiment” to “Renal transplant patients’ preference for the supply and delivery of immunosuppressants: A discrete choice experiment”

2. Incorporation of the essential concept of medication adherence regarding this project

a. Introduction “ADRs would pale somewhat in the face of evidence regarding adherence to immunosuppressants and grant survival. This should be included here”

***The reviewer is correct to highlight that non-adherence to immunosuppressants is a worryingly common behaviour associated with poor outcomes. We have now inserted a sentence to this effect in the introduction including a reference to relevant text.

3. Clearer and more detailed definitions of some key concepts in the study, especially ‘waiting time’

• “Waiting time is a key concept in the article but poorly described – waiting for what exactly? Waiting where? Who is waiting? Etc. If not possible to briefly clarify in abstract, would concentrate on clarifying in definitions in body”

• “Waiting time seems to be a key concept which needs better definition in body of manuscript, if possible, would clarify briefly in abstract”

• “as above, the concept of waiting time needs more explanation. Where are the patients waiting? What are they waiting for? Waiting at home for a prescription to come, if it is ordered a week before it is needed is not a burden for anyone….”

***This has now been clarified in the manuscript, with additions made to the abstract, and methods, where the attribute and level selection is described. Specifically, waiting time refers either to the length of an allocated delivery time slot for a home delivery, or the time waiting in the hospital pharmacy for collection of the prescription.
4. Clearer and more compelling objective. Currently it is weak to the point of appearing to be a methodology (DCE) in search of usefulness in some clinical group. What was the real purpose of this study? It is not at all clear. - P6 L9: This description does not really establish a credible motive for the study, given the time and effort involved in setting up and running a DCE. Pharmacy home delivery is ubiquitous in North America, so this sort of question would not be a high priority, please elaborate on why this was a question pursued – ‘elicit preferences’ is not a specific enough objective”

***This has fair point, which we have now addressed in full. The key issue is that currently most patients receive their immunosuppressants from community pharmacies, under the care of GPs. The change in policy is to bring patient care under the responsibility of hospital consultants, requiring medicines to be supplied from hospital pharmacies. This presents patients with 2 options: collection of their medicines from hospital pharmacies, or receipt of medicines via a home delivery service. The purpose of the DCE is to elicit preferences for these 2 options.

4. Better description of the focus group - both methods and results, as this appears to form the backbone of the DCE itself. –

• Subjects and Methods: “second stage?”

***A more detailed description of the purpose, methods and outcomes of the focus group discussions has now been included. We have removed reference to a first and second stage.

• Focus group recruitment “meaning what, exactly”

***The sentence regarding purposive sample has been removed for clarity

• “Unless there is a separate publication or available report to cite, this is an inadequate description of the focus group methods and results”

***Further details have now been added to the description of the focus group methods and results

6. Better description of the utilities, in Methods, Results and Discussion.

***We have now given specific details of the utility calculation and results in the appropriate sections
7. Currently the major problem with this manuscript is generalizability. This study was carried out in a small region in one of the small countries in the UK. What generalizability does this have to, for example, the much larger geography challenges of Canada or the USA? In addition, since community pharmacy home delivery is routine in North America, what is the international message from this work?

- **KEY ISSUE:** What is the generalizability of these findings beyond this small area, particularly beyond the UK?"

***We justified the subgroup analyses in the context of informing the generalisability of our study results. We have also expanded on this point in the discussion section. While the reviewer mentions that the study was conducted in a small region of a small UK country, the health board actually covers about a quarter of the population of Wales, and within this, we sampled all adult kidney transplant patients receiving immunosuppressants. Wales has a devolved NHS, and so an increasingly divergent system from that in England. Our research, therefore, has high generalisability within the NHS in Wales, but we make no claims of broad generalisability – especially to countries with very different health care systems and geographies.

- P12: “These 2 rows – distance and time to clinic, are important for the discussion. These distances and travel times are tiny compared to many in other countries. In other words for generalizability, what does this study say about much larger expanses of geography?”

***As mentioned above, we cannot claim generalisability to contexts or countries where travel distances are outside the parameter ranges of the DCE. There may be airplane delivery of medicines to remote populations in Australia or Iceland, or systems where patients are required to attend a clinic elsewhere. Had we incorporated different levels and/or attributes to our DCE to represent these, then we would have risked reducing the reliability of the responses among those sampled.

Additional points identified from the bubble comments

P18: “a more fulsome discussion of the potential harms of home delivery, should be provided including a general estimate of the additional cost burden.

***NHS hospitals have to pay VAT (20%) on dispensed medicines; whereas hospitals dispensed in the community – and importantly home-delivered medicines – do not attract a VAT charge. This saving is likely to far outweigh any additional costs associated with transport. In other words, home delivery is less expensive than hospital dispensed medicines. Potential harms might
include less frequent contact with healthcare staff, thus fewer occasions to intervene / monitor / advise on adherence. We have made reference to this in the discussion section.

Abstract: “Somewhat awkwardly worded sentence — what is repatriating prescribing from primary to secondary care? See further comments below” — “These first 2 sentences must have a number of supportive citations, otherwise are opinions only and should be re-phrased. Also what is ‘repatriation of immunosuppressant prescribing…..from primary to secondary care’? would clarify and, in body of manuscript, describe how generalizable this is in UK and internationally…”

***We have now edited “repatriating” to moving; changed sentence to “may result in benefits of…” (in place of “assume benefits of…”); and addressed generalisability in the discussion.

Introduction “anti-proliferative”

***This text has now been deleted

P7: “would define the NHS, for international readers”

***Defined in full

P8: Given the non-local intended readership, a more thorough description of the setting is needed. Is this rural? What is the maximum distance from hospital to a patient’s home in the catchment area? Do all pharmacies carry the immunosuppressants needed?

***Details of the setting have been expanded in the Subjects and Methods sections.

Supply of meds is only one of many issues re med reconciliation, safety, drug levels and therapeutic monitoring, checking for drug interactions, renewals, etc. what was the description provided for the lower level of supervision that would likely be provided in the home delivery vs hospital group

***The clinical team prescribing and monitoring the patient (i.e. nephrologist and transplant specialist nurse) is the same irrespective of type of delivery. Therefore there is no anticipated difference between options in terms of medicines reconciliation, safety, drug levels and
therapeutic monitoring and checking for drug interactions etc. Differences in the prompting of prescription renewals is addressed in the DCE attribute “ordering”.

P10 Pilot “I think you mean ‘either meeting’ here”

***Amended

P11: “Is this the same as ‘all transplant patients’ in the district?”

***Yes. This has been clarified.

P12: “This must seriously bias the outcome of the study. If most patients already get their meds from the local community pharmacy, you are not really comparing ‘secondary care’ (hospital) with home delivery. Your background and objectives need to be clarified.

***The motivation behind the study is that collecting medications from the local community pharmacy will no longer be an option. In the event that this is the case, we wish to elicit preference over collection from hospital pharmacy or home delivery. This has been clarified in the manuscript.

P14: I don’t think this concept of aggregate utilities was explained in your methods – it should be, as utilities are a key part of cost-effectiveness”

***The method for calculating utilities is now described in the methods

P15 “explained in discussion?”

***Nuances of the region are now described in the setting section, which hopefully addresses this comment.

P16: “not clear how this explains the regional differences”

***We hope that this is clearer now that the differences between the regions have been clearly stated.
P17 “largest in sq km, or population, or other?”

***In terms of population – this has been clarified

P17: “Key problem here: waiting at home for a delivery is completely different than waiting in line a pharmacy or hospital with the additional travel time. Please comment”

***This concept is now introduced at the first mention of the attribute, and in the discussion

P17: “Please define these ‘secondary care providers’. Are the transplant centres considered secondary or tertiary”

***Secondary care providers = nephrology clinics in district general hospitals; tertiary centres = transplant centres

Martin Howell (Reviewer 2): Overall - Good question to address given change in policy and transplant patient's lifelong need for immunosuppressive drugs. Good response rate for this type of survey. Well suited to a DCE. Whilst this is aimed at a clinical audience, more should be provided on the methodology - this could be provided in a supplementary file.

***We thank for the reviewer for his careful reading and useful comments on our paper

Specific comments

1. Attributes. A limitation of the study is that it did not include any consequences other than waiting time - namely safety and cost. Are there out of pocket costs associated with travel or is this all covered by the NHS. Could have included cost to the NHS as presumably many might consider this as being relevant i.e. they may be willing to travel to reduce the cost to the NHS. Should be noted in the limitations section.

***These are potentially important attributes, but which weren’t identified as such by the focus group participants. We have now added this as a limitation, in the discussion section.

Another uncertainty relates to waiting time. Waiting time in the home would seem to be different to waiting time in the clinic as the total time for the clinic would also include travel time.
Another option might have been to include travel time as an attribute. The DCE assumes that the travel time remains constant for the participant i.e. it is a characteristic - but they may move or they may have to go to a different clinic and the DCE does not allow assessment of changing travel time.

***The lack of inclusion of travel time within the attribute has been added as a limitation, however we did address travel time in a subgroup analysis.

2. This clearly has to be a labelled DCE as it would not be possible to hide the attribute of Hospital vs. Home.

***We agree with this comment

3. It is unclear to me as how utility has been modelled. I assume that beta values for home and hospital are attribute specific constants with hospital as the reference. The authors should provide more detail on how the analysis was done in particular subgroup analysis. This could be provided in a supplementary appendix. For example the utility function would be helpful. Has sub group analysis been addressed using interaction terms in the utility function or as separate data sets? Also why was 50 chosen as the minimum group size.

***Label was entered using the alternate specific constant. This has now been specified. Subgroup analysis methods have been clarified. We considered small samples (n<50) to lack statistical powering, and so omitted from sub-group analysis. This is now explained in the methods section.

4. It is the log likelihood ratio that is relevant to assessing model fit.

***Yes, in cases of subgroup analysis. This has been clarified.

5. Table 2. Suggest it be edited to make it more useful. For example, age is better described as frequency in age groups rather than mean etc (such as been done for change to medication). Only need to put in one gender. Distance and time travelled would be more useful as frequency across groups rather mean (SD). Not clear why n varies - presumably because of missing responses.

***We have now presented these data as suggested by the reviewer. Specifically, age presented in categories (18-30, 31-50, 51-70, 70+), travel time dichotomised (< or >30 minutes), and
distance dichotomised (< or >20 miles). Gender has been edited to only include male. The number varies due to missing data – noted as a footnote.

6. Table 3. Should report to only 2 decimal places. Also consider whether reporting as an odds ratio might be easier to follow for a clinical audience (I accept that the meaning of the OR is difficult to convey).

***We have now revised all figures to 2 decimal places.

7. Sub group analysis. Unclear as to how this was done (see point 3), however the results in the Supplementary material suggest that there are essentially no differences except for distance to the clinic (mins) the direction of which makes sense. For example - previous experience time betas were -0.0019 and -0.0022 with overlapping CIs - similarly - the MRS values are only marginally different and CIs overlap. Need to justify combining the West and Central regions - are they similar? Overall results section emphasises what appear to be meaningless differences.

***The subgroup analyses have been clarified.

8. Limitations should also include lack of consequences in terms of safety and cost (out of pocket and/or to the NHS). Ability to address travel time is limited by it not being an attribute.

***These have now been included as limitations, in the discussion section

9. The relevance of the cited transplant studies is unclear. It would be more interesting to know what studies have looked at preferences for dispensing/prescribing in other groups if there are no relevant transplant studies.

***The relevant paragraph has now been amended for clarity

P5 L19: “Remove “to””

***Amended