esponse to Reviewers:

Reviewer 1
1. "The authors conclude that the published studies on generic substitution in general are of poor quality. The vast majority of studies was of small sample size, insufficient study design or unclear regarding procedures of randomization. The review did not find that patients on generic immunosuppression suffered more often from acute rejection, nor from worse renal function. In the discussion the authors argue that there is a need for well designed studies on generic substitution. It is questionable whether such studies are really needed. The registration of generic drugs is based on bio-equivalence. If the brand name drug and the generic drug are bio-equivalent the generic drug is registered, without requirement of proof that the two formulations result in similar clinical outcome. The registration authorities assume that two drugs present in blood in the same concentration will result in the same clinical outcome. This assumption, which I do support, has been in place for a long time, and has been used for many other generic formulations. None of the studies in this systematic review was performed as part of a registration process. Some of the studies were performed on the initiative of generic drug companies, to show that their compound was not only bio-equivalent in healthy volunteers, but also in transplant recipients. For marketing purposes such studies may help in the battle with other generic companies. In other studies, often investigator driven, only clinical outcome was reported in cohorts of patients switched from one formulation to the other. These are typically underpowered studies, performed in low-risk patients. I would argue that the transplant community should accept that for two drugs that are bio-equivalent there is no need to perform studies on clinical outcome. As long as patients receive proper instructions, and as long as the introduction of generic drugs is well coordinated the clinical outcome will be fine.The message the authors convey is that although there is no proof that generic substitution is causing a problem, there also is no proof that it is safe. Their claim that well designed studies are needed is not correct. We do not need such studies. This claim will definitely be used by the companies producing brand name drugs to fuel the doubts the transplant community has regarding the introduction of generic immunosuppressive drugs. The authors mention that without the high-quality comparative trials the potential huge savings associated with the use of generics will not be fully realized. I would argue that the request for such studies (that are unlikely to be performed) hinders the introduction of generic drugs, and thus the cost savings. And suppose we do want to perform prospective trials comparing brand name and generic immunosuppressive drugs, with a clinical primary endpoint. Will these studies need to be done in all the different organ transplants? And will we need such studies for all the different generic formulations on the market, or would one proof of concept trial be sufficient? Non-inferiority studies to compare the two formulations will need to have a very large sample size to be sufficiently powered. I do not think it is realistic to assume such studies will be done".

Response: We thank the reviewer for his insightful comments. Although we think that studies examining clinical outcomes would be the ideal method of reducing concerns regarding the equivalence of generic and trade name immunosuppressants, we also recognize the huge barriers to conducting such studies and agree that this approach would likely not be feasible. As such, we have altered the conclusions and recommendations in the discussion and abstract to reflect this. Please refer to the conclusions section of the discussion (final paragraph) and abstract sections of the revised manuscript.

2. "On page 5 the authors claim that in the UK generic substitution of tacrolimus and cyclosporine products was banned. To the best of my knowledge in the UK there is substantial generic substitution for tacrolimus already. Please clarify."

Response: We thank the reviewer for pointing this out. Generics are allowed in the UK however automatic substitution between different brand names is not allowed. We have altered the wording in the introduction to clarify this. It now reads: "Certain countries in Europe have gone one step further, with the United Kingdom now requiring that the brand of tacrolimus be specified on all prescriptions to avoid inadvertent switching, and Denmark banning the generic substitution of tacrolimus and cyclosporine products."

3. "The European Society for Organ Transplantation - guideline on generic substitution is missing (Transplant International 2011;24:1135–1141). Please add."

Response: This reference has been added to the introduction.

4. "On page 18 the authors claim that there is a general consensus that generic substitution should be performed in low-risk patients only. I do not think there is general consensus on this statement".

Response: This specific statement has been removed.

5. "Table 1b has "Neoral" in its title, but this should be "Prograf".

Response: This has been changed.

6. "For a paper on this topic there should be extra attention for conflict of interest information. I would like to ask the authors if they can reconsider.
their statement that the in no conflict of interest for any of the authors."

Response: The original manuscript that was sent to the reviewers stated there were no conflicts. However, in the ICMJE Form for Disclosure of Potential Conflicts of Interest that was sent to the editorial staff, more detail was provided. This has been added to the manuscript on page 2 as follows: "Competing interests: Each author has completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. We have read and understood the BMJ policy on declaration of interests and declare the following interests: Dr. Knoll reports research grants from Astellas Canada, Roche Canada, Novartis Canada and Pfizer Canada, outside the submitted work. All other authors have no competing interests."

Reviewer 2

1. "I would not alter very much within the paper, but may suggest the following to improve the introduction – especially given the very powerful last sentence on page 21 as well as lines 10 – 12 page 5 in the introduction. A suggested order could be:
Generic medicines are seen as essential to help maintain comprehensive and equitable health care especially within public healthcare systems given ever increasing pressure on resources - due for instance to changing demographics and the continued launch of new premium priced medicines to address areas of unmet need. The opportunity for savings is considerable (Ref 1 line 12 page 5) helped by high volume generics priced as low as 2% to 10% of pre-patent loss prices in some countries in (i) Woerkom M, Piepenbrink H et al. Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. Journal of comparative effectiveness research. 2012;1(6):527-38; (ii) Godman B, Wettermark B, Hoffmann M et al. Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance. Expert review of pharmacoeconomics & outcomes research. 2009;9(1):65-83; and (iii) Godman B, Wettermark B, van Woerkom M et al. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. Frontiers in pharmacology. 2014;5:106.
• Initiatives to enhance the prescribing and dispensing of generics versus originators include compulsory generic substitution, e.g. Sweden, substitution targets among pharmacies, e.g. France, and encouraging INN prescribing though education, e.g. UK, and lower co-payments in (i) Dylst P, Vulto A, Simoens S. Demand-side policies to encourage the use of generic medicines: an overview. Expert review of pharmacoeconomics & outcomes research. 2013;13(1):59-72 and (ii) Vogler S. The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries - an overview. GaBI Journal. 2012;1(2):93-100. High voluntary INN prescribing the UK - average over 85% or more of all prescriptions – rising to 98-99% for high volume generics where limited concerns – is achieved starting with education in medical school and continuing post qualification in hospitals and the community - in (i) Ferner RE et al. Controversy over generic substitution. BMJ. 2010;340:c2548; (ii) Duerden MG, Hughes DA. Generic and therapeutic substitutions in the UK: are they a good thing? British journal of clinical pharmacology. 2010;70(3):335-41 and (iii) Godman B, Bishop I, Finlayson AE et al. Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries. Expert review of pharmacoeconomics & outcomes research. 2013;13(4):469-82.
• Published studies have shown no apparent differences in outcomes between generic medicines and

originators in for instance patients with CV diseases despite narrow therapeutic indexes of some of the medicines in (i) Kesselheim AS, Misono AS et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA. 2008;300(21):2514-26 and (ii) Corrao G, Soranna D, Merlino L, Mancia G. Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: evidence from a large population-based study. European journal of clinical investigation. 2014;44(10):933-9. >> • The same was seen for generic and originator medicines to treat patients with epilepsy in Kesselheim AS, Stedman MR, Bubrick EJ et al. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis. Drugs. 2010;70(5):605-21. Having said this, there are concerns among the authorities in the UK with INN prescribing of certain medicines to treat patients with epilepsy – advocating continued prescribing of the originator (brand name prescribing) product as there is generic substitution is not currently allowed in the UK (i.e. if the physician prescribes the originator name when generics are available – the originator must be dispensed) – URL: https://www.gov.uk/drug-safety-update/antiepileptic-drugs-new-advice-on-switching-between-different-manufacturers-products-for-a-particular-drug.
• There is also controversy among the use of generic medicines in patients following solid organ transplantation (various references from 1 to 9 on page 5). This includes the UK where brand name (originator name) prescribing of for instance tacrolimus is endorsed by the authorities to minimise toxicity and graft rejection (not BANNED as stated on lines 48/ 49 page 5) and Denmark where generic substitution is not allowed.
• However – as mentioned at the bottom of page 5 – these recommendations from the authorities are not necessarily based on high quality evidence – with the regulatory agencies arguing their methods of determining bioequivalence are reliable, etc. This includes tighter EMA/ Canadian regulations for cyclosporine (top of page 8). Then onto top of page 6 giving a good rationale and objective for the paper, etc."

Response: We appreciate these suggestions and have incorporated many of these suggested changes and references into paragraphs 1 and 2 of the Introduction. Please refer to the highlighted changes in the manuscript. We have also altered the sentence regarding the banning of generics in the UK.

2. "Page 7 – lines 22 – 27 – may be good initially to clarify that a 'brand name' is the originator name (if this is the case) as there are branded generics in for instance many European countries."

Response: Thank you for this comment. We have replaced the word "brand" with "innovator" throughout the manuscript.

3. "Page 8 lines 46/ 47 – What are the main characteristics of the check list of Wells et al for those not totally familiar with this list?"

Response: The following sentence has been added to the methods section of the manuscript: "Three domains were assessed with the Wells et al. checklist: Study design, confounding, and selective reporting." The specific questions/areas addressed by the checklist are outlined in Supplementary Table 2. For example: Study design is addressed by asking about whether or not a comparison was made and if so was it between two or more groups of participants of the same group of participants over time? Confounding was addressed by asking if the study accounted for confounding at the design or analysis stages and which variables were considered?

4. "Page 9 lines 27 – 32. Need a reference for the Peto method as well as for the statement - 'this is the preferred estimate when cells contain 0 events"

Response: References have been added for the Peto method. Reference numbers 26 and 27.

5. "Page 10 – list of generics – what about INN generics as only branded generics documented?"

Response: We have included all generic formulations that we could locate in our systematic review. The only restriction was on Sandimmune as it is no longer used in clinical practice.

6. "Page 11 – lines 32 to 34 – low number of patients included at 5. Maybe worth saying in the methodology that you did not exclude studies containing small number of patients as results were

pooled, etc."

Response: The following sentence has been added to the methods section: "Studies containing a small number of patients were not specifically excluded."

7. "Page 12 – lines 24/ 25 – may be better to say 'Tables 3A and 4A' as refer to the appendix"

Response: We have not altered this sentence in the manuscript in order to maintain consistency. All other supplementary tables and figures are specifically referred to. If the Editor wishes this to be changed it can certainly be done.

8. "Page 13 – line 27 - Can you recheck ref 44 as the authors in Sayyah et al 2007 in their paper documented no reports of major toxicity or of graft rejection and no need for dose adjustment related to Iminoral and concluded that renal transplant recipients maintained on Neoral can be safely and effectively converted to Iminoral on a 1:1 conversion ratio?"

Response: We thank the reviewer for pointing out this reference error. This has been changed to reference the correct study (Spasovski et al, 2008), which is now reference number 51.

9. "Page 14 – lines 11 – 15 – need to explain why these two studies were included in the analysis if did not meet bioequivalence criteria (if this was the case) – see also next comment"

Response: The purpose of our systematic review was to include all the available evidence on generic immunosuppression. It is not appropriate to only include "positive" studies when pooling data – this will result in a biased sample. The data we have presented represents a summary of the available evidence at the time our review was completed. Thus, we believe it is important to include these two studies.

10. "Page 15 lines 46 – 48 – was this all generic cyclosporines not meeting EMA/ Canadian bioequivalence standards? The same for tacrolimus and mycophenolate mofetil – yet despite this no significant differences in acute rejection rates for generic cyclosporine, tacrolimus or mycophenolate mofetil vs. originators."

Response: Thank you for this comment. We recognize that we were not clear in our statement in the Discussion. We were specifically referring to the pooled data from RCTs of cyclosporine, tacrolimus and mycophenolate mofetil. We have clarified these statements in the revised manuscript (first paragraph of the discussion) and also in the abstract.