Table 1: Invited Peer Reviewer Comments

<table>
<thead>
<tr>
<th>Reviewer*</th>
<th>Section*</th>
<th>Reviewer Comments</th>
<th>Author Response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer 1</td>
<td>General</td>
<td>The purpose of the Study is very appropriate. The research conducted by the University of Connecticut/Hartford has elucidated in great details the question about the possible beneficial effects of pre-transplant blood transfusion according to different immunosuppressive eras.</td>
<td>We would like to thank the reviewer for the comments.</td>
</tr>
<tr>
<td>Reviewer 1</td>
<td>Executive Summary</td>
<td>The summary gives a completed overview of the pre-transplant transfusion issues and advantages including the rationale for the possible beneficial effect of donor specific transfusions (DST) that led to this option in several transplant centers.</td>
<td>We would like to thank the reviewer for the comments.</td>
</tr>
<tr>
<td>Reviewer 1</td>
<td>Introduction/Background</td>
<td>The Background is well written and offers a complete picture of the current knowledge of the role of HLA and its impact on the different kinds of rejection. It is well known that the use of recombinant erythropoietin has minimized the need for blood transfusions in patients with ESRD and anemia but the role of pre-transplant transfusions, in particular donor specific transfusions (DST) need to be revisited. The objectives of the study have been properly focused and addressed.</td>
<td>We would like to thank the reviewer for the comments.</td>
</tr>
<tr>
<td>Reviewer 1</td>
<td>Methods</td>
<td>The systematic literature search, conducted by 2 independent investigators is highly satisfactory. The data extraction, synthesis and analysis, including the tables reporting the different outcomes show a complete overview of the data available and an excellent summary of the conclusions.</td>
<td>We would like to thank the reviewer for the comments.</td>
</tr>
<tr>
<td>Reviewer 1</td>
<td>Results</td>
<td>Although the limitations related to the heterogeneity of the different studies retrospectively analyzed, the results are offering a better and clear understanding of the role of the pre-transplant transfusion, across different immunosuppressant eras, multiple variables and different methodological approaches.</td>
<td>We would like to thank the reviewer for the comments.</td>
</tr>
<tr>
<td>Reviewer 1</td>
<td>Discussion/Conclusion</td>
<td>A study of such magnitude was needed in particular when the status of the art in kidney transplantation is more and more focused on tolerance induction. The study is also very relevant because offers an important background for designing additional multicenter studies that will be able to clarify unknown answers in the transplant immunology field. As a reviewer I am complimenting the authors for the enormous efforts that have been dedicated to this huge and demanding project.</td>
<td>We would like to thank the reviewer for the complementary thoughts.</td>
</tr>
<tr>
<td>Reviewer 1</td>
<td>Tables</td>
<td>The tables and figures are easy to understand and are very comprehensive.</td>
<td>We would like to thank the reviewer for the comments.</td>
</tr>
<tr>
<td>Reviewer 2</td>
<td>General</td>
<td>The overall report is well organized, comprehensive in scope, with appropriate methods, results and conclusions. However, I have three concerns: 1) the conclusions should be clearer; 2) the conclusions do not fully reflect the quantitative findings in the results; and 3) the recommendation for additional studies is not supported by the data nor by the discussion in the report itself.</td>
<td>Thank you for these comments. We worked hard to generate a report that met these facets. (1) &amp; (2) – The conclusions were revised somewhat to reflect our responses to the reviewer's comments. (3) – The recommendation for additional studies is based on the low/insufficient strength of the overall body of evidence of the literature. Future studies with better design (i.e. adequately powered, accounting for confounders, etc) may change the conclusion of this technology assessment. Whether one believes it is ethical to conduct such a study does not change the poor quality of the current body of evidence does not engender confidence in the results that they convey.</td>
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<tr>
<td>Reviewer 2</td>
<td>Executive Summary</td>
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</table>
|            | The Tables in this section and the Results section should provide some sense of the range of Strength of Evidence for each group of studies in addition to the overall averages, which are all either low or insufficient. I assume that for some of the outcomes examined there are some sub-groups of studies that have moderate or high strength of evidence. Likewise, the final conclusions in the discussion should be a bit more granular to reflect the Results; i.e., that the magnitude of effects on some outcome measures are larger than others (albeit, all with low strength).

There is also a trend in several outcome measures for a large beneficial to neutral effect, which should be highlighted in the final summary. It is hard to determine from the final discussion that the transfusion effect on graft survival was consistently in the range of strongly beneficial to neutral. If the outcome was focused on a detrimental (vs beneficial) effect of transfusions, would the strength of evidence that transfusions are not detrimental still be low? I presume not, but this should be addressed explicitly in the methods, results, and discussion, and clarified in the conclusions.

This report is supposedly about the impact of transfusions, but it is written as if the report is simply judging the beneficial impact. I recommend it should be refocused to provide a balance of conclusions between the beneficial and detrimental effects on graft outcome, especially since this is one of the outcomes examined in results. This would lead to dual conclusions that 1) there is no substantial evidence for a detrimental effect (? strength), and 2) some evidence (low strength) for a beneficial effect in some cohorts. Conclusions should be

We provide an assessment of individual study quality ratings in the report (but not for each endpoint) as well as the rating of the strength of evidence. The strength of evidence, according to AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews state that the grading should be on the body of evidence. For each key question we do provide the references which can be cross-referenced with the individual study quality rating. We also pull out the good quality studies and talk about them separately which should help with this comment as well.

We use the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews in determining the strength of the body of evidence and the methodology is specified in the report. Strength of evidence is related to the confidence that we have that future well conducted studies/trials will not likely change the conclusions. So if the quality of the literature is overwhelmingly poor in nature, the strength of evidence will be low. We have altered the conclusions somewhat based on reviewer’s comments.

We do already provide this level of granularity in the tables. However, in order to enhance the readability of the report, which is already large and cumbersome, we do not feel that describing the results in terms of the percentage of trials that shows benefits, has neutral effects, or has detrimental effects would supply additional information over and above assessing a beneficial to neutral effect together. |
provided in the context of the improved maintenance and anti-rejection diagnosis and treatment currently available, and current non-transplant risk-benefit aspects of transfusions.

The Future Research Directions section advocating additional studies is inconsistent with the results and the immediately preceding discussion. I presume that grammar in the last sentence of Discussion is intended to be that “Given the problems with internal validity with these individual studies and the heterogeneity contained within the studies, we only have a low or insufficient strength of evidence for any of these findings. As such, we have low confidence that the results of our report would not change upon publication of additional higher quality evidence.” That is, they have low confidence that additional studies would change their conclusions, rather than not change their conclusions. If so, their call for additional studies needs better justification. If the last sentence is written as intended, it is inconsistent with the discussion, and should be re-written without double negatives; i.e. “we have high confidence that the results of our report would change upon the publication of additional higher quality evidence.” I would disagree if that is indeed their conclusion.

We believe that future studies may very well alter the findings that we have come up with because the body of evidence has low quality and is primarily predicated on data that might not reflect contemporary practice. We now specify in the executive summary and body of the report that “We have low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.”

Reviewer 2

<table>
<thead>
<tr>
<th>Introduction/Background</th>
<th>It would be helpful to provide a better context for the whole issue of transfusions in transplantation relative to sensitization and immunosuppression.</th>
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<tbody>
<tr>
<td>Methods</td>
<td>See comments above for Executive Summary</td>
</tr>
<tr>
<td>Results</td>
<td>See comments above for Executive Summary</td>
</tr>
<tr>
<td>Discussion/Conclusion</td>
<td>See comments above for Executive Summary</td>
</tr>
<tr>
<td>Tables</td>
<td>See comments above for Executive Summary – the tables in the Executive Summary should provide a balance between beneficial effects and detrimental</td>
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</table>

We expanded the discussion section substantially to reflect the issue raised by reviewer. We incorporated information obtained from the USRDS, UCLA, and UNOS in discussing this issue.
effects, to more accurately reflect the tables in the results section.

| Reviewer 2 | Figures | Fig 1 is appropriate. An added figure(s) would be helpful to summarize the outcomes examined, their relationship to each other, and the range of studies available for each. | As above |
| Reviewer 3 | General | I will not provide a section by section review as in my opinion the review provides an excellent, well researched and well written summary of the data. The real question I found difficult to answer for myself was why this study was ever commissioned. The authors provide very adequate criticisms of the limitations inherent to the study given the quality of the work available to them, but I think they overreach in suggesting further studies would be of use to the transplant community. The interest in this area, as can be seen if a “Bell Curve” is constructed of the dates of the publications, started as a consequence of a few papers from influential centers published in the late 1970’s when immunosuppression remained largely based on azathioprine and prednisone and when results were still quite poor making it possible for small studies to have some impact. In spite of this the evidence for the use of pre-transplant blood transfusions was never very strong and both this and peri-operative transfusion (not dealt with in this review) fell out of use as the effectiveness of newly approved immunosuppressive agents entered clinical practice, essentially overwhelming any small effects achieved by transfusion. In the 80’s, |
| | | Thank you for the reviewer's complementary comments. CMS would be in the best position to delineate why the report was commissioned but it may be because entities exist that believe that the literature base strongly suggests that transfusions are detrimental and they wanted an independent body to assess the literature. While we agree that there is improved management in the transplant population and future studies may require large populations, we need to suggest future research if the strength of the body of literature is weak. It may be that the question is not of great enough interest to justify the expenditures but in order to generate high quality data that would answer these key questions, we feel our recommendations would be helpful. |
| | | Thank you. | |
studies started when interest was quite high were fairly numerous, but the numbers tailed off over time, a good measure to my mind that the issue was considered largely irrelevant by the academic transplant community. Thus the number of publications as we move into the late 90's and 2000's is really too small to provide any useful analyses. Large database studies shed little more light than other studies, but do not suggest a significant effect from pre-operative transfusion, some even suggesting it may be harmful.

The authors do attempt to correct for this in the section on Page 38 but they themselves point out the difficulties in so doing.

There are a few further points of importance. The effect of blood transfusion, in as much as it ever had an impact was thought to either be a consequence of an undefined protective effect or the consequence of a winnowing effect whereby a subset of highly reactive patients were not transplantable following the elevation in their PRA following transfusion, with improved results in those that were transplanted. Few of the papers discuss the number of patients so affected.

The authors correctly discuss the improvements in the characterization of pre-formed antibodies and the current context of defining specific antigens to which potential recipients are highly sensitized but this is not germane to the period from which most of the data is drawn.

The section on the use of leukocyte depleted blood transfusions highlights another area of weakness. It is highly likely that many of the studies that do not specifically state this used leukocyte depleted blood as this was essentially the standard of care from at least the early 90's if not before.

Thank you.

Thank you.

Thank you for the comment.

We agree.
As an historical analysis of this area the review is excellent. However the improved and quite excellent outcomes of transplantation have impacted our ability to show differences in outcomes in trials of new immunosuppressive medications unless very large numbers of patients are entered into each arm of the study. For an effect as weak as that of blood transfusion the size and cost of any study would be prohibitive.

The true transfusion effects on renal allograft outcomes is still up for debate as the strength of overall body of evidence for the available literature on this topic is either low or insufficient. Although certain practice over time becomes commonplace, the general acceptance of this practice may not reflect the reality of the science behind the practice. Our position is that, in light of the poor quality of literature, more well-designed studies may shed more light on this area of practice.

**Reviewer 4**

**General**

Terminology should be updated to standard terms. For example, *cadaveric* is no longer considered an appropriate term, and has been replaced by *deceased donor*. Similarly, *chronic rejection* is not considered an entity *per se* and is, in its general form, sometimes referred to as *chronic allograft nephropathy* or the appropriate histopathological description of the process.

The key questions are a bit misled, for several reasons: If the clinical question is "should there be a drive to transfuse patients while awaiting kidney transplantation" then the target timeframe should include the time awaiting transplantation in addition to the post-transplant time. Otherwise there is a survivor bias for those reaching transplantation, and the "endpoint" of achieving a transplant is also missed. For example, if transfusions raise the PRA so high that no compatible donors can be found, the patients will die faster while waiting for a transplant, and those that become sensitized to that level will never reach transplantation, and as such be excluded from the study cohort.

The hypothesis is that transfusions will sensitize a patient to certain antigens. However, since donors and recipients are crossmatched prior to transplant, any antibodies that have developed in the patient as a result of transfusions will be detected during crossmatch testing, and most

These terms were used in the literature. We used the same terms to maintain consistency with the literature included in the TA. We also modified the section that discusses chronic rejection to address this concern.

We understand that you have some reservations about the key questions that were posed. These questions were posed by CMS and we were asked to answer them in a rigorous and unbiased manner. We were not charged with construction of the key questions. So while these are valid points, but they are tangential to the key questions that we are asked to assess or address. Hopefully our expanded discussion section will provide more transparency into some of these areas and flow better into our future research section.
centers will then forego the transplant. In other words, those who are sensitized by previous transfusions who do undergo a transplant will have a negative crossmatch with their donor, and so the harmful effects of the transfusions will not be detected. The only exceptions to these situations would be patients knowingly transplanted across antibody barriers, but these transplants are quite rare, are clustered at a handful of centers, and are reported accordingly.

Several major temporal trends exist. First, outcomes from the 80s are in no way comparable to outcomes from 2000's because of major advances in immunosuppression. Many would argue that every study prior to 1990 or even 1995 should not even be reported, because transplantation was a very different field at that time. Additionally, and quite importantly, crossmatch testing has changed over time, and centers have become progressively more sensitive in detecting antibody. Since a positive crossmatch will block a transplant, then when crossmatch tests are more sensitive, only the lowest antibody risk transplants can occur; when crossmatch tests were less sensitive, it is possible that some degree of low-level antibody existed and caused problems post-operatively.

Because of the above points, one of the "outcomes" related to transplantation should have been degree of sensitization, or PRA / cPRA / whatever was used at the time. A more sensitized patient would have less opportunity for transplantation, so perhaps transplant rates, or pre-transplant death, could have been reasonable surrogates.

Reviewer 4  
Executive Summary  
This is clearly written and, for the most part (see nitpicky terminology comments above), quite informative, at least in the context of an essentially (and predictably) negative study. The limitations of the study design are discussed, These outcomes were not included in the key questions that were posed by CMS. We cannot include new endpoints, add new key questions, or conduct a new literature search at this point. However, we do discuss this now in the discussion which should present the information in a reasonable fashion.

Thank you for these kind thoughts.
although limitations noted in my "general comments" above should also be discussed.

In ES-1, it is unclear to the reader at this point in the document what "Large beneficial to small impact on graft survival" means -- I understand what a "large beneficial impact" is, but what is a "large small impact"?

The conclusions are too strong, however. The inference that "the literature... supports a neutral to positive effect resulting from transfusion and does not support a detrimental effect resulting from transfusion" is just plain misleading, for the reason specified above. Even to say "pre-transplant transfusion was not associated with worse outcomes among those who received transplants" is a bit strong without saying "although many transplant candidates might have become sensitized as a result of the transfusions and not had the opportunity to receive a transplant." But conclusions of this type, in their current form in this document, are far worse and are not appropriate.

The future research section would be much stronger if suggestions were made that the true studies include pre-transplant time at risk, and that "transplantability" (i.e. transplant rates) is the appropriate outcome when considering sensitization resulting from something like transfusions.

| Reviewer 4 | Introduction/Background | As above, the concept of chronic rejection needs to be updated to modern terminology and understanding of this process. It is surprising that a major work investigating issues of sensitization resulting from blood transfusions fails to | We were not charged with assessing or addressing these issues. While they may be important issues, they are tangential to the key questions we are asked to address. |
make any mention, in the introduction/background, of transplantation of sensitized patients, desensitization or incompatible kidney transplant protocols, and technologies for measuring the activity of and characterizing the specificity of antibodies.

<table>
<thead>
<tr>
<th>Reviewer 4</th>
<th>Methods</th>
<th>The systematic review methods are appropriate, albeit quite simple given the heterogeneity of the studies and thus the inability to pool estimates.</th>
<th>Thank you for the kind thoughts. We agree that this is probably the best that can be done given the literature base at hand.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer 4</td>
<td>Results</td>
<td>Text is acceptable and clear. Limitations in the nature of the defined outcomes are addressed above in my general comments.</td>
<td>Thank you.</td>
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<td>It is unclear what &quot;rejection&quot; refers to – acute cellular? acute humoral? hyperacute? Combining these endpoints is somewhat inappropriate, as mechanisms underlying these different types of rejections are differentially related to sensitization and immunosuppression regimen.</td>
<td>Due to the nature of the studies, the vast majority did not define the types of rejections. With the limited definitions from the literature, we concluded that the strength of evidence of the magnitude of rejection was insufficient to reflect this.</td>
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<td>It is unclear if &quot;graft survival&quot; was all-cause or censored for death (some studies consider death with a functioning graft to be &quot;graft loss&quot; and some do not).</td>
<td>We tried to account for many layers of heterogeneity within the trials. This is a yet another type of methodological heterogeneity in this body of literature. The problem really is that slicing and dicing the trials into smaller and smaller groups or defining every study qualitatively rather than grouping results in a large intelligible report. Because ultimately we have three categories here, those with all-cause, those censored for death, and the larger group that is not adequately specified. So we would in effect need three tables instead of one for each key question and numerous other tables to split out the other variables. At some point we had to make some generalizations.</td>
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<td>All of the DST studies are &gt;15 years old (mostly &gt;20 years old) and the relevance of these studies to current</td>
<td>We agree that the relevance, or lack thereof, of trials from the past are hard to determine. We clearly</td>
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practice is unclear (probably none). Kidney transplantation is a very different field in 2010 than it was in the 1980's.

Ascertained number of transfusions can be tricky; it would be nice to have a description of how number of prior transfusions were ascertained (medical records, patient history, etc) and some quality measure of this with regards to potential bias.

The PRA section is reasonable, but fails to draw attention to a significant issue, which is that PRA (or cPRA) quantifies the reactivity to the general pool of donors, but that is not a relevant issue when the patient is transplanted with a specific donor, which is what indeed happens. PRA is a great predictor of likelihood of transplantation, but is not per se in the causal pathway to rejection/allograft loss for a given transplant. The important piece for a given transplant is donor-specific antibody (DSA), in other words the breadth and strength of antibodies that a recipient has to the actual donor whose kidney he is receiving. DSA is NOT captured in PRA. While it is true that some patients with a very high PRA might be transplanted with some low-level DSA, this delineate in Key Question 1 the impact of more recent trials on results. We do find a tendency toward less benefit and more tendencies towards a neutral effect in more recent trials. This is clearly specified in the report. We also pull out the DST trials into a subgroup and view them separately which should help address this comment.

We agree that it is tricky to ascertain transfusion exposure and this does impact the strength of evidence by introducing methodological heterogeneity. Like the graft survival example above, again we would need to subcategorize into numerous groups (those with one or more ways that transfusion exposure can be ascertained and the category where it is simply not defined). We do not feel that the large number of sub-categorizations necessary to tease these things out would yield useful information and would do something other than make it more difficult to read and understand. However, we now review trials of good quality separately which can help to alleviate your concerns.

We recognize that this is an important issue in the transplant world, and we have altered the discussion section of the final report to address this facet.
occurs at the discretion of the center, and there could just as easily be patients with lower PRA but higher-level DSA. Saying that a high PRA is causally associated with rejection or allograft loss is probably somewhat misleading; while it might be associated with it, for confounding reasons (donor choice, immunosuppression choice, etc), it is not causally associated with it; PRA is at most a surrogate for some other unmeasured factors which actually do influence outcomes.

| Reviewer 4 | Discussion/Conclusion | Limitations to inference as specified above in "general comments" and elsewhere apply here. Heterogeneity is appropriately described. | As above. |

1 Peer reviewers are not listed in alphabetical order.
2 If listed, page number, line number, or section refers to the draft report.
3 If listed, page number, line number, or section refers to the final report.
### Table 2: Public Review Comments

<table>
<thead>
<tr>
<th>Reviewer Name</th>
<th>Reviewer Affiliation</th>
<th>Section</th>
<th>Reviewer Comments</th>
<th>Author Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joshua Ofman, MD, MSHS</td>
<td>Amgen</td>
<td>General</td>
<td>Please see Appendix</td>
<td>Please see Appendix</td>
</tr>
</tbody>
</table>
| Joseph V. Bonventre, MD, PhD, FASN | American Society of Nephrology | General | • Donor-Specific Transfusions have not been utilized for more than two decades.  
• The true effect of Donor-Specific Transfusions remains unclear  
• Modern single-antigen antibody tests have supplanted classic PRA analyses and are used to improve the efficiency of organ allocation  
• ESAs are indicated to treat anemia; administration of ESAs prevents patients from risk of sensitization due to transfusions that would otherwise be necessary | No specific changes were made because the comments did not address any specific issues relating to this technology assessment. However, we do now look at DST versus no transfusions separately in a subgroup which should address part of the concern. |
<p>| Karen E. Ryals | American Association of Kidney Patients | NA | The Technology Assessment draft document was for the most part (greater than 90%) a retrospective analysis of observational data. AAKP believes that the document is fundamentally flawed in terms of its ability to adequately inform potential policies or decisions based on the most recent scientific research. We firmly believe that policy-makers who rely on the study in its present form and its outdated information will make poorly reasoned decisions that will impact patients and their access to future care options. | The inclusion criteria for the literature reviewed in this TA was tailored specifically to answer the key questions posed by the CMS. The retrospective and older nature of the literature base shows that interest in this topic has diminished over the years, and we have no control over this. We were charged with summarizing and grading the strength of evidence for the literature base. |</p>
<table>
<thead>
<tr>
<th>Karen E. Ryals</th>
<th>American Association of Kidney Patients</th>
<th>NA</th>
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<tbody>
<tr>
<td>The assessment failed to look at the highly relevant and current United States Renal Data System 2010 Annual Report that stated that the 3-year cumulative incidence of blood transfusions in patients on the transplant list with PRAs over 80% was about 41%. Note that in those who had no antibodies the incidence of blood transfusion was only 24 to 25%.</td>
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<td>We now provide the USRDS annual report information germane to this area in the discussion along with data derived from registries. These data are not peer reviewed, have scant methodology, and generally do not account for confounders. Of note, the USRDS data, which used the OPTN-UNOS registry, do not collect quantitative/qualitative information on transfusions. These data are self-reported, and information on whether patients received transfusions are limited to discrete data (i.e. yes, no, unknown). It is not known if therapeutic transfusions are actually indicated or required.</td>
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<td>The HRSA Organ Procurement and Transplantation Network database further documents that patients who are sensitized must then wait at least one to three years longer on the list for a kidney transplant. If they do receive one, it does not last as long, and the patients have a higher complication rate, including a 19% higher risk of death. The worst part of this issue is that the patients who have high panel PRAs may never receive a kidney transplant. High PRA levels then block access to transplantation. This data compounds data that women who have been pregnant may also develop PRAs, and thus disproportionately limits access to women. In summary high PRA levels are a medical catastrophe for the kidney patient who seeks transplantation and it must be avoided in any way possible. This fact was not considered in the Technology Assessment because this unfortunate population was never studied.</td>
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<td>The statements about waiting times and consequences of waiting for transplants are no longer valid since there are desensitization treatments available for sensitized patients, and patients who are highly sensitized can still receive transplants nowadays. The study by Montgomery et al provided alternative treatment options for patients with HLA sensitization, which provides some insight to the current issue. (NEJM 2011;365:318-26) The information presented here from the HRSA OPTN databases is not directly related to the key questions of the TA, and we have already adopted relevant information from the OPTN database in answering key question 2a in the draft report. We now highlight the data from the book chapters and USRDS annual report in the largely expanded discussion. We cannot change the key questions, as they were developed by CMS, and our task was to answer the questions that were asked.</td>
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| Karen E. Ryals | American Association of Kidney Patients | NA | The Technology Assessment relied on research done before 1992. Only 10% of the studies were performed afterwards. These studies have no real bearing on modern transplantation for a multitude of reasons: That was still an era of intentional transfusions between donors and recipients.  
- Immunosuppression has evolved extensively since then. (Mycophenolic acid, mycophenolate, sirolimus, everolimus, thymoglobulin, steroid withdrawal are all subsequent developments since 1992).  
- Histocompatibility techniques are substantially more advanced – to the point that we can now identify specifically which anti-HLA antibodies are present.  
- The organ shortage is substantially worse.  
- Transplantation is routinely being performed on much older and sicker patients.  
- Multiple strategies for transplantation of high-PRA patients and incompatible pairs (plasmapheresis, | We recognize that the relevance of the body of literature included in the TA is hard to determine. As specified in the draft report, we have clearly outlined in Key Question 1biv-v the impact of more recent trials on results. We did identify that a tendency toward less benefit and more tendencies towards a neutral effect was seen in more recent literature. This is in addition to selecting out DST transfusions into a subgroup and looking only at good quality trials. |
IVIG, Rituxan, splenectomy) are contributing very complex circumstances to the broad national database -- and are often not sorted out in studies that look solely at these national data for outcomes.

<table>
<thead>
<tr>
<th>Edward R. Jones, M.D.</th>
<th>Renal Physician Association</th>
<th>General</th>
<th>The scope of the questions was so narrowly defined that the broader, truer picture of the impact of ESA use in the care of Medicare beneficiaries and other patients with chronic kidney disease (CKD), both on dialysis and not on dialysis, is obscured.</th>
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<tbody>
<tr>
<td>Glenn M. Chertow, MD, MPH</td>
<td>Standford University School of Medicine</td>
<td>NA</td>
<td>None of authors of the Technology Assessment Report were physicians or surgeons experienced in the care of kidney transplant recipients. While the objective evaluation of published evidence can be a valuable exercise, conclusions based on such evidence without the clinical context should not be used to inform or influence policy. The University of Connecticut/Hartford Hospital EPC should have engaged the assistance of one or more physicians or surgeons involved in the care of</td>
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<td>NA</td>
<td>Aside from our group of pharmacists and physicians, we utilized the expertise of a Key Informant - J. Michael Cecka, Ph.D. who is Director of Clinical Research at the UCLA Immunogenetics Center. I believe the impression is that if we had a higher utilization of transplant personnel as key informants that we would have devised other key questions.</td>
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patients with advanced chronic kidney disease or end-stage renal disease and kidney transplant recipients.

While the EPC dutifully addressed the questions posed, they failed to recognize the narrow scope of the questions. Examination of the overriding question of whether blood transfusion is associated with prolonged or foreshortened allograft survival without considering the effects of blood transfusion on sensitization is the most critical flaw of the entire exercise. Had anyone on the EPC considered the effects of blood transfusion on sensitization and the effects of sensitization on transplant eligibility and outcomes, the conclusions of the Technology Assessment Report would have been vastly different.

The statement made in the Technology Assessment Report (page ES-1) "In transplants, the practice of blood transfusion has been shifting back and forth for the last few decades" is grossly inaccurate. Owing to the adverse immunologic effects of blood transfusion (the development of anti-HLA and other antibodies), most transplant physicians and surgeons have aimed to assiduously avoid blood transfusions in all prospective transplant recipients, whether persons with advanced kidney, liver, heart, lung or malignant disease, where solid organ or bone marrow transplant might be a future therapeutic option.

Even in response to the impractically narrow scope of questions posed, the authors concluded that the evidence used to support their conclusions was either "weak" or "insufficient."

However, we did not derive the key questions. We were charged with answering the questions that were posed by CMS. We do not believe that having a transplant surgeon would have altered the results or increased the strength of the body of evidence for the questions we were charged with answering.

Technology Assessments, in comparison to other AHRQ CERs have a rapid turnaround time. We were charged with answering the key questions that were posed by CMS in a scientifically vigorous, transparent, and unbiased manner.

We removed this sentence from the background section.

This is a very weak literature base from which to make healthcare decisions. Future studies may confirm our conclusions or may refute them, it is hard to engender confidence in the results when the
The tallying of studies on one side of the "effect of transfusion on allograft function" effect or the other failed to account for relative differences in data quality (e.g., low versus very low quality of evidence), the magnitude and stability of the estimates and the sample size on which the study and its conclusions were based.

While we understand your concern, we graded the studies on multiple different factors, which included sample size. We rated most of the included studies as poor due to their poor study designs, and we then graded the overall strength of evidence for the body of literature as either low or insufficient (based on AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews, which does not recognize "very low" quality of evidence). Because the heterogeneous nature and the weak strength of the literature base, we believe that there will be no appreciable change to our conclusion.

The authors of the Technology Assessment Report failed to distinguish the use of "donor-specific" blood transfusions and transfusions given for the management of severe anemia. Donor-specific transfusions were used with the hope of inducing "tolerance" - a state in which the recipient's exposure to the donor's foreign antigen might attenuate the subsequent immune response after organ transplantation. This practice has been abandoned as unsuccessful. Both reasons for transfusion can result in sensitization and preclude or limit an individual's access to organ transplantation.

We certainly appreciate the different mechanisms underlying the use of DST and therapeutic transfusion. We have separated the DST and therapeutic transfusion analyses from Key Question 1 for subgroup analysis. The subsequent results are not significantly different, and do not change any of our conclusions.

It is a misunderstanding to conclude that our statement means one, and only one type of study design (clinical trials). Taking the whole paragraph into account, will demonstrate that we are only referring to better methodology of future studies (both clinical controlled and observational studies), and not to any specific study design, as the reviewer seems to have done.
prospective transplant recipient (or Institutional Review or Ethics Board) would allow a trial of transfusion versus no transfusion to be conducted.

The authors of the Technology Assessment Report state "This (referring to immunosuppressive regimens) should be specifically evaluated to determine whether transplants need to be encouraged, avoided, or matched with certain regimens. Such evaluations should adhere to good study conduction practices." The authors must have meant to state "...to determine whether transfusions need to be encouraged, avoided or matched..."

Thank you for pointing this out. We have made the change accordingly in the final report.

The authors of the Technology Assessment Report failed to adequately address residual confounding and selection bias in the observational data. I addressed the "denominator" problem during the discussion period of the MedCAC meeting. In other words, studies in which transfusion and transplantation were evaluated included only individuals who had been transfused and ultimately received an organ, a smaller denominator than the eligible population. Authors of the original manuscripts failed to account for factors associated with the provision of transfusion, and the EPC failed to consider these additional weaknesses.

The TA was commissioned to report the evidence of transfusion effect on renal transplant recipients, and we were not tasked with evaluating all the outcomes related to kidney transplant candidates. Noted that there are desensitization treatments available for patients with HLA sensitization, and these patients can still have the opportunities to receive transplants. (Montgomery et al, NEJM 2011;365:318-26)

Although we have discussed this issue briefly in the discussion section of the original draft report, we have elaborated it to a greater extent in the discussion in the final report. We hope our much expanded discussion section will suffice here.

There appears to be confusion with respect to "retrospective" and "prospective" studies, numerous typographical errors and errors in detail (e.g., considering studies with p-values >0.05 as "significant") that lessen my level of confidence in the overall integrity of the report.

Since this comment did not specify where the confusion appeared to be in our report, we were not able to address this comment. However, we have reviewed our data, and we do not believe that there were errors in interpreting the significant p-values. We have made corrections to the typographical errors in the final report.
Officials at AHRQ and CMS should carefully consider the lives of persons with chronic kidney disease and in particular those with end-stage renal disease (ESRD). Dialysis sustains life, but rarely restores health. Patients on dialysis in the United States experience mortality rates in the range of 18 to 20% per year. Moreover, they experience marked functional impairment and relatively poor health-related quality of life.

Even when considering the risks and costs of immunosuppressive therapy, outcomes associated with kidney transplantation are hugely superior to those on dialysis. Virtually all patients with ESRD would benefit from kidney transplantation if more donor organs (from living and deceased sources) were available.

Restricted access to ESAs for Medicare beneficiaries would result in an unnecessary increase in the provision of transfusions, which would "pull the rug out from under" patients with ESRD, by increasing the likelihood of sensitization. Not only would this affect individual patient, but would result in an overall reduction of "life years with a functional graft" for the entire ESRD population. This would be a tragic outcome.

Thank you. In our expanded discussion section, we now address this in much greater detail. We hope this helps because we cannot alter the key questions, they were provided to us by CMS.

While the reviewer believes that kidney transplantation may benefit all ESRD patients, this statement cannot be validated with the existing data.

Thank you. We were not asked by CMS to evaluate ESA use in dialysis or transplantation. CMS set the key questions for this TA.

Mary Cushman, MD, MSc
American Society of Hematology
NA
The strength of evidence is low. This limits the usefulness of the data in the report. If this remains a clinically relevant question in kidney transplant practice, ASH is supportive of well-designed, multicenter studies to better determine benefits.

We agree with the comments. Hopefully our proposed trial ideas can be a place to start.

Geoffrey Land, PhD
American Society for Histocompatibility
NA
The questions in the assessment only addressed the impact of transfusion on transplant outcomes. They did not address or consider the significant impact of

While the reviewer makes a valid point, it is outside the scope of the key questions set by CMS. Hopefully the newly expanded discussion section will
| & Immunogenetics (ASHI) | sensitization on access to transplantation, particularly for women, pediatric patients and transplant patients requiring second and third transplants.  
The assessment was based on a literature review that was not comprehensive and which focused primarily on older articles where assessment of sensitization was based on PRA levels obtained from cell panels. They did not review or request Organ Procurement Transplant Network (OPTN) data and only included some Collaborative Transplant Study (CTS) data. In fact, the executive summary of the report rates the strength of evidence from the literature cited in the search as “low” or “insufficient” in all questions posed.  
The assessment did not address the fact that more recent studies detailing HLA-specific antibodies in transplant patients are based on much more accurate and sensitive solid-phase assays and, therefore, that the older data cannot be used to draw conclusions for current practices.  
The assessment also included some papers that showed a beneficial impact of donor-specific transfusions (DST). They failed to note that the DSTs in these studies were given to recipients in live organ donor protocols designed to induce tolerance to donor HLA antigens. The transfusions in question in the current discussion are from random donors and are likely to induce sensitization.  
The assessment attempted to address whether or not changes in immunosuppression changed the impact of transfusions, concluding that prior to 1992 transfusion had a beneficial effect, but that after 1992 | help provide this data in an understandable manner even though it is outside the scope.  
Firstly, the OPTN database did not meet the inclusion criteria because it was not an original clinical trial, and the analyses were not peer reviewed.  
Secondly, we included data from CTS in key question 1. There were multiple publications by CTS, and some of these had overlapping populations. We tried our best to account for this. We have now added data from the CTS to our final report for key question 2b.  
The low or insufficient strength of evidence was based on the poor quality of the literature base (poor study design, study heterogeneity). We understand that current practice has changed. We have accounted for these advances in KQ 1biv-v, where we clearly delineate in the impact of more recent trials on results.  
We now provide a subgroup analysis on DST versus no transfusion to try to alleviate these concerns.  
Yes, we agree. You rightly point out that the strength of the evidence is low to insufficient which is what we believe as well. |
the transfusion impact was equivocal. In fact, immunosuppression has changed dramatically since this period, with expanding use of induction therapies, desensitization protocols and rescue therapies directed at preventing antibody-mediated graft loss and reducing chronic rejection of allografts.

Finally, the overall conclusion of the report was that “transfusion has a beneficial to neutral effect on graft survival.” Clearly this is inconsistent with the current standard of care, where transfusion is avoided in order to reduce the possibility of increased sensitization to HLA antigens in this population of patients. Increased sensitization limits access to transplantation and increases the morbidity and mortality related to extended dialysis. It also does not address the needs of patients requiring chronic support for maintenance of adequate hemoglobin levels while on dialysis.

While we recognize the availability of these datasets, and agree that they offer great deal of information on this topic, we excluded them as they did not meet our predefined inclusion criteria as they were not published as original peer reviewed articles. The inclusion and exclusion criteria were specified in the report. We have now included the information from these datasets in the discussion section of the final report which includes the points that you just made. Rather than descriptive/numerical data included from these databases, databases that provide higher level of analyses (i.e. with control groups) can add value to future research. We now specifically say in the future research directions sections of the report “Data from UNOS and USRDS registries in particular could be used for future research but should be published in peer reviewed journals, have an adequate use and

Traditionally, the transplant community has relied on smaller, center-specific reports to bolster changes in therapy and science. Basing policy conclusions on a literature search is problematic given the lack of large, multi-center, adequately powered studies in transplantation, and the failure to examine epidemiologic data.

The relevance of Donor Specific Transfusion (DST) strategies and their impact on transplantation outcomes is difficult to accurately assess as the vast majority of DST studies were undertaken prior to the contemporary era of immunosuppression, e.g. tacrolimus and mycophenolate mofetil. Similarly, the assessment of DST as a strategy for effectively abetting transplantation is hampered by the contractor’s failure to analyze all DST recipients, especially those who became sensitized and thus, could not receive a transplant. Indeed, when analysis is present, e.g. Leone et al. J Urol 1990 or Otsuka et al. Nephron 2001, there is a documented rate of donor sensitization, ranging from 7.5-30%. Thus, patients enrolled in these protocols actually were

description of methods, and account for a myriad of confounders.”

I believe that the quality of the observation data (UNOS, UCLA, and USRDS) that we now include in our discussion section would still not rate as good since they have scant methods, no demographic data in the two comparison populations, do not, by and large account for confounders, and were not published in peer reviewed journals. That is not to say that are not ultimately correct in what they are saying just that the confidence that people can have that a future well designed clinical trial would not come up with a different conclusion is low.

We have separated DST and other non-DST transfusion analyses, and evaluated them separately. We found that there was no material effect on our results, nor does it affect our conclusion. We were explicitly asked by CMS in Key Question 1 to do a transfusion of any kind versus no transfusion analysis and we concurred. We did then do several other analyses in the second part of key question 1.

We excluded Leone et al. 1990 because the study is not related to the key questions of this TA as it compared DST to cyclosporine instead of comparing DST to no transfusion or to non-DST transfusion. We also excluded Otsuka et al. 2001 because this study evaluated a transfusion type that was not of interest
denied the opportunity to receive their transplant, an outcome that obviously is not optimal. The University of Connecticut/Harford Hospital EPC should not have pooled the data from donor-specific and therapeutic blood transfusions in their analyses.

In the contemporary era of immunosuppression (after 2002-4) there has been an increased prevalence of regimens including tacrolimus and/or mycophenolate mofetil and there have been a number of significant changes in induction therapy since the early 1990’s. As a result, current graft and patient survival rates are exceptional one year post-transplant. (See OPTN/SRTR annual report and the SRTR report on the state of transplantation published annually in the Am J Transplant). To assess impact of red blood cell transfusion based upon 1-year outcomes, therefore, could be misleading.

Over the last 20 years, there have been significant advances in immunosuppression with induction, calcineurin inhibition, evolution of anti-proliferative agents, and additional medications, e.g. mTOR inhibition. These advances define eras in transplantation and also confound inter-era comparisons, especially when the prevalence of red blood cell transfusions for transplant candidates and the availability of alternative anemia therapy as the result of the introduction of erythropoiesis stimulating agents were also changing in those eras. The fact that over half of the studies in the technology assessment were conducted before 1984, and less than ten percent of the studies were conducted after 1992 significantly undermines its relevance to current CMS policy considerations.

It may be important to distinguish the impact of to this TA as it evaluated buffy coat transfusion not a red cell/whole blood transfusion.

For the vast majority of the studies (including recently-published studies), 1-year graft survival was the most common time frame evaluated. Furthermore, besides this endpoint, we also evaluated max-duration graft survival.

We understand that current practice has changed, but due to a myriad of reasons, the studies that ended up being included as part of the TA did not reflect those advances. We attempted to account for these advances in KQ 1biv-v, where we clearly delineate in the impact of more recent trials on results. We do find a tendency toward less benefit and more tendencies towards a neutral effect in more recent trials. This is clearly specified in the report.

We added a section to discuss the impact of
transfusion prior to transplantation vs. the impact after transplantation in the data presented, especially if transfusions were part of the transplant surgery.

The definitions and diagnosis of rejection are not consistent over time. Rejection classification defined by Banff criteria in 1993 (Solez et al. Kidney Int) were an attempt to coalesce diverse definitions into a standardized format. Subsequent amendments and alterations to diagnostic criteria for rejection, e.g. Racusen et al. Kidney Int 1999; Racusen et al. 2003 Am J Transplant, demonstrate a shifting and indeed broader definition of rejection over time. Not only were there changes in nomenclature, with current practice nomenclature in that humoral rejection has been replaced by antibody-mediated rejection (either acute or chronic) and dispensing with chronic rejection as terminology but there were efforts towards greater histological definition with a focus on characteristics of the tissue, e.g. interstitial fibrosis/tubular atrophy (IF/TA). Such advances in tissue assessment confound the use of older studies that have used rejection as an endpoint. However, in the absence of standardizing criteria for assessing rejection as an outcome, use of this metric is very difficult to interpret.

We agree with the reviewer’s comment. The vast majority of the studies that reported rejection as an outcome did not classify the specific types of rejection, and there were no standard criteria to assess rejection as an outcome. Thus, we concluded the strength of evidence of the overall body of literature on this outcome was either low or insufficient.

To enhance stakeholder utility of the technology assessment, it would be useful to consider key research questions that are more linked to the chronic kidney disease (CKD) population. The questions addressed in the draft Technology Assessment are currently too narrow to evaluate the role of transfusions and the associated impact on renal transplants. As such, the addition of questions related to anemia management, transfusion avoidance, and the more general CKD population would help address these important considerations.

Thank you for this comment. We have greatly expanded our discussion section to address real concerns such as this, even though they lie tangential to the questions we were asked to answer. This is indeed a complex issue and we recognized in the draft report that some participants in the trials did not end up going for transplant. In this revised version we now specify how many patients that entailed. This does not mean that our data shows those people would have had an adverse outcome because they were not transplanted but it does...
For example, in the transplant candidate population, examining the impact of anemia management and transfusion status/exposure on overall outcomes (time to transplant), or death while awaiting a transplant. By focusing on the population that ultimately received a transplant, the true impact of transfusion in the transplant candidate population cannot be accurately evaluated.

Consideration should be given to the potential differences in the impact of transfusion status/exposure on subpopulations such as women, older adults, and African Americans. Relevant outcomes in these subpopulations include: The impact of transfusions on panel reactive antibodies (PRA) The impact of sensitization on transplant antibodies The potential differential impact of a longer wait time due to sensitization in older populations or populations with a higher burden of comorbid conditions, e.g., mortality either awaiting a transplant or post-transplant.

Another potential consideration not included in the key research questions is transfusion-associated infections or complications (e.g., hepatitis C2, transfusion reactions7, transfusion associated lung injury6) which may preclude a patient from transplantation candidacy or be associated with considerable morbidity or mortality that may not be captured in the current assessment.

Consideration should be given to the potential confounding in the observations of outcomes by transfusion status. Those transplant candidates that increase transparency for an important issue that the report had not adequately addressed previously. Know though that we cannot add new key questions or perform a totally new literature search at this point. These key questions were selected by CMS as being the most important for their needs and we answered those questions in the best manner we could. In our discussion we have a section dedicated to future research needs to elaborate on such areas which have been identified as a result of the TA.

Your comments on considering the potential differences in the impact of transfusion status/exposure on subpopulations are not firmly supported by the literature. Given current inconclusive data, future research is needed in this area. For the rest of the comments, refer to our response to your first statement.

Thank you for this comment. The scope of the TA focuses on the impact of transfusions on renal transplant outcomes such as rejection, survival and patient survival. Transfusion related complications are already a known risk of transfusions and does not seem to warrant an additional key question here.

We agree with your comment and now evaluate the number/percentage of patients who had transplantation delayed or denied through the.
were transfused and ultimately transplanted may be less immunoresponsive/sensitized (manifested by lower PRA) than those that did not get transplanted. It may appear that transfusion has a positive impact on outcomes; however the more immunoresponsive (sensitized) transplant candidates would have been excluded, as they were not transplanted.

In relation to Key Question 2b, sensitized transplant candidates, manifested by higher PRA, who were ultimately transplanted may have been treated by different immunosuppressive regimens than less sensitized transplant candidates. Is it the potential different immunosuppressive regimens /protocols that impact the outcomes and not transfusion status/PRA level? 1) What are the potential outcomes associated with the management of highly sensitized transplant candidates? More aggressive immunosuppressive regimens (induction and maintenance) used to treat the highly sensitized population may be associated with higher rates of complications such as infections, malignancy, and the likelihood of developing diabetes. The current analysis only looks at graft and patient survival.

Consideration of the United States Renal Data System (USRDS) data would strengthen the completeness of the draft Technology Assessment. 3 Conclusions from 2010 USRDS report include: For transfused vs. non-transfused patients the Hazard Ratio was 4.04 for death and 0.72 for getting a transplant. Sensitized candidates wait longer for transplant, as 28% of wait-listed patients received a transfusion within 3 years of listing. Non-sensitized patients (PRA of 0% at listing) were as likely as mildly sensitized patients (PRA < 20%) to receive a transfusion. Highly sensitized patients (PRA 80%+) were more likely to receive a transfusion within occurrence of sensitization in our included studies. Our expanded discussion highlights this even more.

Thank you for this comment. In a TA, we are asked by CMS to evaluate these key questions. We used a time related approach to look at more contemporary practices versus older practice but there simply is not data on whether some people received different regimens due to sensitization than other people. We agree that better research is needed to be able to evaluate this area but such data has not been generated. That is why the strength of evidence is so low. Additionally, we have a section dedicated to future research needs to elaborate on such areas which have been identified as a result of the TA.

Thank you for this comment and the reference you provided. The USRDS data has been incorporated into the discussion section along with UCLA and UNOS data presented in book chapters in our final report. These data are not from peer reviewed sources, do not have adequate methods or demographics in both representative groups, and rarely account for confounders. Of note, the USRDS data, which use the OPTN-UNOS registry, do not collect quantitative/qualitative information on transfusions. These data are self-reported, and information on whether patients received transfusions are limited to discrete data (i.e.
3 years of listing, 41% within 3 years of listing. Transfusion was associated with decreased likelihood of transplantation. PRA at transplant remains associated with adverse outcomes.

An additional consideration is, the venous access needed for transfusion support in the CKD population. The importance of the preservation of veins in CKD patients is a major consideration, as the National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Guidelines recommend that veins should be preserved for future vascular access for fistula creation. Transfusion use and its impact on the availability of suitable veins for vascular access for fistula creation should be considered. Coupled with the longer wait times associated with sensitization due to transfusion exposure and the resulting longer dependence on dialysis, this potential impact on long term vascular access availability to support dialysis needs to be considered.

Thank you for this comment. Vein preservation may be important in this population but evaluating that literature base would be outside the scope of the project we were charged with answering. At this point, we cannot add new key questions or conduct an entirely new literature search. The key questions were set by CMS.

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<tr>
<th>Drs. Maryl Johnson and Michael Abecassis</th>
<th>American Society of Transplantation and American Society of Transplant Surgeons</th>
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<td>In the document put forward for public comment entitled “The Impact of Pre-Transplant Red Blood Cell Transfusions in Renal Allograft Rejection”, it was concluded that “number of transfusions/transfused units versus no transfusion, or a smaller number of, transfusions/transfused units either resulted in either beneficial or small/null effects on rejection, graft survival, or patient survival. So the literature, weak as it is, supports a neutral to positive effect resulting from transfusion and does not support a detrimental effect resulting from transfusion of a larger number of transfusions”. We believe this statement to be inaccurate, and the data presented in the document</td>
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<td>Given the key questions we were posed and the literature search we conducted, which meets AHRQs guidance for a comprehensive search, these are the results of the Technology Assessment. The quoted sentence “number of transfusions/transfused units versus no transfusion, or a smaller number of, transfusions/transfused units either resulted in either beneficial or small/null effects on rejection, graft survival, or patient survival. So the literature, weak as it is, supports a neutral to positive effect resulting from transfusion and does not support a detrimental effect resulting from transfusion of a larger number of transfusions” is from the discussion section, and it</td>
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to be limited in scope and applicability based on the following points: 1) The data are predominantly drawn from publications in the 1980’s, many of which specifically examined the use of Donor Specific Transfusions (DST) prior to transplantation and their impact on graft survival. The conclusion does not take into consideration the effect of DST on access to transplantation and the development of positive cross matches preventing transplantation in up to 50% of cases. Indeed this is briefly mentioned in the document itself: “It should be noted that in some studies, patients who were candidates for transplantation were ultimately not offered the transplant due to high PRA levels. Some other studies did not disclose the number of patients who were ultimately not transplanted due to a high PRA as they focused on the population undergoing transplant.”

2) The extrapolation of DST in the immediate pre-transplant period to the general use of transfusion for chronic treatment of anemia pre-transplant is not based on scientific evidence and is unwarranted. The premise of the benefit of DST is that the transfusion of blood from the potential specific kidney donor results in the direct exposure to donor antigens prior to transplantation resulting in modulation of the immune responses toward those antigens. As noted above, in a significant percentage of cases, this resulted in the development of anti-donor antibodies thereby precluding transplantation from that donor, rather than facilitating graft acceptance. Accordingly, DST is significantly different to transfusion from multiple random donors which likewise exposes the potential recipient to multiple HLA antigens, increasing the risk of sensitization and thereby decreasing the potential candidate donor pool for a

reflects our findings based on the literature. In no way is this to be taken as a conclusive statement of this TA. As it was pointed out in the comment, “Given the problems with internal validity with these individual studies and the heterogeneity contained within the studies, we only have a low or insufficient strength of evidence for any of these findings”, both the statement and the strength of evidence need to be viewed together when assessing a TA. However, in the light of the comments, we have revised the sentence to “So the literature, weak as it is, demonstrates at neutral to positive effect resulting from transfusion and does not reflect a detrimental effect resulting from transfusion.” in the discussion section, so it will not be mistaken as a conclusive statement.

We do identify several limitations for this literature base including the fact that some people are not given transplant or had transplantation postponed. We now make the percentage impacted in these studies specific to address your concerns. We also now pull out the DST data in Key Question 1 out in subgroup analysis and demonstrate that it really does not markedly alter the results and does not alter our conclusions. Previously, we analyzed the results over different time points which show the impact of relying on studies of older time points. As such, we do provide information that specifically addresses one of your concerns and will stay with our original analyses.

We agree largely with your final statement that the review and conclusions are markedly limited and the strength of evidence is low. As you say, our report makes it clear that “Given the problems with internal
prospective recipient [1, 2].

3) The data used refer to Panel Reactive Antibodies, a measure of general reactivity toward the potential donor pool. This measure is used in the allocation of organs and does not indicate reactivity to the recipient’s specific donor. Current methodology is based on the identification of Donor Specific Antibodies (DSA), a better predictor for an adverse impact on graft survival through the development of acute or chronic antibody mediated rejection [3-5]. In short, the review and conclusions are largely irrelevant to current practices and do not take into account current technology and immunosuppression. The difficulty with generating any broad conclusion based on the data presented is further emphasized by the following statement in the document itself: “Given the problems with internal validity with these individual studies and the heterogeneity contained within the studies, we only have a low or insufficient strength of evidence for any of these findings”. The strength of evidence presented for all articles referred to was ranked as low to insufficient data.

We would strongly urge that more recent data, which provide stronger evidence for the deleterious effects of sensitization and transfusion on transplant outcomes, and access to transplantation, be considered. A recent study examining the effect of DST and random pre-transplant blood transfusion (rPTF) on sensitization found that 25% of potential recipients did not receive a transplant following DST due to the development of DSA. Of those that received a rPTF, 27% developed anti-HLA antibodies and these were donor specific in 20.3% of cases.

Synder et al presented data at the National meeting of the American Society of Nephrology in 2010 based on findings from the USRDS 2010 report. This data showed that patients with PRAs greater than 80% at validity with these individual studies and the heterogeneity contained within the studies, we only have a low or insufficient strength of evidence for any of these findings”. Clearly, in order to truly determine the impact of transfusions on these outcomes, rigorous trials and studies will be needed.

Thank you for this comment and for the reference you provided. Although we recognize the availability of the USRDS data, the inclusion criteria allows only for the controlled studies (both clinical and observational) published in peer reviewed literature to be included. As such, future USRDS data from peer reviewed longitudinal cohort studies would meet the criteria. Additionally, the USRDS data is incorporated into the discussion section of the final report.

Of note, the USRDS data, which use the OPTN-UNOS registry, do not collect quantitative/qualitative information on transfusions. These data are self-reported, and information on whether patients received transfusions are limited to discrete data (i.e.
the time of listing had a higher three year cumulative incidence of transfusion prelisting compared to those with PRAs less than 19% while patients with PRAs of 20 to 79% were intermediate. Patients that had a transfusion prior to listing had an increased adjusted hazard ratio of 4.04 risk of death on the transplant waiting list compared to those who had not received a transfusion, and a 28% reduction in the likelihood of transplantation. Fifty percent of waitlisted patients with a PRA of >80% die on the waiting list. Patients with a PRA >80% comprise 30% of the current renal transplant waiting list. The adjusted hazard ratio for death with a functioning graft was 1.41 for those with a PRA of 80%, compared to 1.21 for 20-79%, and 1.08 for 1-19%, with 0% as reference. The effect of transfusion is greatest for African Americans and women, with both groups being more likely to become sensitized [6]. This further disenfranchises two groups that already have decreased access to transplantation due to immunological and social factors. Kakaiya et al examine the prevalence of anti-HLA antibodies in blood donors that had previous transfusions themselves using current methodologies [7]. They found that overall there was an increase in anti-HLA antibodies, and this was particularly so for parous females that received a transfusion compared to those that had not (OR 1.39). Similarly, Eikmans et al found that 35% of parous females that received a single transfusion developed sensitization. These are just a few of the more recent publications linking transfusion and sensitization [8].

There is limited evidence that treatment of post-transplant anemia is beneficial to anemic kidney transplant recipients since large randomized studies have not been performed in this population. The TREAT study examining ESAs versus placebo in diabetic patients with CKD demonstrated that 24.5%

yes, no, unknown). It is not known if therapeutic transfusions are actually indicated or required.

The second reference by Kakaiya et al 2010 examines the prevalence of anti-HLA antibodies in blood donors that had previous transfusions themselves. It does not evaluate the transfusion effect in renal transplant candidates or recipients. It is important to include a study that meets predefined inclusion criteria. Study inclusion and exclusion criteria are presented in the draft report.

Similarly, the study by Eikmans et al 2010 examines the effect of blood transfusions but not in renal transplant population which is the scope of this TA.

In regards to high PRA and the waiting times, one should note that there are desensitization treatments available for patients with HLA sensitization, and these patients can still have the opportunities to receive transplants. (Montgomery et al, NEJM 2011;365:318-26)

In the future research sections of the report we now state that “Data from UNOS and USRDS registries in particular could be used for future research but should be published in peer reviewed journals, have an adequate use and description of methods, and account for a myriad of confounders.”
of patients in the placebo control arm required transfusion [9]. The impact on sensitization was not measured in this study but studies referred to above and others would suggest that this population would have a significant risk of developing anti-HLA antibodies. This is also inferred from data from the USRDS 2010 report which shows that the rate of pretransplant transfusion has decreased from 49% to 15% from 1991 to 2008, reflecting the increased use of ESAs in ESRD patients. At the same time the percentage of patients with 0% PRA on the waiting list has increased from 20% to over 40%. Vella et al showed that the number of transfusions in waitlisted patients decreased by 34% in the period before and after the introduction of ESAs [10]. Parallel with this the number of patients sensitized as a result of transfusion decreased from 63% to 28%, and this was associated with a significant reduction in the mean time to transplantation.

The origin of anemia after transplantation is multifactorial. In the absence of ESAs renal transplant recipients would almost universally have anemia due to ESRD at the time of transplant. While recovery of erythropoiesis occurs following transplant this is not immediate and fails to occur in up to 30% of patients. In the perioperative period anemia is worsened by the intraoperative loss of blood, the presence of delayed graft function, the initiation of immunosuppression (sirolimus and mycophenolate mofetil) and other medications, including ACEI. Perioperative anemia is recognized to contribute to perioperative complications [11]. In a study by Djamali et al, they found that in a population of patients on ESAs at the time of transplant, with hematocrits (Hct) ranging from 17% to 40% on post-op day 1, the average drop in Hct was 5.9±5.6% [12]. Patients that had a Hct of
less than 30%, representing 60% of the study population, had 17% incidence of acute cardiovascular events, significantly greater than those with a Hct > 30%. Increasing Hct was associated with a significant risk reduction for CV events. Death due to an acute CV event is the greatest cause of death with a functioning graft in the months post-transplant.

One must also consider that from the practical perspective, reliance on blood transfusions for treatment of anemia prior to transplant would require referral to a hospital and potentially an admission, since most free standing dialysis units do not have the capabilities to transfuse patients in the unit. This has implications for cost and must be considered in the financial analysis overall.

In conclusion, we strongly disagree with the statement that “number of transfusions/transfused units versus no transfusion, or a smaller number of, transfusions/transfused units resulted in either beneficial or small/null effects on rejection, graft survival, or patient survival”. The rationale leading to this conclusion is severely flawed for the following reasons: (1) the age and the weak scientific strength of the data considered; (2) failure to take into consideration newer data and techniques; and (3) failure to consider the overall impact of pre-transplant transfusion on access to transplantation. Use of these data in any decision-making process regarding the use of ESAs relative to transplantation would be misguided and has the potential to significantly impact our patients’ ability to get transplanted and their outcomes following transplantation.

We strongly urge that appropriate randomized control trials of the treatment of anemia in the transplant population be conducted, and that the results from

Noted

When interpreting this statement, one should take into account the low to insufficient strength of evidence. The statement quoted from the draft report was based on the findings of the included studies, which were tailored to answer the key questions.

We also believe that these trials should be conducted and applaud your organization’s willingness to participate.
these studies form the basis for any future decision-making regarding appropriate therapy in our patients. The AST and the ASTS stand ready to provide any needed assistance as this important issue is considered.

1 Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.
2 Affiliation is labeled "NA" for those who did not disclose affiliation.
3 If listed, page number, line number, or section refers to the draft report.
4 If listed, page number, line number, or section refers to the final report.
APPENDIX: Response to Amgen

GENERAL THOUGHTS

We would like to thank Amgen for the detailed review and comments on the technology assessment. In order to address the comments systematically, we have listed in blue all our responses to the comments in the format that Amgen provided us. Please refer to the final report for specific changes.

EXECUTIVE SUMMARY

As the executive summary is an abbreviated version of text from other sections of the technology assessment, please refer to Amgen’s detailed comments in the individual sections. Below is a high-level summary of Amgen's comments.

The objective of the draft technology assessment was to evaluate the evidence regarding the impact of transfusions on renal transplant outcomes. However, the technology assessment has serious limitations and therefore should not be used in its current form to inform policy decisions. In this document, Amgen provides a review of the technology assessment and identifies its key limitations. The limitations have been grouped into two categories – design limitations and analysis limitations.

*Design limitations*

1. The questions formulated to address the stated objective in the technology assessment were inappropriately narrow as they failed to include the impact of transfusions on eligibility for organ and transplant wait times, which are critical renal transplant outcomes that significantly affect the lives of chronic kidney disease (CKD) patients. Exposing transplant candidates to transfusions and their risk of allosensitization, may prolong organ wait time and/or preclude them from receiving a suitable organ, and thus, may relegate them to lifelong dependency on dialysis [1-3]. This can be even more pronounced among African Americans, who have a higher likelihood of being sensitized by transfusions and a lower probability of finding a suitable matching organ, which unnecessarily disadvantages their opportunity to receive a transplant [4-7].

   We understand the concern that the reviewer had. The key questions were posed by CMS and we were asked to answer them in a rigorous and unbiased manner. Although the outcomes of interest discussed above are valid points, they are tangential to the key questions that we are charged to answer. However, please understand that there are very important limitations to answering a key question when you need to use one data set to establish a link between an intervention and a surrogate outcome and another data set to show a link between the surrogate and the outcome as we discuss at length in the background section response. In addition, the assertion of increased likelihood of sensitization by transfusion in African American is not supported by current available data, in which the literature revealed that African Americans tended to be transfused inappropriately given that the indifference of their hemoglobin reference range to the standard range. Also, it has
been reported from historical observational studies that worse renal transplant outcomes have been observed in African American although etiologies for such is unknown.

2. The technology assessment missed key publications from the peer review nephrology literature, and data from the US transplant registry, that are relevant to the use of therapeutic blood transfusions in CKD patients. Importantly, the US transplant registry captures data on the entire US wait-listed and transplanted patient populations. A selected list of these publications is provided in Appendix A.

   With the list of 27 publications provided by the reviewer, only three studies meet the inclusion criteria of the TA. [Alarif et al, 1987 (2), d’Apice et al, 1982 (7), Opelz et al, 2005 (19)] Please see Appendix A for the rationale of exclusion for the other 24 publications. The inclusion and exclusion criteria for the technology assessment were listed clearly in the report. The inclusion criteria allows only for controlled studies (both clinical and observational) published in peer reviewed literature to be included. Although we recognize the availability of US transplant registry data, we opted not to include such data in our evaluation since the data were not published as peer reviewed original controlled trial. Clearly, peer reviewed longitudinal cohort studies would meet the criteria.

3. The technology assessment failed to acknowledge the important distinction between transfusion for the purpose of immunomodulation (eg, donor-specific transfusions [DSTs]) and therapeutic transfusions for the management of chronic anemia in CKD [8]. The differences in the clinical purpose, sources of blood, and volume of blood make these specific types of transfusions distinct; consequently, outcomes associated with immunomodulation transfusion strategies are not generalizable to those associated with therapeutic transfusions. For the purpose of this technology assessment, combining the evidence for these distinct types of transfusions confounds the conclusions rendering them invalid as a basis for clinical decision making.

   We recognize the distinction between different types of transfusion, and their clinical purpose of immunomodulation. We now separate the analyses for DST and therapeutic transfusion in Key Question 1, and evaluate the impact of transfusion on renal allograft outcomes in the 2 subgroups of analyses. The results of the subgroup transfusion are not markedly different from our original analyses, and they do not change the overall conclusion of the TA. Please refer to Tables 14-19 of the final report for the results of these subgroup analyses.

Analysis limitations

4. Inappropriate weighting: All studies were weighted equally in the evaluation of the literature.

   a) Due to the vote counting methodology employed, results from studies of markedly different sample sizes (eg, 37,000 versus 732) were weighted equally. This approach for summarizing evidence is prone to bias, considered the least robust method, and is not the recommended approach for systematic reviews [9].

   We understand the reviewer’s concern in this aspect. With the poor literature base available, this was the best we can do, and in fact, we did address this
limitation in the discussion section of our draft report: “This approach has limitations because analyses of varying quality and sample size were evaluated together but it provides that only type of independent qualitative analyses that can be done on such a literature base.”

b) Results from studies in the pre- and post-cyclosporine era were weighted equally. The development of cyclosporine and the later development of multi-drug immunosuppressive regimens transformed transplant medicine. Given that the vast majority of studies in the technology assessment pre-date these advancements, the conclusions drawn in the technology assessment are not relevant to current medical practice.

We account for the changes in practice by comparing the analyses in different time periods and display what happened in all of the available studies. It is clear that most of the data is older in nature, as illustrated in our report. We cannot do anything about the nature of the evidence we have to review. Amgen can help to fill in the research gap by funding future studies of reasonable quality that provides insight into these key questions that obviously is important to CMS. All we can do is evaluate the available literature in the best available manner and to report it with transparency and rate the strength of evidence as such. We hope Amgen understands that we are not saying that transfusions are beneficial in transplant. We believe that the available evidence is incredibly weak and that firm conclusions cannot really be drawn. However, we feel it is disingenuous to suggest that the data for harm from using transfusions is strong.

5. Selection bias: Transplant candidates who receive transfusions may become allosensitized and consequently be precluded from receiving a kidney transplant. This was most clearly demonstrated in studies of DSTs where up to 30% of patients became allosensitized to their donor and were not able to receive the donor organ [10-13]. Preclusion from transplant is a clinically relevant renal transplant outcome and the exclusion of these patients from the technology assessment analysis introduces a significant selection bias. The failure to acknowledge this inherent selection bias, and the failure to account for it in the evaluation of the evidence, undermines the validity of the conclusions drawn regarding the impact of transfusions on transplant outcomes.

This is a valid concern, and a very important limitation to this data set. We tried to be quite transparent in the discussion section alerting people to this very large confounder. To account for this, we have now added evaluations on the impact of sensitization on eligibility for transplantation in transfused patients (see pages 69-73, Table 43). We found that a proportion of patients who were sensitized from transfusion were precluded from their planned kidney transplantation, and the graft outcomes, if any, for this particular population was unclear. Thus, we cannot be sure whether transfusions have a beneficial to neutral effect on outcomes in this subgroup of patients.

6. Factual errors: Errors were made reporting data from the original articles that contributed to misclassification of results and inaccurate conclusions.

Given the limitations in the body of evidence, we evaluated and summarized the data sufficiently to show what the literature suggests and that the strength of evidence is low to insufficient. We appreciate the review that Amgen provided and looked at each carefully and made alterations where necessary. None of the
“Factual Errors” or “Transparency Issues” in any way alters the conclusions of our Technology Assessment. We feel that with the number of studies included and the number of endpoints evaluated, that we are proud of our ability to accurately extract and categorize the data.

7. Lack of transparency: Insufficient detail was provided throughout the technology assessment, preventing reproducibility of the analyses.
   See above

As a result of these limitations, the technology assessment did not adequately address the stated objective and the conclusions drawn in the technology assessment are not fully and appropriately informed by the totality of the available evidence. The conclusions in the technology assessment contradict current practice and evidence-based clinical guidelines, and have the potential to adversely impact patient care.
INTRODUCTION AND BACKGROUND

In this section of the technology assessment, there are two major areas of concern. One relates to the source of the information cited as guiding the conceptualization of the research question. The second relates to statements that contradict current clinical viewpoints regarding the adverse consequences of transfusions on transplant outcomes.

The technology assessment’s review of the field of renal transplantation cites two sources:

- Pharmacotherapy: Principles & Practice, 2nd Edition
- The Organ Procurement and Transplant Network (OPTN) website.

There was no reference to authoritative textbooks of transplant medicine, kidney transplant medicine, or transfusion medicine. The textbook that the technology assessment did reference (Pharmacotherapy) and directly quotes (page 2), provides in subsequent paragraphs useful information regarding the assessment of pre-transplant immune risk factors of transplant recipients. The specific text reads as follows:

“To avoid acute or chronic rejection, assessment of pre-transplant immune risk factors of recipients plays an important role in the prevention of immune-mediated allograft injuries. Evaluation of the presence or absence of alloantibodies and T cell activities to HLA antigens plays a significant role in individualization of immunosuppressive therapy. Patients with a high panel level of reactive antibodies (PRA) have a greater risk of immune-mediated injuries to the transplanted allograft. The PRA test measures the recipient’s mismatches and pre-formed antibodies against 50 to 60 different individuals (not donor). If 25 cells react, it is considered 50% reactive (PRA of 50%). Patients with higher PRAs and pre-formed antibodies have lower long-term allograft survival.” (p. 943, Ch. 55 Solid Organ Transplantation, In: Pharmacotherapy: Principles & Practice, 2nd Edition)

This text clearly states that allosensitization (PRA) is an important predictor of renal transplant outcomes. Thus, the impact of transfusions on allosensitization should have been considered when evaluating the impact of transfusions on renal transplant outcomes.

We chose the textbook we did because we wanted to reference a text that would concisely present an overview of the topic in a manner understandable to many stakeholders including healthcare policymakers and patients. The introduction was to introduce the topic not to report the opinions of experts in the field that had written book chapters. That is not what systematic review is about. In addition, we were not charged with deriving the key questions. Key questions were provided to us by CMS. We were asked to answer the key questions that were asked in a transparent and scientifically rigorous manner. That being said, I think there can be a rigorous defense made by CMS for the key questions they posed. Their questions have an advantage of limiting the dataset to those studies that directly evaluate the link between transfusion and outcomes. There are very important limitations to looking at two steps which may or may not be related. Here we are referring to the link between transfusions and sensitization using one data set and then the link between people who are sensitized (whether by transfusion or a host of other reasons) and outcomes in another set of data.
The AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* is clear that direct evidence is far superior to indirect evidence.

The second concern relates to the statements made in the “Evolution of transfusion in renal transplantation” section (p. 3). The technology assessment makes the following statement: “the practice of blood transfusions has been shifting back and forth for the last few decades.” This is not a proper characterization of the evidence. Therapeutic transfusions have well-known risks, including the development of allosensitization, and thus were curtailed once other therapeutic options became available for the treatment of chronic anemia in CKD patients [15, 57].

We have removed this sentence from the background section.

Below is a listing of specific comments for consideration. Please note this list does not include a number of minor editorial or factual errors that were not included for brevity.

1. The second paragraph, last sentence on page 1 states that “The use of hemodialysis, transplant, transplantation wait list, or peritoneal dialysis in patients covered by CMS in 2006 is provided in Table 2.” A more complete presentation of the wait-listed population would have included data on the distribution of panel reactive antibody (PRA) levels, which are known to impact wait-times. Sensitized patients have longer wait times on the transplant list and remain on dialysis resulting in greater morbidity and mortality than in transplanted patients. The OPTN reports that the median transplant wait time for patients with a peak PRA of 0%-9% was 1,276 in 1999-2000 and 1,329 days in 2001 compared with 4,059 days and 3,448 days, respectively during those timeframes, for patients with a PRA of = 80%. Amgen recommends that the authors consider updating this table to include that information.

The causes of sensitization in transplant candidates were not captured in OPTN/UNOS database (i.e. sensitized for any reason, not just from transfusion). The data you propose be used is not limited to those sensitized from transfusions but rather sensitized for any reason and as such, the ability directly extrapolate to outcomes is problematic. Our report does bring to light that issue in the discussion section.

2. Page 2, Allograft Rejection, Acute Rejection, first sentence states that “Acute rejection is a cell mediated process that generally occurs within 5 to 90 days after a transplant, although it can rarely occur after this time.” The source for this information does not conclude that acute rejection “rarely” occurs after 90 days. Amgen recommends removing “rarely” from this sentence.

We removed the word “rarely” from the report to comply with this comment.

3. Page 2, Allograft Rejection, Acute Rejection, fifth sentence states that “Pretransplant assessment for the presence or absence of alloantibodies and T cell activities to HLA antigens is touted to reduce the risk of acute rejection.” The overwhelming evidence in transplant nephrology suggests that pre-formed alloreactive anti-HLA antibodies sufficient to cause a positive cross match are a contraindication to kidney transplantation (Patel and Terasaki P. NEJM 1969[60]; Bergentz et al 1970[70]). Therefore, Amgen recommends the sentence be modified to “Pretransplant
assessments for the presence or absence of alloantibodies and T cell activities to HLA antigens reduces the risk of acute rejection."

We have not systematically evaluated this data set and rated the strength of evidence using an objective measure. The data you quote is from 1969 to 1970 and its applicability to contemporary practice cannot be determined. Does it still have the same importance as it did before induction, cyclosporine, etc? Therefore, we would rather not make a definitive statement such as the one Amgen would like.

METHODS

The limitations of this technology assessment are classified as 1) design limitations and 2) analysis limitations. As a result of these limitations, the technology assessment did not adequately address the stated objective and the conclusions drawn in the technology assessment contradict current practice and evidence-based clinical guidelines, and have the potential to adversely impact patient care. Below, each of these limitations is summarized.

Design Limitations

The translation of the stated objective into the specification of the research question was inappropriately narrow and therefore did not permit a full evaluation of the effect of transfusions on transplant outcomes among transplant candidates. The clinically relevant underlying question is “should transplant candidates receive RBC transfusions for the management of chronic anemia?” To comprehensively address this question, the technology assessment needed to examine the effect of transfusions on eligibility for suitable organs and the time a transplant candidate spends on the wait list, in addition to an assessment of the impact of transfusions on graft survival among transplants that do occur. The technology assessment fails to acknowledge that waiting time for transplant and not receiving a transplant are transplant outcomes. To an individual patient, eligibility and wait-times for an organ are critically important because the longer a patient is on a transplant wait-list, the higher the likelihood the patient will die on dialysis rather than receive a transplant. Therefore, the scope of the question that the technology assessment evaluated was too narrow to adequately inform on the effect of transfusions on the range of relevant and important kidney transplant outcomes.

We understand the concern that the reviewer had. The key questions were posed by CMS and we were asked to answer them in a rigorous and unbiased manner. Although the outcomes of interest discussed above are valid points, they are tangential to the key questions that we are charged to answer. However, please understand that there are very important limitations to answering a key question when you need to use one data set to establish a link between an intervention and a surrogate outcomes and another data set to show a link between the surrogate and the outcome as we discuss at length in the background section response.

The technology assessment missed key publications from the peer review nephrology literature, and data from the US transplant registry, that are relevant to the use of therapeutic blood transfusions in CKD patients. Importantly, the US transplant registry captures data on the entire US wait-listed and transplanted patient populations. A selected list of these publications is provided in Appendix A.
With the list of 27 publications provided by the reviewer, only three studies meet the inclusion criteria of the TA. [Alarif et al, 1987 (2), d’Apice et al, 1982 (7), Opelz et al, 2005 (19)] Please see Appendix A for the rationale of exclusion for the other 24 publications. The inclusion and exclusion criteria for the technology assessment were listed clearly in the report. Although we recognize the availability of US transplant registry data, we opted not to include such data in our evaluation since the data were not published as an original controlled trial.

The technology assessment failed to acknowledge the important distinction between transfusion for the purpose of immunomodulation (eg, donor-specific transfusions [DSTs]) and therapeutic transfusions for the management of chronic anemia in CKD [8]. The differences in the clinical purpose, sources of blood, and volume of blood make these specific types of transfusions distinct; consequently, outcomes associated with immunomodulation transfusion strategies are not generalizable to those associated with therapeutic transfusions. For the purpose of this technology assessment, combining the evidence for these distinct types of transfusions confounds the conclusions rendering them invalid as a basis for clinical decision making.

We recognize the distinction between different types of transfusion, and their clinical purpose of immunomodulation. We now separate the analyses for DST and therapeutic transfusion in Key Question 1, and evaluate the impact of transfusion on renal allograft outcomes in the 2 subgroups of analyses. The results of the subgroup transfusion are not markedly different from our original analyses, and they do not change the overall conclusion of the TA. Please refer to Tables 14-19 of the final report for the results of these subgroup analyses.

Analysis Limitations

When summarizing the evidence and drawing conclusions, the authors used a vote-counting methodology, that is, classifying studies as positive, neutral, or negative and summarizing the literature based on counting studies in each category. This is not a preferred approach [9, 66] even for qualitative systematic literature reviews because it gives equal weight to all studies irrespective of their sample size or the time period in which they were conducted. For example, a study of 100 patients would be considered equivalent to a study of 10,000 patients, and a study conducted in the 1980’s would be given the same weight as a study conducted in the 2000’s, even if medical practice has changed. Moreover, conclusions drawn from analyses using vote-counting can differ substantively from conclusions drawn using more robust methods, and the conclusions can become more misleading as the amount of evidence (the number of studies) increases [66], in contrast to other statistical methods.

We understand the reviewer’s concern in this aspect. With the poor literature base available, this was the best we can do, and in fact, we did address this limitation in the discussion section of our draft report: “This approach has limitations because analyses of varying quality and sample size were evaluated together but it provides that only type of independent qualitative analyses that can be done on such a literature base.”

Below are two examples from the technology assessment that illustrate the problem of equal weighting of studies. The first occurs in the assessment of the multivariate analyses examining the affect of red blood cell (RBC) transfusions on renal graft
outcomes and the potential impact by the number of transfusions, the number of units of blood, and/or the number of donors (Question 1bii). The following table summarizes the results provided in Table 23 (p. 32-34) of the technology assessment:

Table 1. Illustration of the bias introduced by vote counting: Summary of studies examining effect of transfusion on graft survival included in Table 23 of the technology assessment

<table>
<thead>
<tr>
<th>Sample Size (# of patients studied)</th>
<th>Percent of total sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significantly worse graft survival</td>
<td>11,240</td>
</tr>
<tr>
<td>Neutral effect (not statistically significant)</td>
<td>3,810</td>
</tr>
<tr>
<td>Significantly improved graft survival</td>
<td>143</td>
</tr>
</tbody>
</table>

The technology assessment summary of these results states the following: “Transfusions were not an independent predictor of rejection, graft survival or patient survival in either direction in a large number of analyses.” The methodology used to arrive at this conclusion is not scientifically valid when 74% of the evidence is conclusive in one direction, 1% is conclusive in the other direction, and yet the technology assessment concludes that there is no effect in either direction.

The second example occurs in the summary of the analyses evaluating “how useful are PRA assays in predicting sensitization, and renal transplant rejection/survival --- especially in the setting of question 2a?” (Question 2b). The summary states “The 1-year graft survival, where the direction of effect regardless of significance was assessed, for the lower PRA groups had higher graft survival in five of eight (62.5 percent)33,101,132,151 analyses and lower survival in three of eight (37.5 percent)12,29,153 analyses.” For the eight analyses used to evaluate this outcome (Table 33 [p. 49-51] in the technology assessment), the total sample size of the analyses showing statistically significant worse 1-year graft survival with higher PRA levels included ~37,000 patients (7 analyses) while the total sample size showing a trend towards better graft survival with higher PRA levels included 732 patients (1 analysis). Notably, in the technology assessment, the results of the Bucin et al (1988) study were misinterpreted and the results of the Opelz et al study (1972) were incorrectly reported from the original article. The technology assessment concluded in the discussion section that “lower PRA generally has a beneficial to neutral effect on outcomes”, which does not appear to incorporate the overwhelming evidence showing a beneficial effect of lower PRA levels.

Conclusions did not distinguish between the pre-cyclosporine and modern era

Prior to the advances in immunosuppression, acute rejection was a major obstacle and contributed to a significantly lower 1-year graft survival compared to current survival rates (65% vs. 96%) [1, 67, 68]. Thus, in the 1980s, the potential for immunomodulation offered by transfusions may have outweighed the concerns about sensitization and preclusion from transplantation [7]. However, with the availability of better immunosuppressive regimens (eg, cyclosporine) and the significant improvement in
early graft survival, any potential benefits of immunomodulating transfusions were no longer considered to outweigh their risks [15]. Consequently, transfusions are now avoided and this change in the clinical management of transplant candidates is described in the authoritative textbook on kidney transplant medicine, Medical Management of Kidney Transplantation:

“Blood transfusions: Early in the history of solid organ transplantation, the “transfusion effect” was observed by Opelz et al. (21) and others (22) when they demonstrated a benefit on graft outcome if preoperative blood transfusion were given in combination with immunosuppressive drugs or x-radiation (23,24). … over the years it has also become clear that blood transfusion may also induce sensitization, and by the late 1990s the previously noted beneficial “transfusion effect” had given way to a deleterious effect, with worsening graft survival associated with the greater numbers of transfusions in sensitized and nonsensitized patients (26).”

The technology assessment acknowledges the substantial changes in the outcomes of renal allograft outcomes following the introduction of cyclosporine in 1984, and further notes that practices changed after 1992 with the introduction of multi-drug immunosuppression regimens. However, less than 10% of the studies reviewed in the technology assessment report outcomes of transplanted patients treated in the current era. Importantly, the more recent data show no benefit for the use of therapeutic transfusions on renal graft survival.

We could not pool data due to the poor and heterogeneous nature of the studies. It seems that Amgen is suggesting that we should not give a general overview for what the results are in a qualitative sense through counting. We believe that we would be left with just putting together one very large table with every study in it and not saying anything summative at all if we listened to this advice. This would be completely noninformative and believe strongly that our approach of summarizing what is there in a qualitative way with a correspondingly low to insufficient strength of evidence is the appropriate way to go.

We feel confident that looking at significant results and then looking at direction/magnitude of effect gives people a general feel for where the data is going. In so doing, we account for studies that might have been underpowered to show significant effects in another analysis. It seems disingenuous to us that some of the limitations are being pointed out because if we show that in 85-100% of studies that they are beneficial to neutral effects and the magnitude shows beneficial to neutral effects that slicing and dicing will not yield disparate results. We believe that is exactly what we found when we did our previous subgroup analyses and still show with our newly added subgroup analyses. It certainly will not change the quality of the data and strength of evidence for the analyses which are low to insufficient. We account for the changes in practice by comparing the analyses in different time periods and display what happened in all of the available studies. It is transparent that most of the data is older in nature, it is clearly in our report. We cannot do anything about the nature of the evidence we have to review but Amgen could have. Amgen had the ability to fund studies of reasonable quality that provided insight into these key questions that obviously is important to CMS. All we can do is evaluate the available literature in the best available manner and to report it with transparency and rate the strength of evidence as such. We hope Amgen understands that we are not saying that transfusions are beneficial in transplant. We believe that the available evidence is incredibly weak and that firm conclusions cannot really be drawn.
However, we feel it is disingenuous to suggest that the data for harm from using transfusions is strong.

**Preclusion from transplantation due to transfusion-related allosensitization (selection bias) confounds the results and conclusions**

In the technology assessment’s review of the literature, many of the studies that examined the impact of transfusion on transplant outcomes also provided data on the patients who became allosensitized following transfusion and were precluded from receiving the donor organ. For example, in Akiyama et al. [1984; citation # 112], 12% of patients who received a DST became allosensitized and did not receive the donor kidney; in Glass et al., [1985, citation # 114], 20% of patients who received a DST became allosensitized and did not receive the donor kidney; and in Cochrum et al., [1981, citation # 20], 30% of patients who received a DST became allosensitized and did not receive the planned donor kidney. These were studies in the setting of DSTs, and thus it is reasonable to conclude that a similar or greater sensitization effect would apply to therapeutic transfusions.

Preclusion from transplant is a clinically relevant renal transplant outcome related to transfusion and the exclusion of these patients from the analysis introduces a significant selection bias.

Failure to include the outcomes of these patients in the technology assessment undermines the validity of the conclusions drawn regarding the impact of transfusions on transplant outcomes.

To illustrate this selection bias, consider a situation where 100 transplant candidates being evaluated for the impact of transfusions on their transplant outcomes, where 70 patients received a transplant and 30 did not due to allosensitization. The approach taken in the technology assessment was to examine the effect of transfusions only in the 70 patients who ultimately received the transplant, ignoring the impact of transfusions on the 30 patients who were never transplanted due to transfusion-related allosensitization. Since allosensitization is a determinant of who is selected for transplantation, excluding this consequence of transfusion exposure biases toward benefit the assessment of exposure to transfusions on transplant outcomes [69].

This is a valid concern, and a very important limitation to this data set. We tried to be quite transparent in the discussion section alerting people to this very large confounder. To account for this, we have now added evaluations on the impact of sensitization on eligibility for transplantation in transfused patients (see pages 69-73, Table 43 of the final report). We found that a proportion of patients who were sensitized from transfusion were precluded from their planned kidney transplantation, and the graft outcomes, if any, for this particular population was unclear. Thus, we cannot be sure whether transfusions have a beneficial to neutral effect on outcomes in this subgroup of patients.

In addition to the above limitations, the search strategy differed between Medline and EMBASE in the technology assessment. Medline was used to identify all English and non-English studies. The EMBASE search strategy was designed to exclude English-language studies and non-trial data. In doing so, the English and non-English studies
were not treated equally. Since EMBASE and Medline do not completely overlap in journal coverage, searching both using the same strategy is preferred.

In a comprehensive search, we must balance precision and recall. We conducted a broad search in Medline and Cochrane Central databases. This, in addition to citation tracking, meets the criteria for a comprehensive search in the AHRQ CER Methods Guide. While we did do a targeted rather than broad search of EMBASE, remember that Cochrane Central includes most of the pertinent medical journals included in EMBASE. As such, a full exhaustive search of Cochrane Central and EMBASE would have reduced precision considerably without impacting recall in a realistic way. Amgen has not substantiated that an exhaustive search of EMBASE would have yielded a treasure trove of additional missing studies of high quality. We are confident that it would, in no way, have changed the strength of evidence, or the general conclusions since those conclusions are so firmly in the beneficial to neutral camp. This can be illustrated by the list of references that Amgen provided. We have evaluated all the references that were listed by Amgen in the Appendix, and have now included the eligible studies in our final report. The conclusion and strength of evidence of our report is not impacted by the addition of these studies.
RESULTS

Given the substantial flaws in the methodology employed in this technology assessment, both in the design and analysis, the validity of the results and conclusions are questionable. Amgen requests the authors revisit the evidence in light of the comments provided. Beyond the design and analysis limitations that impact all results and conclusions, there are two additional general issues in the Results section: factual errors and lack of transparency.

Given the limitations in the body of evidence, we evaluated and summarized the data sufficiently to show what the literature suggests and that the strength of evidence is low to insufficient. None of the “Factual Errors” or “Transparency Issues” in any way alters the conclusions of our Technology Assessment. We appreciate the review that Amgen provided and looked at each carefully and made alterations where necessary. We feel that with the number of studies included and the number of endpoints evaluated, that we are proud of our ability to accurately extract and categorize the data.

Factual errors

There are factual errors in the document that impact the conclusions drawn by the technology assessment. These include errors in the reporting of data from the original papers. For example, as described above, the results of the Opelz et al (1972) study were reported incorrectly (graft survival at 12 months [%] among PRA < 5 reported as 36% and > 5 reported as 55%; however, the reverse is what is reported in the article) and the results of the Bucin et al (1988) study were misinterpreted (no data on PRA were reported in the paper, but were listed in the technology assessment showing no effect of higher PRA). The incorrect reporting of results in the technology assessment was used to support the conclusion that the evidence regarding the relationship between PRA and graft outcomes was mixed. In fact, seven of the eight studies evaluated in the technology assessment showed that higher PRA levels are associated with increased graft failure.

The results of the Opelz et al (1972) study are now reported appropriately. Regarding the results of the Bucin et al (1988) study, even though the study did not specifically state that the presence of antibodies was assessed by PRA, we consulted our key informant and confirmed that the presence of antibodies described in table 1 of the study was some sort of PRA test (even though the specific of the test was not described). We have put in a footnote to account for the ambiguity present in the study and changed the terminology used in our table to reflect what was reported in the study.

Transparency: Insufficient detail was provided to enable reproducibility

In high-quality technology assessments, it is important for the peer-review process that the evaluation methods are sufficiently detailed and documented to enable appropriately trained and skilled individuals to follow the rationale and reproduce the results. For key questions 2a and 2b, specifically, the details of the search strategy including the search terms used and the databases queried were not provided. Moreover, throughout the document, tables which summarize directionality of results based on analyses within studies do not identify the source of each analysis.
As specified in the method section, the search strategy was designed to answer both key questions 1 and 2b, and the search strategy is available in Appendix A. Since this technology assessment was commissioned to evaluate the transfusion effects on renal allograft outcomes, and the correlation of PRA to renal allograft outcomes in the transfused patients, the search terms we used should capture a majority of the studies, and we also performed citation tracking as well. In addition, our method section described clearly that key question 2a was intended to provide an overview of the use of PRA in renal transplant patients, and thus, it was not conducted systematically. References have now been added to each section to clarify the source of analyses.

Below is a listing of specific comments. Please note this list does not include a number of minor editorial or factual errors that were not included for brevity.

**Question 1a (pages 8-18)**

1. **Multivariate Analysis, page 11, 2nd paragraph, 6th sentence** states that “The other analyses found that prior transplantations were not independent predictors of graft survival in either direction.” There may be an error in the statement where “transplantations” should be replaced with “transfusions”.

   Thank you for pointing out the textual error. Change was made accordingly.

**Question 1b.i (pages 19-21)**

1. **In Table 11 on page 20, “Insight into body of literature: Donor-specific transfusions (KQ 1bi)”**: In the validity of studies column, there is a total of 11 studies. However, there are 12 studies covered in this section of the assessment. Eleven of the unique studies were included and referenced in the first sentence (Page 19). The Jin DC (1996)[71] reference is missing in the text, but is listed in Table 15 on page 21. Amgen recommends citing the specific studies aligned to the evidence presented in the appropriate tables for greater clarity.

   The eleven unique studies refer to the studies with a clearly defined experimental group and a control group that reported univariate results. We have added a heading in each section to clarify this. The final study is a multivariate analysis and would not be included in this section of the text. We have now provided more references in the final report.

2. **The third sentence of the paragraph under Rejection (Page 19)**, states that “to be considered for this analysis, studies had to provide a p-value, 95% CI, or explicitly state whether or not statistical significance was achieved.” There were 11 studies reviewed in the assessment of question 1b.i. A review of these studies indicates that only 1 (Glass NR [1985][12]) meets these criteria; therefore, it is unclear why the others were included. Amgen recommends either removing those studies that do not meet these criteria or providing rationale for their inclusion.

   The statement quoted by the reviewer refers to the section which we reported that “three analyses found either a significant reduction in rejection or no significant effect associated with DST” (a sentence before the quoted sentence). The following publications are the 3 analyses that we reported in the report:

1. The study by Reed A et al, 1991 reported that significantly fewer patients in the DST group had a rejection episode (50%) in one year as compared to the patients in random
transfusion group (75%) (p=0.0008) [Other rejection outcomes also show similar significant results] (p.383 of the publication)

2. Table 2 of the study by Casadei R et al, 1987 specified that the number of patients with rejection in DST group and non-DST group were not statistically significant (footnote of table 2 in the Casadei R, 1987 study).

3. Table 2 of the study by Jovicic S et al, 2010 reported the number of patients with acute rejection, the p-values were specified for each of the intergroup comparisons (DST versus No transfusion, DST versus random transfusion). All of them showed significant reduction of acute rejection in DST group. (footnote of table 2 in the Jovicic S et al, 2010 study)

   Note: Unlike the study conducted by Jovicic S et al, 2010, the significance of the results for acute rejection reported in the study by Glass NR et al, 1985 (Table 6) provided the overall p-value of the intergroup comparison (i.e. DST versus Imuran+DST versus HLA-identical). Thus, we opted not to include the significance of the results in our analysis.

3. In Table 13 on page 21. “Impact of DST on graft and patient survival outcomes (KQ 1b)”: The specific studies and analyses evaluated in this section (Table 13) are not directly identified in the table, and hence, it is not possible to reproduce the results. Furthermore, it is unclear what types of transfusion were evaluated in each of these studies. Amgen recommends that additional information be provided to enable reproducibility of the analysis.

   The references for the specific studies have now been added to the main body of the report. All the analyses included in this section evaluated the impact of DST versus non-DST or any other types of transfusions.

Question 1b.ii (pages 22-35)

1. Key Question 1bii, page 22 asks “Is any such impact of red blood cell transfusions on renal transplant outcomes altered by the number of transfusions, the number of units of blood, and/or the number of donors?” The answer to this question and subsequent conclusion may be biased because of the variability in the way transfusion exposure was assessed and reported. The distinction between “transfusions” and “units of transfusion” are unclear as they may be referencing similar quantities, yet they have been categorized into 4 distinct groups for this analysis. This lack of clarity about the specific assessment of exposure to blood transfusions potentially confounds the assessment of the studies and the subsequent interpretations. Amgen recommends that this limitation be noted in the report.

   We understand the reviewer’s concern. While the definitions for “number of transfusions” and “units of transfusions” were poorly defined in the weak literature base, we classified analyses in the 2 categories based on the terminology that was used in the studies. We excluded the analyses that were ambiguous. Each analysis could only be included in either “number of transfusions” or “units of transfusion” evaluation.
2. **Key Question 1bii, page 22, second paragraph, first sentence** states that “Thirty-six unique studies were included in the evaluation of the impact of different number of transfusions on renal allograft outcomes.” As noted throughout this review, the technology assessment does not provide adequate detail to determine how the authors assigned each article and/or study to the groups. Amgen recommends that the authors provide sufficient information to ensure reproducibility.

   See response above

3. **Graft Survival, page 23, Number of transfusions, paragraph 1, sentence 4** states that “None of the analyses found transfusion to have a significant negative impact on ... graft survival.” Data reported by Chavers et al (reference 121) contradict this statement. Chavers et al found that “the risk of graft failure was increased in LD and CAD in recipients who received > 5 pre-transplant transfusions”. Amgen recommends modifying the statement to read “Chavers et al found repeated transfusion to have a significant negative impact on graft survival.”

   Corrected. Please refer to the report for the changes.

4. **Graft Survival, page 23, Number of transfusions, paragraph 2, sentence 2** states that “In all cases the 1-year data was the maximum duration of follow-up for graft survival.” There are a number of articles that report graft survival beyond 1 year. Feduska et al (reference 29) evaluated graft survival up to 5 years and Andrus et al (reference 120) evaluated graft survival up to 2 years. Amgen recommends that the statement be corrected.

   Corrected. Please refer to the report for the changes.

5. **Patient Survival, page 25, Number of transfusions, paragraph 3** states that “Eight and seven analyses performed evaluations of the magnitude of different transfusion intensities (1-5, 5-10, or =10) compared to no transfusion on 1-year and maximum duration patient survival, respectively. All analyses found either a >10 percent increase or a small change within 10 percent in either direction in 1-year and maximum duration patient survival (Table 20). We concluded that there was a large beneficial to neutral effect of different number of transfusions versus no transfusion on patient survival and we graded the strength of the body of evidence as low.” Amgen does not agree with the conclusion because there are no data for 1-year patient survival and maximum duration patient survival for all 4 categories (1-5 vs. 0, 5-10 vs. 0, or =10 vs. 0). Amgen recommends that the statement be modified to reflect this insufficient evidence.

   There were analyses for different number of transfusions reported for 1-year and maximum duration patient survival, and the grading for the strength of evidence should remain the same. The confusion came from the mislabeled table number. Instead of Table 20, it should refer to Table 18 in the draft report (or Tables 31-32 in the final report). We also reorganized the tables in this section to increase the readability.
6. **Table 22 and 23, pages 32-34 and Table 24, page 34** includes a number of references that are not listed on page 22 and in the reference section at the conclusion of the Assessment. The conclusions are based on an incomplete data set that discounts literature that suggests that pre-transplant transfusion is associated with poorer graft survival and poorer patient survival.

- The following publications were identified by the technology assessment but were not among the citations listed in the evaluation on page 22: Higgins RM (Table 22); Tang H, Park YH, Bunnarpradist S, Agarwal SK, Montagnino G, Poli F, Sautner T (Table 23); Herget-Rosenthal S, Agarwal S (Table 24). It is unclear whether the data from these papers were included in the analysis and the conclusions drawn. However, it appears that they were not included because the results in these articles contradict the conclusions.

  We separated the discussion into univariate and multivariate sections. Page 22 of the draft report includes citations that reported univariate analyses, so citations of the studies referred to by the reviewer would not appear there. It should be obvious to every unbiased observer, that we had no preconceived notions and performed a completely objective evaluation of the data. We accepted the key questions presented from CMS, assured that we understood what they were asking, identified an outside expert without financial conflict of interest, defined a priori the methods that we would use given our horizon scan, and then steadfastly adhered to the methods. The relevant citations you are interested in are in the Multivariate Analysis section as are their results.

- There are references published between 1994-2008 that were not used, that provide more contemporary information, and report that transfusions worsen graft survival (Park et al, Bunnarpradist et al, Sautner et al) [72-74] and patient survival (Herget-Rosenthal et al, Tang et al) [75, 76]. When drawing conclusions on univariate analyses, it appears that the authors do not include univariate analyses that appear in articles that contain multivariate analyses. These omissions impact the conclusions drawn. For example, Herget-Rosenthal et al, 2003 [75] (not cited on page 22, or listed in the Reference list) is noted in Table 24 with multivariate analysis showing that transfusion of > 40 units worsens patient survival. In this article, a univariate analysis also notes this worsened patient survival. It is uncertain if this result is included in the Patient Survival section (page 25) where the AHRQ report states that transfusion has a small impact on patient survival. Sautner et al, 1994 [72] (not cited on page 22, or listed in the Reference list) is listed in Table 23 with multivariate analysis showing that 5-10 or > 10 pre-transplant transfusions increases risk of graft failure. However, the univariate analysis from this study also demonstrates an increased risk of 1 or >1 transfusion versus 0 transfusions (P = 0.002). Amgen recommends that the authors revisit this literature to ensure that all relevant univariate analyses are included.

  Although the univariate analysis included in Herget-Rosenthal et al [2003] reported the negative effect of >40 units transfusions, we decided not to include this result since the range used in the study did not fit into the predefined categories of the units of transfusions. While > 40 technically fits under >10, the group to whom it was being compared could have had a substantial number of patients with 10-39 transfusions...
and would therefore not meet our criteria. It should be apparent why we would not have wanted to do this when we decided on our approach to analyzing this data.

Regarding the study by Sautner et al. [1994], Amgen seems to be referring to prior transplants rather than pretransplant transfusions. The data that was quoted by Amgen (p=0.002) could not be matched to any results in the study regarding transfusions. However, there is some data regarding blood transfusions in Table 1 as well. We understand that honest mistakes sometimes happen, especially with very large reports including over a hundred studies with many variables. They performed a 3x2 Chi squared analysis of the impact of blood transfusions and found a p-value of 0.01 (with no post-hoc 2x2 evaluations) for primary non-functioning grafts. This is not measuring overall graft failure but rather only one type of graft failure, namely primary non-functioning of the graft. As such, we did not originally include it in univariate analyses. However, in retrospect, we see some value in its inclusion and now add it in as requested. We had to generate our own post-hoc analyses to include it and the results came out as follows (0 versus 1-5 transfusions: p=0.627, 0 versus >5 transfusions: p=0.016, 1-5 versus >5: p=0.003, >5 versus ≤5: p<0.001). As far as the other studies quoted by Amgen (Park et al, Bunnarpradist et al, and Tang et al), none of them reported univariate analysis results on transfusion effect on survival outcomes.

In Tables 22 and 23, Chavers et al. [77] is listed with multivariate analysis although it is uncertain if these are multivariate analyses. In Tables 22, 23, 24, most of the analyses types are not listed and are specified as NR, though the analysis types may be found in the articles (logistic regression, for example, in Higgins et al [78] and Sautner et al [72]) that casts doubt on the attention to detail in the report and the reported conclusions. Amgen recommends a re-examination of the statistical methods in the papers reported in tables 22, 23 and 24 followed by an update to the tables.

Changes were made accordingly. Please refer to the final report.

**Question 1b.iii (pages 35-37)**

1. In Table 25 on page 37, “Insight into body of literature: Leukocyte-depleted blood (KQ 1bii), the second column “Rejection” it states that there are no Clinical Control Trials (CCTs) or Prospective Observational Studies (POBs). However, of the cited references evaluating graft rejection, one (67) is a CCT and one (135) is a POB. Amgen recommends that the authors include these references in Table 25.

   We classified reference 67 (Nubé et al, 1983) as a POBS. To be classified as a CCT, the authors need to be instrumental in the logical allocation of patients to the different treatment groups, either in a randomized or non-randomized design. Here, the authors were prospectively observing patients who were receiving protocol or random blood transfusions.

   In reference 67 (Nubé et al, 1983), the authors discuss rejection only in reference to graft loss. They describe the number of grafts lost to irreversible rejection. There is no description of rejection episodes experienced in the entire patient population, regardless of graft loss. As a result, the precise number of rejection episodes is not reported. In reference 135 (Persijn et al, 1981), there is a similar situation where rejection is discussed but only in the context of graft loss. There is no accounting for rejection throughout the patient population.
2. **In Table 25, on page 37**, "Insight into body of literature: Leukocyte-depleted blood (KQ 1bii), under the third column, the Max time for graft survival in CCT should be noted as 2 years rather than 1 year. Amgen recommends this error be corrected.

   In Table 36 of the final report, column 3, there is no specific time listed for the Max Time. For graft survival, the CCT listed provides graft survival for 1-year, as well as the Max time. The time frame for Max Time reported is variable in the included studies.

3. **In Table 25, on page 37**, “Insight into body of literature: Leukocyte-depleted blood (KQ 1bii): the POBS times for graft survival are incorrect as currently listed in the third column. They should be listed as follows: 2 year (1 study), 6 months (1 study), Max time (2 year; 2 studies). Also, in the fourth column of Table 25, the POBS only included one patient survival analysis with Max time (ie, study 137) rather than the two analyses currently listed. Amgen recommends correcting these errors.

   Number of analyses for each outcome was reported in Table 25 of the draft report (or Table 36 of the final report) rather than the number of studies. This was done to account for studies that included more than one analysis. The study by Nubé et al, 1983 (reference 67 of the draft report) reported 2 analyses on the impact of leukocyte-depleted blood transfusion versus no transfusion on 1-year and 2-year (max duration) graft survival, and 2 analyses on the impact of leukocyte-depleted blood transfusion versus therapeutic transfusion on 1-year and 2-year graft survival were also evaluated within the same study. For the POBS times for graft survival listed in the table, two POBS studies (references 67 and 135 of the draft report) reported three analyses on 1-year graft survival, and 3 analyses on max duration graft survival.

   For the patient survival analysis, reference 67 provides two analyses, each of which provide data at a Max time followup (i.e. 2 years) only. There was no data provided at 1 year patient survival.

4. **In Table 25, on page 37**, the specific analyses in the 4 studies included in the table are not specified. Amgen recommends incorporating this information.

   The specific references utilized in answering Key Question 1biii are now detailed in the text of the report.

**Question 1b.iv-v (pages 38-44)**

1. **Under Graft Survival section, page 39, second paragraph, fourth sentence** states that “The conclusion was that regardless of the time period, transfusion has a beneficial to neutral effect on graft survival. We graded the strength of the body of evidence to be low.” As opposed to the earlier studies (pre-1984) none of the studies reviewed in the technology assessment for the period 1992 to present demonstrated significant benefit for the use of therapeutic transfusions on renal graft survival, which contradicts the authors’ conclusions.

   What we were trying to say is that every study from before 1984 to present found either a beneficial or neutral effect. We clearly stated in the sentence before the offending sentence that the trend was towards neutral but we now alter the concluding sentence to comply as follows: “The conclusion was that regardless of the time period,
transfusion has either a beneficial or neutral effect on graft survival with a shifting away from beneficial to solidly neutral in more contemporary practice. With this in mind, we also graded the strength of evidence for this conclusion to be low.

Question 2b (pages 47-53)

1. Key Question 2b, page 47, Rejection, first and second sentences state that “Two studies with two analyses evaluated the impact of PRA on graft rejection (Table 32). In both analyses, the risk of rejection was not significantly elevated for the higher PRA group but was qualitatively lower when lower PRA groups were compared with higher PRA groups.”

The authors reviewed two older studies, but did not consider a more recent study by Opelz et al [2005] of ~160,000 transplanted patients [32]. In this study, elevated PRA levels were associated with significantly reduced graft survival. Amgen recommends that the statement be expanded. For example, the authors may want to include the following statement: “A more recent study of ~160,000 transplant patients evaluated the impact of PRA on graft rejection that demonstrated the association between elevated PRAs and the risk of graft failure. Additionally, a meta-analysis concluded that patients with an elevated PRA at the time of transplant had shorter graft half-lives.” Amgen recommends this article be added to Table 32 and included in their analysis and subsequent conclusions.

We are a bit confused with Amgen’s comment here. The specific section of the TA that they commented on was specifically evaluating the impact of PRA on graft rejection. While the Opelz et al [2005] study only reported outcomes on graft survival, the recommendation of adding a statement from Opelz et al [2005] study in this section would be inappropriate. The results of Opelz et al [2005] are included in the analysis for graft survival of key question 2b.

In addition, we are not sure which meta-analysis that Amgen is referring to in that statement, and the results of a meta-analysis should not be used in answering the key question since it is not an original controlled trial and would either duplicate studies already included or would allow studies not deemed to be included into our search strategy into the results.

2. Key Question 2b, page 47, Graft Survival, second and third paragraphs state that “The 1-year graft survival was significantly better with lower versus higher PRA levels in three of five (60.0 percent) analyses that assessed for significance and not significantly different in the other analyses. The 1-year graft survival, where the direction of effect regardless of significance was assessed, for the lower PRA groups had higher graft survival in five of eight (62.5 percent) analyses and lower survival in three of eight (37.5 percent) analyses.”

“The maximum duration graft survival was significantly better with lower versus higher PRA levels in one of nine (11.1 percent) analyses that assessed for significance and not significantly different in the other analyses. The maximum duration graft survival, where the direction of effect regardless of significance was assessed, for the lower PRA groups had higher graft survival in 11 of 14 (71.4 percent) analyses and lower survival in 3 of 14 [bd1] (28.6 percent) analyses.” This statement omits adjusted, pooled data (2002-2007) from the USRDS 2009 Annual Data Report (ADR) on transplant outcomes [57]. These data show, for deceased donor transplants, a 30% increased hazard of all-cause graft
failure for transplant recipients with a pre-transplant PRA > 50% compared with transplant recipients with a pre-transplant PRA = 50% (hazard ratio [HR] = 1.3; 95% CI 1.18-1.41; P < 0.0001). For living donor transplants, there was a 50% increased hazard of all-cause graft failure for transplant recipients with a pre-transplant PRA > 50% compared with transplant recipients with a pre-transplant PRA = 50% (HR = 1.5; 95% CI 1.25-1.74; P < 0.0001). For completeness, Amgen recommends that these data be included in the report.

The data from USRDS 2009 Annual Data Report will not be incorporated into this key question as the technology assessment included only original peer reviewed studies. However, we have now incorporated this type of ancillary information in the discussion section of the final report. It should be noted that including 6 book chapters and an annual data report using the same data sets over similar time periods does not mean that there are multiple individual studies showing the same thing. I think that there needs to be greater attention paid to the overlap in the sources of the data so as not to triple or quadruple count.
DISCUSSION/CONCLUSION

Discussion

The comments presented here summarize what has been included in previous sections. Amgen notes that there is a substantial body of literature informing the field that was not consulted in this technology assessment. Our review identifies several serious limitations in the design and analysis of this technology assessment which undermine the validity of the conclusions in the technology assessment. These include:

- The questions formulated to address the stated objective were inappropriately narrow as they failed to include the impact of transfusions on organ access and transplant wait time, critically important renal transplant outcomes.

  We did not formulate these key questions; rather, CMS posed the key questions and we were asked to answer them. We did so in a completely unbiased and transparent way and the level of transparency has been enhanced even more in this revised draft and appreciates Amgen’s review and their suggestions for improvement.

- Key publications and data from the US Transplant Registry that are relevant to the use of therapeutic blood transfusion in CKD patients were not included

- Inappropriate aggregation of evidence regarding the use of transfusions for immunomodulation and transfusions for chronic anemia management

- The vote counting methodology used in this assessment is recognized as among the weakest in quantitative methods, and weights all studies equally (regardless of sample size or medical era) in the evaluation of the evidence.

- Failure to account for the selection bias due to transfusion-related allosensitization resulting in the preclusion from receiving a transplant, a critically important renal transplant outcome.

  In the previous sections above we defended the use of our methods. I believe Amgen fails to understand that we are not making this literature base out to be something that it is not. We gave the lowest strength of evidence ratings to these analyses because the literature base is poor. Pooling this data would have been completely inappropriate and summing data which would allow for larger studies to have greater weight without accounting for variance is even worse. We simply had a poor literature base and the result is a Technology Assessment that cannot confidently provide answers to the key questions posed. We did include a few of the studies that Amgen recommended that would have fit our inclusion and exclusion criteria and reconsidered a couple of choices we made for a couple of additional studies. We had already alerted readers to the huge confounder which is that allosensitization precluded some people from receiving a transplant including a statement in the conclusions. We have now have added two tables explicitly showing where and to what extent this occurred (Table 43 and Appendix D in the final report). We also include book chapter and annual
report data in the discussion but could not add it to the methods and the results because of the reasons stated in those sections.

- **Factual errors**

  Even in your review of our report, there were several factual errors in your comments. This is to be expected in such a large report with so many lower quality studies and we do not hold it against you. We have examined all of your suggested changes and made alterations where appropriate. Such factual errors do not impact the conclusions or the strength of evidence.

- **Lack of transparency preventing reproducibility of the analyses**

  We were very transparent, using two different counted methods to allow the largest possible evaluation and writing a very lengthy report with numerous subgroup analyses and explicit tables. We understand that you wanted references for each outcome of the key questions and now provide them. Understand though that at a certain number of pages of text that the report becomes inaccessible to end users given its density and the overall conclusions can be lost. So we need to balance that in this revision.

Below is a listing of specific comments. Please note this list does not include a number of minor editorial or factual errors that were not included for brevity.

1. **Paragraph 3, page 55**: The technology assessment arrives at the following conclusion: “So the literature, weak as it is, supports a neutral to positive effect resulting from transfusion and does not support a detrimental effect resulting from transfusion of a larger number of transfusions.” This conclusion does not reflect the totality of evidence or appropriate analysis, and therefore lacks validity and contradicts evidence-based guidelines about the use of transfusions. This highlights the need for this technology assessment to be peer-reviewed by experts in transplant nephrology. Amgen disagrees with the statement that the evidence regarding the use of transfusions in kidney transplant candidates is weak because a large body of evidence which was not included (see list of citations) provide fair to good evidence that transfusions cause allosensitization, which effects access to available organs and prolongs time on the transplant wait-list, in addition to significantly increases graft failure.

   Amgen’s purported good evidence would not be rated highly using objective measures. Observational studies not published in the peer reviewed literature, where the funding sources are not explicitly reported, without demographic comparisons or explicit methods, and a lack of confounder control to not yield high strength of evidence. In addition, they want to use data that predominantly shows that transfusions increase sensitization and then use other data in people who were sensitized by any cause (one of which could be transfusion) that shows patient harm and then state that the literature is conclusive that transfusions cause harm.

2. **Paragraph 4, page 55**: Amgen disagrees with the statement that “lower PRA generally has a beneficial to neutral effect on outcomes.” The available evidence including the Opelz et al. (2005) [32] study of 160,000 patients (not included in the technology assessment) show that higher PRA levels are associated with
significantly shorter graft survival compared to low PRA levels. The statement that the effect is neutral is not consistent with the preponderance of available evidence. Amgen recommends inclusion of this definitive study before finalizing the technology assessment.

We included Opelz et al 2005 in graft survival.

Future Research Directions

Amgen comments on the two recommendations offered in the technology assessment.

1. Recommendation #1 (page 55): “We believe that additional adequately powered studies should be conducted. In these studies we believe that they should be multi-institutional because individual center practices and procedures are so variable, have adequate reporting of demographics and either use statistical means to account for confounders (propensity score adjustment or matching) or use of randomization, have standard definitions of outcomes, and have a standard follow-up time of at least 1-year. Patients receiving or being randomized to no transfusions should be screened to assure that this not only includes transfusions within the dialysis or transplant center but other transfusions as well.”

In order to randomize a subject to a treatment with the potential for harm, several conditions must be met. Among these are equipoise, the presence of genuine uncertainty in the expert community as to whether a treatment is beneficial, and the potential for patient benefit from the proposed intervention. Both of these elements are lacking with respect to this question by the expert community practicing in this field.

In order to answer this question with good quality evidence, adopting more of these techniques would lead you there. Continuing to generate observational data with little to no reported methods, no control for confounders, and little to no demographics will not get you there.

2. Recommendation #2 Page 55: “We believe that standard PRA testing should be supplanted with updated CPRA testing so that specific HLA antigen sensitivities resulting from transfusions can be identified and perhaps correlated with outcomes.”

The inclusion of this recommendation lacks relevance as it does not bear upon current clinical practice. The calculated PRA (CPRA) has been almost universally adopted since 2009 as noted in their reference 137. The specific antigen specificities detected by the CPRA are used to preclude transplantation of kidneys when antibodies to kidney’s antigens are found, also noted in reference 137. This is because it is well accepted that the presence of these specific antibodies results in a high frequency of acute rejection.

We feel that Amgen misunderstands the point. Yes, everyone is doing CPRA now because it is so much better, but the available literature evaluating transfusions and final health outcomes did not use CPRA. As such, future studies should use the newer CPRA and PRA data would be of less value.
Conclusion

The technology assessment has numerous critical design and analysis limitations that undermine the validity of its conclusions. Importantly, these conclusions also contradict current evidence based guidelines and clinical practice. Therefore, Amgen strongly recommends the technology assessment receive peer-review by transplant nephrology experts prior to finalization. To let the current conclusions stand misinforms decision making bodies and is a true disservice to the affected population. When the totality of the evidence is considered with inclusion of all pertinent transplant outcomes, the modern of immunosuppressive medications, the differences between transfusions for immunomodulation and transfusions for anemia management, the conclusion is clear: the evidence does not support a beneficial impact of transfusions on transplant outcomes. Indeed, the evidence is to the contrary. Transfusions can cause allosensitization, which is associated with longer time on the wait-list, and can preclude transplantation, and transfusions are also associated with worse graft survival.

Finally, the overall conclusion of the technology assessment was:

“…transfusions generally have a beneficial to neutral effect on renal allograft outcomes.”

(p. 55)

In light of limitations of the technology assessment and the additional important literature cited herein, Amgen strongly disagrees with this conclusion and believes that the evidence is clear that in the contemporary setting therapeutic transfusion is detrimental to renal transplant outcomes. Given the serious limitations of the draft technology assessment it should not be used to inform policy decisions.

We believe that our conclusions are explicit and conservative. We clearly identify that there is low or insufficient evidence. This means that we have low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. Ultimately, that is the point that Amgen is missing. We are not saying that the main result is that transfusions have beneficial to neutral effects on renal allograft outcomes but rather there is low to insufficient evidence from which to draw conclusions. Given the available evidence, it is hard to say that people who receive transfusions have worse renal allograft outcomes. While we were not charged with answering this key question, the literature suggests that it limits the number of allografts offered to patients using the older PRA system and that staying on dialysis longer is associated with untoward effects but I do not think you can honestly say the literature shows that those who receive transfusions and undergo transplantation in the studies that have been conducted show worse outcomes.
TABLES

There are a number of factual inaccuracies in the tables of the technology assessment. For illustrative purposes, please find below a sample of these inaccuracies.

1. On page 10 of the technology assessment, under Key Question 1a. Specific references are not listed for many of the studies in Tables 9; additionally, there some of the studies seem to be mis-categorized or omitted. For example, Tang H (2008) appears in the multivariate tables; the univariate analysis in the study by Tang H (2008) shows significant decreases in graft survival associated with 6 or greater transfusions, yet no papers in the univariate analyses are categorized as showing a significant decrease in graft survival associated with increased use of transfusions (Table7).

We are confused with the reviewer’s comments, as there is no mention of Table 9 on page 10. We listed all the first authors’ last names and publication years for the included studies in Table 9. As far as we could tell, there was no univariate analysis reported in the study by Tang H et al [2008], and therefore the reviewer’s comments regarding Table 7 are not applicable.

2. In Table 8 on page 14, from the citation Reed A (1991), the sample size of “N=127” is for the full study, not the subset in the multivariate analysis. Further, Amgen believes the N should be reported 119, not 127 as stated in the technology assessment.

The N represented in Table 8 is indicative of the number of patients assessed in the analysis of transfusion and its effects. As a result, we feel the accurate N for the above cited study is 127.

3. In Table 9 on page 15, it was not entirely clear why the citation Jin (1996), which appears in Table 15 on DSTs and transfusion does not also appear on Table 9. Because there is a covariate “blood transfusion” in that multivariate analysis in addition to the covariate “DST” that is used in table 15.

In Jin, 1996, the precise number of patients receiving non-specific transfusions within the non-DST group is not reported. As a result, the data regarding these transfusions were not used in alternate analyses.

4. In Table 9 on Page 15, the column heading describing the outcome evaluated is “graft survival”, but the presentation of data from the studies is not consistent with respect to the outcome evaluated, and is confusing. Further, the authors should evaluate if the relative risk estimates were interpreted correctly from the original studies.

We listed the outcome evaluated as the manner in which the data were presented in the original study. The reported significant effect is derived from the original study.

5. In Table 9 on page 15, Amgen believes it is not be appropriate to consider the population in the citation Peters TG (1995) as a “separate analysis”, given that the 2 subsequent analyses presented are derived from the same study population.

We agree, and have removed the two sub-analyses from the table. Only the results from the overall multivariate analysis are included.
6. In Table 9 on page 17, the analysis type on the Sautner T (1994) study should be “stepwise logistic regression” rather than not reported (NR) as presently stated.

   We have changed the analysis type as suggested.

7. In Table 15 on page 21, under the heading of “Multivariate Analysis” It is noteworthy that significance was determined at an alpha of 6% rather than the conventional 5% level in the one analysis that suggested DST as being an independent predictor in benefiting graft survival (Sanfilippo [1990]).

8. In Table 22 on page 32, the Higgins (2004) citation should have its analysis type identified as “multiple logistic regression”, as opposed to “not reported” (NR)

   We have changed the analysis type as suggested.

9. In table 22, on page 32, in Chavers BM (1997) they state “Proportional Hazards Regression” but it would be more appropriate to be more specific regarding the analysis.

   The authors do not provide any further detail regarding the analysis methods used.

10. In table 23, on page 32, in Tang H (2008) graft survival should be changed to graft failure in the 3 instances that occur in the table

    We use graft survival as this is how the study authors report the data in their tables.

11. On page 47, under the heading of Graft Survival, in the first sentence, citation #154 should have been included.

    Citation included

12. On page 47, under the heading of Graft Survival, in the third paragraph, “the maximum duration graft survival was significantly better with lower versus higher PRA levels in one of nine” should be “the maximum duration graft survival was significantly better with lower versus higher PRA levels in two of ten”. The percentage of studies should be changed to 20% from the current 11.1%. Citation #152 should have been included in the body of this text, and citation 101 should have been cited at the end of the sentence.

    Citations were updated accordingly

   The following sentence, “….for the lower PRA groups had higher graft survival in 11 of 14” should be corrected to: “for the lower PRA groups had higher graft survival in 12 of 14”. Hence, the percentage of studies should now change from 71.4% to 85.7%. The citation #153 should be included in this sentence. In the same paragraph, “analyses and lower survival in 3 of 14 (28.6 percent)” should be corrected to: “analyses and lower survival in 2 of 14 (14.3 percent)”. Citation #153 should not be cited in this sentence.

    Citations were updated accordingly
13. In Table 33 on page 50, for Bucin (1988a), “N=116” should be “N=79”, updated based on Table 1.

The N represented in Table 33 is indicative of the number of study population. As a result, we feel the accurate N for the above cited study is 116.

14. In Table 33 on page 50, for Garvin, 1983a, “N=118” should be “N=37”. Black cohort, only 37 patients had PRA available (Table 2 in the paper).

The N represented in Table 33 is indicative of the number of study population. As a result, we feel the accurate N for the above cited study is 118.

15. On page 51, for Opelz (1973), under Graft survival “P=NR” (not reported) should be correctly stated as “P=0.001”. The sentence in the Results column should be corrected by deleting the words “with no statistical analysis”. It would correctly read as: “Graft survival better for PRA <5”.

Change was made accordingly.

FIGURES

Not applicable
Appendix A (from Amgen’s Comments)

Of the following list of references, only 3 publications meet the inclusion criteria of the report (in bold), the rationales for exclusion are listed below for each of the citation.


   This publication included data from the UCLA database, and we were not confident that the results of this publication included a unique patient population since we suspected a potential overlap with one of the publications included in the TA (Takiff H et al, 1988). Since the study by Takiff H et al was published in a peer-review journal with more robust methodology, it was included in our TA instead of the study by Ahmed et al.


   Added to the final report. Please refer to section key question 2b.


   The concern we had in including publications from book chapters was that many of these publications may have included overlapping population from other publications. The vast majority of the book chapters did not provide sufficient information on the methodology (i.e. no information on patient demographic, study design, use of controlled group) to allow us distinguish one publication from the other. In order to avoid duplicate reporting, we opted to exclude book chapters. The publication suggested by the reviewer above (Ahmed et al) serves as an example of our concerns.


   This is listed in our original search. It was excluded due to no outcomes of interest for the KQs. (Note: Reported transfusion effect on sensitization, but no graft outcomes reported)


   Since the publication from the UNOS database is not a peer reviewed study, and had insufficient description of methodology, it did not meet our inclusion criteria. However, we have now included the information in the discussion section of the report.


   Please refer to comments above (#5).

Added to the final report. Please refer to section key question 2b.


Book chapter. See above (#3)


Book chapter. See above (#3)


It was listed in our original search. It was excluded since there were no outcomes of interest. The study is a decision analysis comparing the decision of DST versus cyclosporine use.


It was listed in our original search. It was excluded due to no outcomes of interest for the KQs. (Note: Reported transfusion effect on sensitization, but no graft outcomes reported)


Book Chapter. See above (#3)


This study did not evaluate the direct effect of transfusion on graft outcomes, and thus it was not included.


This study did not evaluate the direct effect of transfusion on graft outcomes, and thus it was not included.


It was listed in our original search. It was excluded because the study groups were not in direct comparison to each other (DST versus cyclosporine).
   It is excluded because it is a guideline, not a controlled trial.

17. Meier-Kriesche, H.U. and B. Kaplan, Waiting time on dialysis as the strongest
   Transfusion effect on graft outcomes was not evaluated in the study. Outcomes (i.e.
   waiting time on dialysis) reported in the study were tangential to the key questions of
   the TA.

18. Opelz, G., Improved kidney graft survival in nontransfused recipients. Transplant
    We were not confident that the population included in the study consisted of an
    unique dataset, and there was a suspected overlap of population with other
    publications from the Collaborative Transplant Study that were included in the
    technology assessment.

19. Opelz, G., Non-HLA transplantation immunity revealed by lymphocytotoxic
    Added to the final report. Please refer to section key question 2b.

    It was listed in our original search, but it was excluded because the type of
    transfusion evaluated in the study (i.e. buffy coat DST) was not red cell component
    transfusion.

21. Raftery, M.J., et al., Controlled trial of azathioprine and cyclosporine to prevent anti-
    671-6.
    This publication did not meet the inclusion criteria because it did not have controlled
    group comparison.

22. Scornik, J.C., et al., Assessment of the risk for broad sensitization by blood
    It was listed in our original search, but was excluded due to no outcomes of interest.
    (Reported transfusion effect on sensitization only, no graft outcomes reported)

23. Keogan, M., et al., Causes of sensitisation in patients awaiting renal transplantation
    It was excluded because the outcomes reported in the study (i.e. effect of
    sensitization on transplant waiting time) were not of interest in answering the key
    questions of the technology assessment.

24. van den Berg-Loonen, P.M., et al., B cell antibodies after planned transfusions.
There is no comparison between transfusion and no transfusion.

   It was listed in the original search, but it was excluded since it did not evaluated the direct link between transfusion effect, sensitization rate and allograft outcomes.

   It was excluded because the outcomes reported in the study (i.e. factors affecting access to transplantation) were not of interest in answering the key questions of the technology assessment.

   The focus of the study was not relevant to kidney transplantation, and none of the outcomes reported was of the interest to the topic. Thus, it was excluded.