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| Peer Reviewer 3 | General Comments | This is an important report that will be quite useful both clinically and with respect future clinical research. The results will influence clinical practice in a way, it is to hoped, that will prevent kidney transplant recipients from being exposed to unnecessary risk by attempts to withdraw calcineurin inhibitors. In addition, the observations of differences in outcomes when comparing early vs late CNI minimization suggest that there is critical window after transplantation for establishment of a regulatory immunologic milieu; this should be a fruitful area for future mechanistic research. | Thank you for reviewing the report. |
| Peer Reviewer 3 | General Comments | The report is well structured and well organized. I think it unlikely that it will be the basis for policy decisions, because the evidence is not yet strong enough. | Thank you for your comment. |

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| TEP Reviewer 1 | General Comments | Overall, I thought that this report was excellent. However, I ranked it as "Good" for quality of report because I don't understand the inclusion of KQ2 given the OPTN/SRTR 2013 data showing how little cyclosporine is used in clinical practice. I think your efforts would have been greater served by focusing on the adverse event differences seen with KQ3. Overall, for the questions that you posed, the work was well done and summarized in a way that was easy to read and draw conclusions from. | The intent of Key question 2 was to assess the impact on clinical outcomes of monitoring cyclosporine 2-hours post-administration (C2) versus trough monitoring (C0). This area was identified as an area of uncertainty by laboratory medical experts who were part of the stakeholder panel convened by the EPC program to provide input on the relevance and usefulness of the key questions. Although cyclosporine is used less frequently than tacrolimus, input from several clinical investigators, Key Informants, and Technical Experts suggested that cyclosporine monitoring remains relevant in the clinical setting. |
| TEP Reviewer 1 | General Comments | Overall, the paper is clear and well written. It is structured in a manner that is easy to read and understand. The major problem are the data for the questions. None of the answers to the key questions are definitive, giving clear answers for all readers to implement into clinical practice. Answers, although giving us a good idea as to the quality of the included studies, are vague and leave a lot of room for interpretation. But, that is how organ transplant practice is. | Thank you for reviewing the report. We agree that the limitations in the evidence prevented us from making some conclusions. |
| TEP Reviewer 2 | General Comments | The report summarizes mostly known findings but will be helpful to the community. | Thank you for reviewing the report. |

*Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2193*
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| TEP Reviewer 3 | General Comments | The report is clinically meaningful and will likely interest the transplant community. The target population and audience are well defined. The questions are precisely stated. In general, the authors have compiled a vast amount of information and distilled the main findings in a clear way. They are to be congratulated for succeeding in that task. | Thank you for your comment. |
| Public Reviewer 1<br>Joseph Vassalotti, MD<br>Chief Medical Officer<br>National Kidney Foundation (NKF) | General Comments | The National Kidney Foundation NKF would like to comment on one finding of AHRQs Systematic Review of Calcineurin Inhibitors for Kidney Transplant. This report seems to give equal weight to tacrolimus and cyclosporine as posttransplant CNIs in its conclusion however we would like to point to a recent clinical trial and an NKFsponsored clinical practice guideline that both favor tacrolimus as the first line drug of choice. The Kidney Disease Improving Global Outcomes KDIGO 2009 clinical practice guideline on the Care of Kidney Transplant Recipients states in recommendation 2.2 We suggest that tacrolimus be the first line CNI used. 2A. The Symphony Trial conclusion states The Symphony study showed that at 1 year post transplant a regimen based on daclizumab induction 2 g mycophenolate mofetil MMF lowdose tacrolimus and steroids resulted in better renal function and lower acute rejection and graft loss rates compared with three other regimens two with low doses of cyclosporine or sirolimus instead of tacrolimus and one with no induction and standard cyclosporine dosage. Additionally many transplant centers in the U.S. currently use tacrolimus as the first line CNI. We would ask that the authors make sure to clearly highlight the deciding factors in making an alternative recommendation. | Thank you for reviewing our report. We specify in the Introduction that tacrolimus is currently used far more often than cyclosporine. We have added text throughout the Results and Discussion sections to emphasize that the evidence base is limited because of the disproportionate number of studies that examined cyclosporine. We also identified, where relevant, differences between the results of studies of cyclosporine and tacrolimus. Several of our clinical investigators, Key Informants and members of the Technical Expert Panel suggested that it was appropriate to conduct analyses that combined studies of both therapies, as well as separate analyses. Please note as well that this systematic review is intended to inform clinical decisions, but we do not make any recommendations |

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| | | | for clinical practice. End-users must weigh the benefits and harms in making decisions about clinical care. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | General Comments | As an innovator pharmaceutical company interested in implementing best practices for calcineurin inhibitor (CNI) use, Astellas Pharma, Inc. (Astellas) is pleased to respond to AHRQ's request for commentary on its comparative effectiveness draft entitled, "Systematic Review of Calcineurin Inhibitors for Renal Transplant." In doing so, we would like to first commend the Evidence-Based Practice Center (EPC) and Technical Expert Panel (TEP) for such a thorough and comprehensive review. We similarly applaud the effort undertaken by the AHRQ to improve the quality of health care in the United States. At Astellas, we recognize the need to provide comprehensive, evidence-based reviews that are relevant to patients, physicians, health plans, purchasers, government programs, and for the U.S. health care system in general. Our careful appraisal of this draft document takes these necessities into account. Based on a 25 year heritage as a pioneer in transplant immunosuppression, we are sharing the following comments out of concern for patient safety as well as a deep and abiding respect for the difficult work done by the TEP. | Thank you for your review of the report. |

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| Public Reviewer 3<br>LiSheng Chen, PhD<br>Submitted on behalf of the American Association for Clinical Chemistry (AACC) | General Comments | It is important to summarize the findings of different types of studies to provide a framework for formulating the appropriate review strategies, obtaining meaningful outcomes as well as for understanding the limitations and applicability of synthesized data and the impacts of these factors on the conclusion drawn from this systematic review. | We appreciate your comment. For the questions that considered the effectiveness of different drug level monitoring methods (KQ1 and KQ2), we included both prospective and retrospective comparative trials. However, for the question that focused on the different CNI strategies (KQ3), we considered RCTs to be the most suitable evidence. |

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| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | General Comments | The traditional RCT is not necessarily the gold standard for comparing the effectiveness of different techniques (e.g. immunoassay vs HPLC/ LC-MS/MS) on the clinical outcomes of CNI monitoring. Neither is it the best way for assessing monitoring time points (e.g. C0 vs C2 for Key Question 2). | In addition to RCTs, we also included non-randomized prospective and retrospective comparative trials to assess the effectiveness of different monitoring techniques on analytical performance outcomes. Additionally, in the Discussion section of the report, we discuss a previous review by Knight and Morris on C0 vs. C2 monitoring that included single-group pre-post studies. Despite differences in the evidence base, the conclusions drawn in the Knight and Morris review were similar to our review. These authors found evidence that C2 monitoring was associated with detecting higher levels of CNI than C0 monitoring, but they found no clear evidence that C2 monitoring affects renal function or acute rejection. Thus, Knight and Morris concluded that little evidence from prospective studies supports the theoretical benefits of C2 monitoring. |

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| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | General Comments | Future RCTs may benefit from including patients at high risk for graft rejection, population with advanced age, those who developed severe complications and patients under multi-organ transplants in order to closely reflecting routine clinical care. Long-term pragmatic clinical studies and large simple trials might be most informative for comparing the immunosuppressive regimens designed to reduce or eliminate exposure to CNI toxicity risks. | We agree with your comment. Our review sought to include evidence on high-risk patients, but our searches of the literature found little evidence with inclusion criteria that addressed these populations. We discuss the need for studies that include high-risk populations in the Discussion section of our report. |
| Public Reviewer 4 Roger Bertholf, PhD Professor Department of Pathology and Laboratory Medicine University of Florida College of Medicine – Jacksonville Submitted on behalf of the AACC | General Comments | I have no comments. It appears to be a very nice review and summary. | Thank you for reviewing the report. |
| Peer Reviewer 1 | Introduction | The introduction is clear and purpose clearly stated I would only add that as the quality of many of the studies was poor, recommendations are in most cases based on inferential evidence | We agree that this is a limitation of the evidence base, and we address this in the Discussion section. |
| Peer Reviewer 2 | Introduction | The information provided was appropriate. | Thank you for your comment. |

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| Peer Reviewer 3 | Introduction | One comment about language: referring to minimization, conversion, withdrawal, and avoidance as "alternative" regimens may suggest a legitimacy that is unwarranted. Only belatacept (Nulojix) is labelled for CNI-free immunosuppressive after transplantation. It might be better to refer to these regimens as "other-than full dose" or "off-label" regimens. | Thank you for your suggestion. We considered several terms and phrases for the general designation of these regimens. After consultation with clinical experts including the Technical Expert Panel, and discussion with AHRQ, we selected “alternative” as a concise, comprehensible, neutral label for the broad range of regimens we examined. |
| Peer Reviewer 3 | Introduction | Page 3, Lines 23-24: the increased access to transplantation for individuals with well-controlled HIV infection is probably not attributable to improved immunosuppression or transplant outcomes, given that these have not changed appreciably in the last 10 to 15 years, but rather to the willingness of a small group of committed clinicians to demonstrate, through rigorous clinical research, that HIV infection does not preclude good outcomes. | Since the studies we reviewed did not include this population, we have removed this discussion of patients with HIV and now refer more generally to populations that are immunocompromised, immunosensitive, or otherwise high risk. |
| Peer Reviewer 3 | Introduction | Page 3, Lines 27-28: the description of desensitization regimens should probably include plasmapheresis. | Thank you for your suggestion. We added plasmapheresis to the text. |
| TEP Reviewer 1 | Introduction | The Introduction does a good job reviewing the current state or renal transplant, outcomes and immunosuppressive use. It clearly states the 3 key questions and outlines why and how these questions will be tackled. The writing is clear and accurate. | Thank you for your comment. |
| TEP Reviewer 2 | Introduction | Clear | Thank you for your comment. |
| TEP Reviewer 3 | Introduction | The introduction is well written. | Thank you for your comment. |

*Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2193*
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| Peer Reviewer 1 | Methods | I may have missed it, but were any Forrest plots done? | We reviewed forest plots for all of the outcomes reported in the Results, and added select forest plots in Appendix F. We describe the use of forest plots in the Methods. |
| Peer Reviewer 1 | Methods | how was heterogeneity assessed? | We evaluated statistical heterogeneity of the pooled analyses using the $I^2$ statistic, and we considered an $I^2$ of 50 percent or more as evidence of substantial heterogeneity. We have added text to the Methods section describing how heterogeneity was assessed. |
| Peer Reviewer 1 | Methods | I am concerned that many of the studies were pharma driven and may include certain selection biases | We also considered industry funding as a source of bias and included it as an item in our risk-of-bias assessment of the included individual studies. The overall risk of bias of a study was rated higher if the study received financial support through a pharmaceutical company. Risk-of-bias assessment of all studies is included in the Appendix. |
| Peer Reviewer 2 | Methods | The inclusion and exclusion criteria were clearly stated and well-justified. The search strategy was very clear. The outcomes measurements were appropriate. The statistical methods used, and where described the inability to apply statistical methods were appropriate. | Thank you for your comment. |
| Peer Reviewer 3 | Methods | The methods are extensively described, and appropriate. | Thank you for your comment. |

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| Peer Reviewer 3 | Methods | Page 10, Line 27: the word "text" is missing. | We have made the appropriate correction. |
| Peer Reviewer 3 | Methods | Line 43: "alternative" is misspelled. | We have made the appropriate correction. |
| TEP Reviewer 1 | Methods | The study inclusion/exclusion criteria seemed fair and consistent with similar analyses. The tables/figures explaining definitions and diagnostic criteria were clearly made. The statistical analysis used in the review is appropriate and well explained. | Thank you for your comment. |
| TEP Reviewer 2 | Methods | Clear | Thank you for your comment. |
| TEP Reviewer 3 | Methods | The inclusion and exclusion criteria are reasonable. The search criteria are logical and clearly stated. The statistical methods seem reasonable. | Thank you for your comment. |
| Peer Reviewer 1 | Results | Very good job, thank you | Thank you for your comment. |
| Peer Reviewer 2 | Results | The level of detail and conclusions drawn in the results section were appropriate. I am unaware of any studies that were overlooked. There are no additional comments. | Thank you for your comment. |
| Peer Reviewer 3 | Results | The selection of manuscripts and level of detail are appropriate. | Thank you for your comment. |
| Peer Reviewer 3 | Results | For studies that involved reduction in the dose of CNI (that is. all but the avoidance studies), it would be useful to know at what point the measurement of drug levels was abandoned and only dose was followed. This of course is relevant to KQ 1 & 2; the evaluation and significance of CNI levels in low-dose regimens is unknown. | Immunosuppressive regimens for transplant recipients are guided by therapeutic drug monitoring (TDM). We are not aware of any study that only followed doses, without TDM. |

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| Peer Reviewer 3 | Results | The first key point with respect to minimization (page 29, lines 30-33) might be qualified to specify that this refers to early CNI minimization, and this same qualification would be appropriate for the first sentence of the Summary of the minimization section (page 32, lines 28-29). The difference in outcomes between of early vs late minimization should not be an afterthought; the finding that early minimization leads not only to improved renal function but also decreased rejection is somewhat surprising and perhaps immunologically important. | Thank you for these suggestions. We have added text to clarify the differences we observed in early versus late minimization, and we highlight the potential importance of these findings. |
| Peer Reviewer 3 | Results | In the section on conversion, there is a grammatical error (page 43, line 13); should be "lower incidence", not "fewer incidence". | We have made the appropriate correction. |
| Peer Reviewer 3 | Results | With respect to CNI withdrawal, it would be interesting to know if it is possible to identify at what point in the withdrawal process the risks for rejection and graft loss become evident. As noted above, early minimization of CNI was found to be beneficial. Almost all withdrawal studies involve gradual reduction in CNI dose, that is, they start as minimization studies. It is not clear where the benefits of minimization end and the risks of withdrawal begin. | This is an excellent point, however the studies we reviewed did not provide evidence to address this issue. We have added this consideration to our discussion of areas for future research. |
| Peer Reviewer 3 | Results | The summary of the Avoidance section glosses over the finding that belatacept is associated with increased risk of rejection in standard criteria donors. This research finding has been born out in clinical practice and probably should be mentioned in the summary. | We have added text to that section to address more directly the risk of rejection associated with belatacept. |
| TEP Reviewer 1 | Results | Taking into consideration the strength/bias of the papers, the results were well supported. The key outcomes to each question are well developed, clear and concise. I believe that the authors included all relative studies in their analysis. Overall, it does seem that the take home message is that, despite the number of available studies, the data is not overwhelmingly in favor of one monitoring assay, TDM technique or CNI minimization strategy. | Thank you for your comment. |

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| TEP Reviewer 2 | Results | Clear | Thank you for your comment. |
| TEP Reviewer 3 | Results | The amount of detail is reasonable. The results could be improved in the following ways:<br>1) In certain places like Table 4 and the accompanying text, they use the word "bias" in two different ways. In some places, they are talking about bias in the sense of analytic bias when comparing chemical assays. In other places on the same page (17), they refer to bias in the epidemiological sense, eg information bias when analyzing outcomes. They need to more clearly specify the meaning when they use the term bias, particularly when two different senses of the word are being used in the same section. | Thank you for your comment. We have clarified our use of the term “bias” in the Results section for Key Question 1 of the report. |
| TEP Reviewer 3 | Results | 2) In multiple parts of the paper related to Question 3, the authors make statements about certain findings without specifying the comparison group. As one example, they write "Regimens using mycophenolic acid formulations and CsA are associated with better renal function, lower risk of acute rejection (Strength of Evidence: Moderate), and lower risk of graft loss (Strength of Evidence: High)." (Page 29). I am unclear who is the comparison group. Is this mycophenolate vs. azathioprine? Is this CsA vs. tacrolimus? Is this mycophenolate and CsA vs. any other combination? | We have revised the Results section in numerous places to specify or clarify comparison groups. |
| TEP Reviewer 3 | Results | 3) In the labelling of tables, it would be more informative if - instead of writing "Question 2", they instead found an abbreviation for the question and put that in the title. | Thank you for your suggestion. We have changed the titles of Tables 6 and 8 to be more specific. |

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| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | In brief, our observations highlight the potential for the review's conclusions on Question 3 to be misinterpreted by the very constituency it was intended to reach and is predicated on the following:<br>• Misstating the conclusions set forth in the majority of studies under review | Thank you for reviewing the report. We recognize that the results of individual studies were often equivocal or not statistically significant. However, we conducted numerous meta-analyses in order to identify effects that may not be evident at the level of a single study, but which are nevertheless significant at the level of an entire evidence base. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | • Asserting improved patient outcomes based on randomized controlled trials (RCTs) reporting only one or two year results and oftentimes lacking biopsy data | We agree that these are important limitations of the evidence base, and discuss these limitations in the Results and Discussion sections. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | • Relying heavily on low-risk patients for inclusion in most studies | The eligibility criteria for the population of this systematic review was broad, and we included all adult renal transplant recipients treated with full-dose or alternative dose immunosuppression. We did not exclude individuals at high risk for graft rejection. We agree that this is also an important limitation of the underlying evidence base, and we have highlighted this issue throughout the report. |

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| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | • Extrapolating early clinical experiences with cyclosporine to that of tacrolimus (tac) | Thank you for your comments. Several of our clinical investigators, Key Informants and members of the Technical Expert Panel suggested that it was appropriate to conduct analyses that combined studies of both therapies, as well as separate analyses. We have included in our Key Points and Applicability sections that the majority of CNI minimization trials we examined used modified cyclosporine, and trials evaluating standard dose tacrolimus compared to tacrolimus minimization were lacking. Therefore there are insufficient data to draw conclusions about these two regimens when compared to each other. We also identified, where relevant, differences between the results of studies of cyclosporine and tacrolimus. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | • Imprecisely defining “low dose regimens” for cyclosporine and tacrolimus | We reported full details of the regimens used in each study in the Evidence Tables in Appendix E. Due to the length and complexity of the report, we refer generally to “low-dose” regimens in the main text. |

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| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | • Acknowledging that the term “CNI minimization” invokes a different meaning in contemporary practice than when the majority of studies in this review were conducted | We agree that clinical practice has changed in recent years, and we have added text in the Results (for the minimization studies) and the Discussion (in the Applicability section) to help readers recognize how these practice changes may affect the applicability of our findings. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | • Recognizing that a majority of referenced studies on tacrolimus minimization had difficulty achieving the level of CNI reduction targeted in their respective study protocols | We also describe this factor as a limitation of the evidence base. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | • Inexact accounting of the rates of acute rejection and graft loss | We reported full details of the outcomes we extracted for every study in the Evidence Tables in Appendix E. |

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| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development Medical Affairs, Americas | Results | The paramount concern inherent in this draft document is that it misstates the conclusions of the studies under review. In fact, after close inspections of publications available to us for download on PubMed, only two of the thirteen studies examining tacrolimus minimization in Table 9 showcased a statistically significant benefit in any of the outcomes measured, and that was only in eGFR.[1,2] Otherwise, the conviction that tacrolimus minimization fails to demonstrate a measurable benefit is upheld regardless of whether eGFR, graft survival, or rejection rates are scrutinized. While many of these studies admittedly achieve their primary non-inferiority endpoints and allude to comparable safety profiles with respect to standard regimens, none imply that outcomes are in any way improved with tacrolimus minimization. In fact, of the remaining studies exclusively examining CsA minimization, very few of those demonstrated a difference in acute rejection or graft loss, despite showing a statistical improvement in eGFR.<br><br>1. Ekberg H, Tedesco-Silva H, Demirbas A et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007; 357(25):2562-2575.<br>2. Bechstein WO, Paczek L, Wramner L et al. A comparative, randomized trial of concentration-controlled sirolimus combined with reduced-dose tacrolimus or standard-dose tacrolimus in renal allograft recipients. Transplant Proc. 2013; 45(6):2133-2140. | We recognize that the results of individual studies were often equivocal or not statistically significant. However, we conducted numerous meta-analyses in order to identify effects that may not be evident at the level of a single study, but which are nevertheless significant at the level of an entire evidence base.<br><br>Several of our clinical investigators, Key Informants and members of the Technical Expert Panel suggested that it was appropriate to conduct analyses that combined studies of both therapies, as well as separate analyses.<br><br>We have also described in several sections throughout the report the important limitations of individual studies as well as the overall evidence base. We also identified, where relevant, differences between the results of studies of cyclosporine and tacrolimus. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology | Results | A key aspect of this investigation was the methodology employed to synthesize a wide range of heterogeneous data. Manufacturing a document taking into account different degrees of clinical homogeneity with regard to study populations, monitoring methods, | We agree that there are important limitations associated with the one-year time frame for outcomes that is usually reported in these |

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| Astellas Pharma Global Development Medical Affairs, Americas | | CNI protocols, and outcomes is no easy task and the authors should be congratulated on their wide-ranging effort. Not to be surpassed, a similar level of industry was likely required to determine the strength of the overall body of evidence, which is notable predicated on estimated GFR, graft survival, and rejection rates, primarily at *one year*, in mostly idealized populations. It may follow from consensus that this limited time horizon may represent a narrow view of outcomes overall, especially given that many of the studies under review are lacking biopsy data, which is, in itself, the gold standard when compared to eGFR. Given the results of investigations tracking longitudinal outcomes, many of which reveal severe biopsy changes despite well-functioning grafts at one year and beyond, it may be more accurate to avoid claims on how CNI minimization improves universal outcomes, opting instead to qualify summary statements within the draft document to account for these exigencies.[3,4] Recognition of this need may impact the strength of the overall body of evidence. Likewise, without a disclaimer that the studies in Table 9 examine minimization strategies in what is essentially a low-risk population, the danger exists that conclusions within the draft document may be misappropriated and applied to individuals who are at highest risk for immunological graft loss.<br>3. Gloor JM, Sethi S, Stegall MD et al. Transplant glomerulopathy: subclinical incidence and association with alloantibody. Am J Transplant. 2007;7(9):2124-2132.<br>4. Park WD, Larson TS, Griffin MD and Stegall MD. Identification and characterization of kidney transplants with good glomerular filtration rate at 1 year but subsequent progressive loss of renal function. Transplantation 2012;94(9):931-939. | studies, and which we used for our meta-analysis. We also agree that our findings, like those of most studies, focus on several outcomes that represent only a subset of all the important clinical outcomes that should ideally be measured. Additionally, we recognize that most of the studies were limited to low- or average-risk patients, and therefore our findings have limited applicability to higher-risk populations. We have added text throughout the Results and Discussion to highlight these limitations, and identify the need for long-term data, inclusion of more comprehensive clinical outcomes, and studies of higher-risk populations, as important areas for further research. |

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| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | Another major strength of this review is the great length to which the authors went to evaluate the relevant medical literature. However, a large percentage (22/36) examines cyclosporine (CsA) minimization exclusively and may not be generalizable to tacrolimus. In the remaining studies that do involve tacrolimus, six compare minimization strategies with CsA (Xu, Gaston, Spagnoletti, Ekberg, Hernandez, Hang, and Holdaas). The largest of these was the 2007 study by Ekberg published in the *New England Journal of Medicine* that enrolled 1645 patients.[1] Patients in this and many of the twenty-eight other CsA-containing studies who received low dose CsA registered improved outcomes compared to those receiving standard dose CsA. Compared to cohorts receiving standard CsA, reduced CsA, and reduced sirolimus (SRL), patients receiving low dose *tacrolimus* achieved better allograft function, lower rates of biopsy-proven acute rejection, and lower rates of graft loss. While these and other results may speak to the benefits of using tacrolimus in the clinical setting, the lack of a “standard dose” tacrolimus arm in the six CsA / tac minimization studies makes it difficult to conclude with certainty that the improved outcomes are secondary to tacrolimus minimization, only that outcomes with tacrolimus are improved over other CNI-minimization strategies. In fact, an analysis of several of these peer-reviewed publications suggests that graft survival is critically dependent on the mere presence of tacrolimus itself and is not impacted by any particular tacrolimus reduction strategy. This is an important distinction for readers who may infer from this review that results observed with reduced CsA dosing are duplicated using tacrolimus. In the best interest of patients, this may be ill-advised given the challenge of documenting a single RCT asserting that reduced dose tacrolimus statistically improves graft survival and lowers acute rejection rates when | Thank you for your comments. We have included additional text in the Discussion section stating that studies including a standard dose tacrolimus arm as well as a tacrolimus minimization arm were lacking in this review, and therefore it was not possible to differentiate the risk or benefit of tacrolimus minimization from tacrolimus use itself. |

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| | | compared to standard dose tacrolimus. Likewise, it should also be noted that *none* of the studies quoted in Table 9 included a protocol-based, conventional-dose tacrolimus arm.<br><br>1. Ekberg H, Tedesco-Silva H, Demirbas A et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007; 357(25):2562-2575. | |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Results | Conventional wisdom has long equated CsA toxicity with that of tacrolimus, and so for the purposes of study design, the inclusion of a standard dose tacrolimus arm may have been considered redundant. This supposition may be unfounded given the differential effects of CsA and tacrolimus on cardiovascular risk factors, as well as the kidney, itself.[5 6] The accumulation of additional evidence in recent years on the dangers of tacrolimus minimization also calls attention to this type of omission. While these studies may not necessarily be the subject of this review, they are no less pertinent to the discussion at hand. Herein, we have cited two such representative examples from the literature, one being an NIH sponsored, multi-center trial in low immunological risk, living donor recipients; both highlight the risk of extrapolating results observed with CsA minimization to studies involving tacrolimus.[7,8] Given the weight of this evidence and the dearth of RCT data to substantiate claims of improved graft survival and reduced rates of acute rejection with low dose tacrolimus when compared to conventional dosing regimens, an imprudent reduction in tacrolimus dosing may be the unintended consequence of this review. It may therefore be reasonable to draw attention to this missing design element (lack of conventional-dose, tacrolimus comparator arm) in many of the studies reviewed and to underscore the fact that improved graft survival and lower rates of acute rejection were | We have included additional text stating that studies including a standard dose tacrolimus arm as well as a tacrolimus minimization arm were lacking in this review. |

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| | | confined solely to studies comparing standard-to reduced-dose CsA regimens.<br><br>5. Kihm LP, Blume C, Seckinger J et al. Acute effects of calcineurin inhibitors on kidney allograft microperfusion visualized by contrast-enhanced sonography. Transplantation 2012; 93(11):1125-1129.<br>6. Nankivell BJ, Chapman JR, Bonovas G and Gruenewald SM. Oral cyclosporine but not tacrolimus reduces renal transplant blood flow. Transplantation. 2004;77(9):1457-1459.<br>7. Hricik DE, Formica RN Nickerson P, et al. Adverse outcomes of tacrolimus withdrawal in immune-quiescent kidney transplant recipients. J Am Soc Nephrol(epub)04-29-2015.<br>8. Collaborative Transplant Study. Tacrolimus trough levels and kidney graft survival. http://www.ctstransplant.org/public/newsletters/2014/png/2014- 1.html?ts=5298585711253254 . Accessed June 15, 2015. | |

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| Public Reviewer 3<br>LiSheng Chen, PhD, on behalf of the AACC | Results | Commercial immunoassays have been employed for CNI monitoring for decades and the problem of cross reactivity has been well documented. HPLC and LC-MS/MS are technical demanding but more accurate methods and can be used to simultaneously monitor CNI metabolites. However, this review only included seven studies published in literature that compared the use of chromatographic techniques to immunoassay techniques to measure CNI concentration levels. In fact, proficiency testing and external quality assessment programs for Toxic Drug Monitoring (TDM) have been existed for decades and method comparison data have been systemically generated for immunosuppressant monitoring for quality control purposes by accrediting agency such as CAP. These data if included will provide valuable information about the trends of methodological advances, medication changes and the cutoff value changes over time. | Thank you for making us aware of the proficiency testing data collected and published by the College of American Pathologists (CAP). For this report, we only included data from studies published in peer reviewed journals. However, we have added a reference to the study by Soldin et al. (Arch Pathol Lab Med, 2003) that uses data collected by CAP to evaluate the cross-reactivity of cyclosporine (CsA) metabolites in commonly used assays for CsA. The authors of this study concluded that metabolite interference impacts the specificity of immunoassays to measure CsA levels. |

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| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | Results | The evidence presented by this review was considered insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes. The laboratory monitoring of immunosuppressants is no doubt provide valuable information for maximizing the benefits and minimizing the harmful effects related to CNI management in renal transplant. However, comparative effectiveness between the monitoring techniques using clinical outcomes in traditional RCT may not be appropriate, since the effect size (differences in the clinical outcomes) is too small compared to other more important contributing factors that are not easy ( or not possible) to control. As the new CNI agents such as prolong release tacrolimas and volcosporin entered market recently, and CNI minimization become more established as the mainstream regimen, the minimum effective dose and maximum tolerant dose should be systematically investigated using available methodologies with proper study design, study duration and end-point analysis. | Thank you for highlighting this important point. We agree that future studies of CNI monitoring in the era of CNI minimization should be performed with rigorous study design. We have mentioned this in the Discussion section. |

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| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | Results | Only 6 comparative trials are included in this review, all the studies have obvious drawbacks on study design which weakening the strength of evidence for the conclusions drawn from the data synthesis. Only one study include stable renal transplant recipients while others only focused on new renal transplant patients. More studies with better study design are required to obtain conclusive evidence on the question address here. (Table 8 on page 34 and 35) | We agree that the evidence comparing different drug monitoring times (C0 vs. C2, Key Question 2) was limited in both quantity and quality. The six studies included in our review represent what we believe is the best available evidence to address the key question, as these studies directly compared different drug monitoring times. We hope that more studies of better methodological quality will become available to provide clearer evidence about the advantages of one measuring point over another. |

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| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | Results | Trough monitoring (C0) versus 2-hour post-administration monitoring (C2) (p31): The trending of trough levels (C0) is the most frequently implemented TDM strategy in transplant recipients. Monitoring C0 offers a simple and consistent way for guiding therapy, but it is poorly correlated to AUC, the pharmacokinetic parameter most closely related to efficacy. Existing data suggests that CNI drug levels observed two-hours post-administration (C2), representing an attainable surrogate for peak concentration (Cmax), have a strong relationship with AUC. However, in clinical practice, external influences such as deviation in diet or eating habits, taking additional over-the-counter or prescription medications without practitioner awareness, self-prescribing with herbal remedies and teas may result in unnecessary reductions or increases in dose, potentially producing an ineffective or toxic drug regimen. A thorough understanding of the pharmacokinetics parameters related to the most frequently used CNI medications, including the newly marketed CNIs, are required to ensure optimal monitoring. | Thank you for pointing out additional external factors that could influence the C2 monitoring strategy. We have added text to the Discussion section addressing the tradeoff between efficacy and effectiveness (i.e., real world experience) of C0 vs. C2 monitoring. |

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| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | Results | From the limited strength of evidence presented in this review, the C2 monitoring in new renal transplant recipients (within 20 days after transplant), led to a significantly higher CsA mean cumulative dose increase compared to C0 monitoring; in contrast, among stable renal transplant recipients at 3 or more months after transplant, C2 monitoring led to significantly more CsA dose reductions than C0 monitoring. (lines 37-52 on page 22 and lines 36-48 on p24).<br><br>By understanding the pharmacokinetics meaning of the C0 and C2 mentioned above, it will be easier to explain the observed discrepancy for C2 monitoring in new versus stable renal transplant recipients: for the new renal transplant recipients, the target C2 level was set too high and therefore 75% of patients did not reach the target C2 level within observation period of 20 days, while most of the patients reach C0 target level by day-5 post-transplant. For stable renal transplant recipients, both C0 and C2 are in steady-state, however, the fluctuations in blood CNI levels will be relatively easier to detect with C2 monitoring due partly to the higher absolute value for C2 and partly to the its higher sensitivity to the external influences mentioned above.<br><br>With the implementation of CNI minimization regimen, the future study should lower the target C2 level to reflect the CNI dosage reduction. | Thank you for highlighting the pharmacokinetic differences in CsA early vs. later post-transplant. We refer to this consideration in the detailed synthesis of the Results Section for Key Question 1. In future studies involving CNI minimization, a lower C2 target range will require validation with clinical outcomes showing that a given C2 range is high enough to prevent rejection but low enough to confer protection against dose-related adverse events. |
| Public Reviewer 5 Adil Khan, MSc, PhD, Department of Pathology and Laboratory Medicine, Temple University, Philadelphia, PA, on | Results | This systematic review found that although chromatographic methods are more precise and accurate compared to immunoassays, they authors were unable to determine the clinical significance of these differences.<br><br>However, it is important to note that external quality assessment (EQA) schemes that provide insight into | Thank you for your comment. In the Background section of the report, we added a reference describing the bias observed with immunoassays, based on the paper published by the College of American |

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| behalf of the AACC | | the performance of diagnostic assays have demonstrated that immunoassays can exhibit a positive or negative bias compared to the liquid chromatography coupled with mass spectrometry which often serves as the reference method against which the immunoassays are compared. These EQA schemes further underscore that clinicians must be aware of the differences in results that can be obtained from these different methods. This will aid them in adjusting drug target levels accordingly, to avoid potential effects on efficacy and toxicity (Holt et al., 2014).<br><br>Immunoassays, because they are based on primary antibodies recognizing the analyte of interest and secondary antibody inked to a chromophore, and recognizing a different epitope of the antigen can be affected by heterophilic antibodies. These are human antibodies present in the patient that can recognize the animal raised primary and secondary antibodies used in the immunoassay. Hence these heterophilic antibodies can form a bridge between these primary and secondary antibodies in the absence of analyte thus giving a false positive result. Such cases studies have been noted in the literature (Barceló Martínet al, 2009; Parikh et al., 2010; Moscato et al., 2010; Morelle at al., 2011) and should be kept in mind when interpreting results that do not correlate with other clinical criteria.<br><br>**References:**<br>1. Holt DW, Mandelbrot DA, Tortorici MA, Korth-Bradley JM, Sierka D, Levy DI, See Tai S, Horowitz GL. Long-term evaluation of analytical methods used in sirolimus therapeutic drug monitoring. Clin Transplant. 2014 Feb;28(2):243-51.<br><br>2. Barceló Martín B, Marquet P, Ferrer JM, Castanyer | Pathologists (Soldin et al. Arch Pathol Lab Med, 2003). |

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| Peer Reviewer 1 | Discussion | I did not see data on adjunctive agents with CNI? | The focus of our analysis for Key Question 3 was on the use of CNIs. We conducted subgroup analyses based on type of adjunctive agents, but independent evaluation of those agents was outside the scope of this review. Complete details about the regimens used in each study, including adjunctive agents, are presented in the Evidence Tables in Appendix E. |
| Peer Reviewer 1 | Discussion | A summary page would help i.e. no defined range to prevent AR with tac C0 equal to C2 in long term outcomes etc.... | Thank you for your suggestion. We have revised the Results, Discussion, and Conclusion to provide more useful summaries of the evidence base. |
| Peer Reviewer 2 | Discussion | The discussion was clear, relevant, and reflective of the data. The future research recommendations were clearly stated and useful. | Thank you for your comment. |

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| Peer Reviewer 3 | Discussion | The "Implications" section would benefit from being more clearly linked to the data presented and from removal of some of the generalities; as written, the section is not particularly helpful. | Thank you. We have revised the text to present a more valuable analysis and summary. |
| Peer Reviewer 3 | Discussion | One implication of the studies presented is that, despite their well-known toxicities, CNIs remain the most effective immunosuppressive agents for kidney transplant recipients, though not necessarily as they have been traditionally dosed. | We have added text in the Discussion to emphasize the value of CNIs, as suggested. |
| Peer Reviewer 3 | Discussion | The most beneficial of the tested approaches seems to be early minimization of CNI. The methods that have been developed for monitoring CNI levels were developed for much higher target levels than those used in minimization regimens, so another implication is that the findings presented about drug monitoring may not be applicable in the setting of CNI minimization. | We have added text in the Discussion to highlight the findings of early as opposed to late minimization. We have also addressed the potential limitations of current monitoring techniques in minimization studies. |
| Peer Reviewer 3 | Discussion | With respect to research gaps, the need for well designed studies that have clinically meaningful outcomes at 5 years or beyond is stated but could perhaps be emphasized more strongly. | We have highlighted more directly the need for longer-term outcomes in future research in our Research Gaps section of the Discussion. |
| Peer Reviewer 3 | Discussion | There is no mention of the need for clinical research directed at understanding the immunology that underlies the described clinical outcomes, which I believe is crucial to progress. | We agree that such research is critically important. However, we focused our suggestions regarding future research on the gaps that are most closely related to the existing evidence base, and that might be addressed in the near future through clinical comparative effectiveness studies. |

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| Peer Reviewer 3 | Discussion | Given the limited number of transplant recipients available to participate in clinical trials, and the heterogeneity of that population, it is likely that many of the questions that need to be addressed cannot be answered through traditional RCTs, but rather will need to be answered by a better understanding of transplant immunology, which would allow the development of more targeted clinical trials with alternative designs. | Thank you for emphasizing the important role that transplant immunology research will have in refining immunosuppressive pharmacology and improving care for transplant recipients. |
| TEP Reviewer 1 | Discussion | The discussion summarizes the findings concisely and discuss its applicability in modern practice. The section on clinical/policy decision making was well done. The sections on limitations were also well written and appropriate given the included studies. The gaps section clearly outlines where this analysis might allow for future studies. | Thank you for your comment. |
| TEP Reviewer 2 | Discussion | Overall, I think the paper needs to clearly highlight that there is more than renal function that the patient and clinical need to worry about - infections are a major factor and the limited data available to inform the impact of these important complications should be very clearly highlighted as an area in need of strengthening. | Thank you for your comment. We have added text to the Results and Discussion to emphasize the limited data available on infections in studies of immunosuppression, and cited this as an important gap to be addressed by future research. |
| TEP Reviewer 3 | Discussion | 1) The biggest challenge with interpreting the literature is that these immunosuppressant medications are not given alone; they are given in combinations. For that reason, it is often difficult to isolate one strategy, e.g. calcineurin minimization, without considering other elements of that strategy. My main objection to the interpretation of the Question 3 results is the statement that calcineurin minimization leads to less rejection. ("Thirty-six studies of low-dose CNI treatment provided high strength evidence that minimization was associated with improved clinical outcomes, including | Thank you for your comments. We have added text discussing the challenge of examining one aspect of a global immunosuppressive regimen when evaluating CNI minimization strategies. We also discuss trial heterogeneity, and note the lack of literature comparing tacrolimus standard dose |

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| | | improved renal function and reduced risk of acute rejection and graft loss")<br><br>For instance, the authors cite Ekberg et al. trial in the NEJM, in which calcineurin minimization was delivered with induction with daclizumab and contrasted to standard dose cyclosporine regimen without daclizumab. So what caused the reduced rejection? Was it the low dose calcineurin or the induction therapy?<br><br>From a biological perspective, we usually think of higher calcineurin doses as reducing the risk of rejection, albeit at the cost of lost of side effects and possibly more nephrotoxicity.<br><br>The authors should consider changing this assertion about reduced rejection, or else (or in addition) they can consider a clear statement about how calcineurin minimization must be considered as a 'bundled strategy' in which reduction in calcineurins is often accompanied by other changes that intensify global immunosuppression. | regimens to tacrolimus minimization strategies. |

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| TEP Reviewer 3 | Discussion | 2) The authors should more directly address the problem of side effects with these medications. I am not asking that they rewrite the report and add a big focus on side effects. But, for example, the decision to take on a strategy like switching a patient from a calcineurin to an mTOR is often motivated or impeded by side effects. Side effects are a big patient-centered issue. So it should be addressed in major places in the document. | We agree that side effects are at the forefront for patients. We attempted to capture all endpoints, including side effects, as reported in each of the studies. Some of the major side effects, such as renal dysfunction and opportunistic infections, were widely reported across most studies. Very few studies reported other side effects such as hypertension or metabolomics complications. We identify the need for better data on lesser reported outcomes as an important area for future research. |

*Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2193*
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| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Discussion | At this point, it is important to comment on how the lack of uniformity in defining low-dose CNI regimens impacts the generalizability of the results under review. Although the review calls attention to this limitation, it does not address its implications, which are significant. In an attempt to mirror the CsA experience, trough target concentrations associated with tacrolimus minimization strategies have evolved in the last decade such that the contemporary vernacular now consistently defines CNI minimization to reflect tacrolimus levels <5.0 ng/ml for the intended purpose of mitigating side effects. However, this is also a threshold around which real-world outcomes studies now recommend exercising caution given the potential threat of alloimmune activation, antibody deposition, and graft dysfunction over the long term.<br><br>8. Collaborative Transplant Study. Tacrolimus trough levels and kidney graft survival. http://www.ctstransplant.org/public/newsletters/2014/png/2014- 1.html?ts=5298585711253254 . Accessed June 15, 2015. | We have highlighted the impact of heterogeneous definitions of “low-dose” on the applicability of the evidence base. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Discussion | While the draft document explicitly states on page 32 that this review "cannot identify a specific target range for minimization that is associated with better outcomes," the certainty remains that this is a distinction made on behalf of patients and acted upon by knowledgeable transplant physicians each and every day. In truth, few would agree that in 2015, a state of clinical equipoise exists between patients maintained on tacrolimus at concentrations of 1.3 to 3.0 ng/ml and those dosed to achieve higher levels in the 10-12 ng/ml range. The fact that many of the referenced studies on tacrolimus included in this review failed to meet their target minimization concentrations lends credence to this assertion. Whether this stemmed from the personal experience of the physician investigators or an a priori knowledge of | We have added text emphasizing that our findings our limited by characteristics of the studies we reviewed, including heterogeneity in dosing, failure to reach pre-specified target levels, reliance on short-term outcomes, and the prevalence of studies using CsA over those using tacrolimus.<br><br>It was not feasible to evaluate and compare outcomes associated with |

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| | | real world outcomes data remains to be seen. It would be reasonable to suggest that the studies involving tacrolimus do purport to show how short-term renal function can be improved by optimizing (not minimizing) tacrolimus dosing. Either way, the repercussions are clear. By not drawing a distinction between the non-uniform approaches to tacrolimus minimization, by making broad claims that understate the differences between CsA and tacrolimus, and by not specifying that improved rejection and graft survival rates are claims that do not appear in any of the referenced studies on tacrolimus, even a sophisticated reader could inaccurately surmise that as far as tacrolimus is concerned, less may certainly be more. By indirectly endorsing this perspective, this review risks exacerbating a trend toward overzealous tacrolimus minimization, of which the implications for patients are easily recognizable in the results of real-world outcomes data specifically addressing this issue. | specific dosing or target levels within the broad range of “minimization”. |
| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | Discussion | The selection of laboratory methods for CNI monitoring is not solely determined by the analytical performance of the assays under consideration. It is actually more dependent on the available sources (funding, personnel and technical support), the medical needs of the physician customers. The cost-effectiveness is also another major determinant but will be calculated on the basis of the laboratory operation as whole, not heavily influenced by any single testing procedure per se. | Thank you for highlighting these important factors. We have described several of them in the section on implications for clinical and policy decision making. |

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| Public Reviewer 3 LiSheng Chen, PhD, on behalf of the AACC | Discussion | From a laboratorian perspective, the standardization of quality control material is the essential step for making meaningful accuracy/precision comparisons between different assay methodologies. Besides, the reference ranges for the minimum effective dose and maximum tolerant dose for a particular CNI agent may differ significantly between high risk and low risk populations, individualized monitoring employing other laboratory parameters, even new molecular diagnostic modalities, may be necessary in some cases as long-term outcomes/side effects, replacing early graft loss, become the major concerns in immunosuppressive management. | We appreciate your insight and comment. |
| Peer Reviewer 1 | Conclusion | I believe you have done a nice job, but would emphasize that these summaries are aggregate data without true scientific consensus in terms of safety or efficacy | We have revised the Discussion section to acknowledge the lack of consensus about the safety and efficacy of the regimens we reviewed. |

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| Peer Reviewer 3 | Conclusion | A strong and succinct description of the risks and benefits of the various reduced CNI dose strategies presented would be helpful to clinicians. This should include, if possible, specific information about rejection rates, and CNI dose thresholds at which the risk of rejection increases. | We have revised the Conclusion to include a more useful description of the risks and benefits of different strategies. However, risks and benefits will vary greatly depending on what type of donor organ is being used, type of induction therapy, type of concurrent immunosuppressive agents, and characteristics of the population. The evidence does not yet support conclusions regarding CNI dose thresholds at which rejection risk increases, and this is likely different for CsA vs. tacrolimus. |
| TEP Reviewer 3 | Conclusion | The report is well structured and organized and the main points are very clearly presented and reiterated across summaries and tables, except as noted above. The results can inform policy and also future research. | Thank you for your comment. |
| Public Reviewer 2<br>Jason Schwartz, MD<br>Medical Director, Transplant / Immunology<br>Astellas Pharma Global Development<br>Medical Affairs, Americas | Conclusion | In conclusion, Astellas is aligned with AHRQ in promoting best practices for the use of CNI. We very much appreciate the opportunity to comment on AHRQ's Comparative Effectiveness Review Draft Document and would welcome the prospect of further discussing the points raised in our response. As one of the many stewards who are committed to improving the lives of transplant patients, we offer these comments to aid in the interpretation of the review's findings. In summary, it may be worthwhile to consider emphasizing this document reflects one year data and outcomes, instead of implying a potential long term benefit seen with CNI minimization. Next, it may be advisable to comment on the low-risk patient | As you suggest, we have increased our emphasis on the limitations of the studies we reviewed, and the implications of these limitations for the overall evidence base. We greatly appreciate your careful review of the report. |

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| | | population enrolled in many of the studies and to differentiate between CsA and tacrolimus. Similarly, it may be important to correct inaccuracies in what the studies profess in terms of acute rejection and graft survival for tacrolimus. Finally, a greater emphasis on the non-uniform approaches to tacrolimus minimization and the implications thereof will help lessen the likelihood that a reader could potentially misunderstand the conclusions and contribute to inadvertent patient harm. Ultimately, patients are likely to be better served by examining those therapies which foster an improvement in long term graft survival and decrease the need for retransplantation, rather than those of unproven potential like CNI minimization strategies, which focus only on short-term gains. On behalf of those who receive the precious gift of organ transplantation, we hope that we have called attention to the need to revisit some of the conclusions put forth in the draft document and look forward to a well-balanced review after a full consideration of the available evidence. | |