European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL INVESTIGATION OF IMMUNOSUPRESSANTS FOR SOLID ORGAN TRANSPLANTATION

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	EFPIA	
2	IPTA (International Pediatric Transplant Association)	
3	Roche	
4	EKHA (European Kidney Health Alliance)	
5	Wyeth Research	France
6	Fresenius Biotech GmbH	Germany
7	EU FP6 integrated project 'RISET'	

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Table 2: Discussion of comments

GENERAL COMMENTS – OVERVIEW
1. However, the guideline does not appear to address the concern that it is becoming increasingly more difficult (almost impossible) to do ***superiority studies*** showing *improvement of rejection, patient or graft survival*. Therefore, non- inferiority trials appear to be the implicit expectation. Clarification would be desirable as to whether the guideline would allow outcomes alternative to reduction of rejection (e.g. benefit vs. adverse events). (EFPIA). ***Comment:*** The non-inferiority as well as other comparative options are highlighted in the updated version of the guideline.
2. The guideline implies that independent and blinded evaluation of ***transplant biopsies***, according to "accepted" criteria is crucial for clinical studies of immunosuppressive agents, suggesting this represents the most relevant evaluation criteria. It is important to recognize that substantial uncertainty (even controversy) surrounds the interpretation of biopsy histology. Accordingly, the guideline should be more flexible, allowing adaptation to changing scientific evidence, as well as to evolving diagnostic approaches (e.g. molecular diagnostics, genomics, proteomics, etc) which will very likely to improve the accuracy and reliability of results interpretation. (EFPIA). ***Comment:*** The current level of flexibility to use biopsy as well as the use of other diagnostic approaches and biomarkers is reasonable to maintain.
3. The guideline places particular emphasis on ***long term graft dysfunction***. However, patient conditions may change during long term follow up (e.g. poor compliance, development of co morbidities etc.). Such changes may have no relationship to the drug(s) under study but may impact outcomes considerably. Similarly, it is difficult, or even not feasible to maintain sufficient numbers of patients in rigorous trial environments for the 3-5 years needed to reach the required hard clinical endpoints. While effective molecular ***biomarkers*** may have future promise, no such measures have yet been validated. Therefore, long term outcome data may be better captured using alternatives to traditional controlled clinical trial strategies such as well designed registries. Combining trial results with data captured from ***registries***, for example may provide an approach to gain insight into this important aspect of unmet need. In that regard, an EU based registry, perhaps similar to the U.S. SRTR would be desirable and welcome. The long term safety follow-up remains flexible regarding what Sponsors actually need to collect on patients going out into the 5-10 year period. (EFPIA). ***Comment:*** The concern is shared whereas usefulness of approach should be based on case-by-case, depending on objectives.
4. We would welcome more specific guidance regarding establishment of ***dosing recommendations*** for new agents when combined with established drugs, or of new combinations of already established agents. (EFPIA). ***Comment:*** No specific guidance is reasonable at this stage.
5. The section on comparators is very general and should provide more concrete guidance. (EFPIA). ***Comment:*** Section on comparators (Choice on comparators) should be seen in line with the section 1.2 (Treatment).
6. The IPTA task force expresses enthusiasm in partnering with both the EMEA and the FDA in the undertaking to establish appropriate testing of medicines used for transplantation in children and to better understand how they can be optimally employed in treating this vulnerable patient population. We feel that the draft document is of high quality and has certainly the potential to improve the proper development of new immunosuppressant for solid organ transplantation. However, one concern of the IPTA task force is that paediatric aspects are underrepresented in this document: only one paragraph (Section 4.5., Studies in special populations) addresses briefly paediatric issues. The IPTA task force feels that the paediatric solid organ transplant population is unique and distinct; we would therefore recommend that paediatric issues should be ***considered*** and ***incorporated into all aspects*** of the guidelines with unique aspects where appropriate. (IPTA). ***Comment:*** Specific scientific and methodological points are expanded in Section 4.5 for consistency reasons.

7. The point in time within the investigational plan of a novel immunosuppressive drug, when it should be tested in the pediatric transplant population, should be defined. Ideally, the pediatric trial design could be developed while the ***adult Phase III study is ongoing***, but the trial should not begin until initial safety and efficacy data is available from a large adult trial that *indicate a* ***favorable benefit/risk ratio***, because some relevant side effects may become apparent only in large clinical trials. (IPTA). ***Comment:*** Considered.
8. The appropriate design of clinical trials for novel immunosuppressants in paediatric patients should be defined. One has to define, for which patient groups only ***PK/safety data*** are required and sufficient, and for which patients a ***randomized controlled trial*** compared to a standard regimen is required. Also studies in paediatric patients should be ***sufficiently powered*** to evaluate safety and efficacy in children. One has to define, ***which organ*** transplants might be most appropriate for larger trials as compared to PK/PD and other small trials. Kidney transplants in older children and liver transplants in infants may be the prototypical models for designing larger trials, with smaller confirmatory investigations with other transplant models. The IPTA task force may be able to be of help in enabling enrollment of adequate patient populations. (IPTA). ***Comment:*** These specific issues should be treated on case by case.
9. Age-related issues within the paediatric age group must be acknowledged. There are registry data at least for paediatric renal and liver transplant recipients that infants ***below the age of 2 years*** experience ***less frequent acute rejection episodes*** and are ***more prone to infections***; therefore, ***they probably need less immunosuppressive therapy*** than children above the age of 2 years. In addition, appropriate study endpoints for clinical trials in paediatric patients are to be defined. They should comprise beside others ***growth***, ***pubertal development***, ***quality of life outcome criteria*** and ***compliance***, which are major outcome variables for studies in adolescents. (IPTA). ***Comment:*** Considered.
10. A specific issue are potential age- and development-related ***side effects*** of novel immunosuppressive drugs in paediatric patients. One example is the potential induction of ***hypergonadotropic hypogonadism*** by mTOR inhibitors, which, at least to our knowledge, has never been studied systematically in paediatric and adolescent patients. The task force feels that the statements in Section 4.5. ("For adolescents, PK/PD studies are sufficient") should be modified. (IPTA). ***Comment:*** Considered.
11. The paediatric-specific issue of primary EBV infection and EBV-triggered PTLD should be the focus of discussion. It might be reasonable to begin trials in ***older children*** before including infants, especially with the sense that they may need ***less immunosuppression*** and have higher risk of primary EBV infection and PTLD. Data on use in EBV-negative adult individuals would be helpful before exposing EBV-negative children to potential risks. (IPTA). ***Comment:*** Considered in general terms.
12. The most important consideration for future RCTs is to build in a provision for the ***long-term follow up*** of all patients recruited. These will be crucial data currently sadly lacking in the literature. The problem is (to) convince those who are funding the study to provide sufficient resource for this to be undertaken. (IPTA). ***Comment:*** Considered in general terms.
13. Future randomized controlled trials on ***novel immunosuppressants*** in paediatric solid organ transplant recipients should comprise also mechanistic and pharmacokinetic/pharmacogenetic sub-studies. Such sub-studies are frequently undertaken in the adult population, but the results cannot necessarily be extrapolated to the paediatric patient population, because not only drug-metabolizing enzymes, but also drug targets such as enzymes or receptors in specific immune cells may be developmentally regulated. (IPTA). ***Comment:*** No specific proposals for paediatric Tx.

14. The guidelines state that gender, age, immunological risk etc should be included in the study, but 'second choice' organs are not mentioned. Because of the current lack of donors, 'second choice' organs are becoming more and more important in transplantation. EKHA recommends that this is therefore taken into consideration by the guidelines. (EKHA). ***Comment:*** Second choice donors are discussed as extended donors in general part. Other criteria to exclude additional donor variables are stressed in several places therefore no additional provisions seem reasonable.
15. This document considers these circumstances and provides guidance for proper development of new immunosuppressant for solid organ transplantation. (Fresenius Biotech GmbH). Proposal is for line 22: "This document considers these circumstances and provides guidance for proper development of new immunosuppressant for solid organ transplantation. **For established substances a more flexible approach can be taken.** (Fresenius Biotech GmbH). ***Comment:*** Well established substances are discussed in guideline already (as comparator). New indications for established substances products should be investigated properly.
16. As a matter of fact this guideline that also addresses "Other treatment concepts that are explored include steroid withdrawal or total avoidance of steroids, drug minimisation and induction of tolerance"(line 19 - 20) is very much related to the aim and topics explored within the Riset consortium. Also (line 338): "Clinical studies aiming to investigate the development of immunological tolerance are encouraged." Part of the Riset consortium activities aim at such clinical studies, hence, this is particularly acknowledged. The document was very positively received as a useful, reasonable and well documented set of guidelines. It was considered a bit vague in some parts (see below) and some comments of general relevance were made: The general Riset comments relate to underlining more strongly the importance of issues related to ***quality of life*** of patients, the specificities of ***living donors*** and their follow-up and to specific aspects in patients with ***cancers***. In general the uses of ***abbreviations*** do not add clarity to the document. ***Comment:*** Quality of life and living donors are reflected additionally after public consultation phase. For cancer patients and abbreviations - see specific comments.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no. + paragraph no.	Comment and Rationale	Outcome
1. Executive summary + Introduction		
Line 28 - 29	"Exploratory trials should reflect concepts of immunosuppression for investigated agent and base strong rationale for confirmative investigations". – **Add process after agent; strong rationale is not a well defined concept.** (RISET). ***Proposed text:*** Exploratory trials should reflect concepts of immunosuppression for investigated agent ***or process*** and base strong rationale, ***that needs to be explicit*** for confirmative investigations".	Useful clarification as regards process. Accepted. Further precisions not necessary.
Line 42	"Due to the dynamics of the field, frequent revisions and amendments are foreseen": **yes but a provisional calendar would help.** (RISET).	This issue is out of the scope of this guideline.

	Proposal: Add "***typically on an annual basis***". [or any other reasonable time period that make sense]	
Line 70	« acceptance of extended criteria donors"; **please give examples**! (RISET). ***Proposal:*** Add, such as … and **give several examples of such criteria (age, quality of function of the organ, compatibility rules disregarded, etc. There is also the risk of commercial circuits.**	This area is under constant development and could be left open for this guideline.
Lines 72-84	Given the improved graft survival rates with current practice, and that it is not ethically acceptable to deliberately target a sub-therapeutic dose level, it would be useful to provide ***examples*** on what evidence from ***exploratory studies*** would constitute adequate dose finding before phase 3 (e.g. rejection rates). (EFPIA).	Current position to seek for same EP within shorter time frame is encouraged.
Lines 90-95	Acknowledging that acute rejection incidence has become low, and chronic "graft deterioration" has become increasingly important, does this imply that new claims should favour agents/ regimens that specifically address these matters? Please provide clarification as to whether claims focusing on improving graft deterioration are favoured? (EFPIA).	No priorities are expected to be encouraged by this guideline.
Line 106	Suggest adding Mycophenolate Mofetil as an example. (Roche and EFPIA). *Please amend as follows: 'Inhibitors of de novo nucleotide synthesis: purine synthesis* (e.g. **Mycophenolate mofetil**, *mycophenolic acid…*	Accepted.
Lines 111-114	*"Some immunosuppressive drug use reflects clinical experience only, and region specific differences are common…".* Does this imply that such approaches are acceptable, e.g. in selecting an active comparator in a clinical trial? We understand this could be a subject requiring specific discussions with EMEA. (EFPIA). **It could be advisable to seek EMEA Scientific Advice to discuss this topic** An additional statement is proposed. Cyclophosphamide (alkylating agent) is mentioned but is not assigned to a mechanism of action category. It would be helpful to clarify this as the information on this drug comes straight after the list of different Mechanisms of Action	Considered already.
Line 111 and 112	It is not clear to which Mechanism of Action category cyclophosphamide (alkylating agent) belongs. It would be helpful to clarify this as the information on this drug comes straight after the list of different Mechanisms of Action. (Roche).	Considered.
Line 120	Initial therapy, "triple therapy": Since there other mycophenolic acid products available this	Accepted

	language should include MPA, not only MMF. (EFPIA). Please add "**<u>mycophenolic acid</u>**"	
Section 1.2, line 140	In an effort to assure consistency within the guideline (see also Section 4.1, Lines 197-198) and to maintain the inclusion of 'prophylaxis" language when referring to CAD, we suggest the addition of "and/or prophylaxis" in the following context. (EFPIA). *'Treatment* **<u>and/or Prophylaxis</u>** *of CAD.* *At present, no approved therapy exists for CAD. Many different approaches have been tested, but are not sufficiently supported by data.'*	Accepted
4. MAIN GUIDELINE TEXT		
Line 211 and 212	Patient inclusion in clinical studies should reflect the intended target population, but may be restricted, at least in initial clinical studies, e.g. based on immunological risk if properly justified. Suggest adding sentence on applicability of the studies. (Roche). Patient inclusion in clinical studies should reflect the intended target population, but may be restricted, at least in initial clinical studies, e.g., based on immunological risk if properly justified. **In cases when the target population is restricted in the initial studies, it may still be possible to extend the initial indication to the intended target population during the initial MAA, provided this can be appropriately justified and supported**	Further explanations seems adding more redundancy to the guideline.
Line 211 and 212	*Patient inclusion in clinical studies should reflect the intended target population, but may be restricted, at least in initial clinical studies, e.g. based on immunological risk if properly justified.* Suggest adding sentence on applicability of the studies. (EFPIA). *Patient inclusion in clinical studies should reflect the intended target population, but may be restricted, at least in initial clinical studies, e.g. based on immunological risk if properly justified.* **<u>In cases when the target population is restricted in the initial studies, it may still be possible to extend the initial indication to the intended target population during the initial MAA, provided this can be appropriately justified and supported</u>.**	Further explanations seems adding more redundancy to the guideline.
Line 209-210	(RISET). ***Proposal***: "validated scales for the assessment of **global transplantation risk… ». A reference to such existing scales and a suggestion of comparative studies between countries would be welcome**.	This area is under constant development and could be left open for this guideline.

Line 211	(RISET). ***Proposal***: "Patient inclusion in clinical studies should reflect the intended target population" **Some populations are special, like cancer patients; may be an example naming the criteria to characterize a "target population" would be welcome; for example there may be differences of responses to treatment according to genetic factors or environmental exposure; should those criteria be taken into account?**	Unless clear consensus regarding specificities for cancer patients and genetic factors specific for immunosuppressants in transplantation are available to be generalized for all immunosupressants it would be preferable to stay as it is for this guideline.
Lines 213-250	EMEA acknowledges that patient and graft survival has improved, and the number of graft failures attributed to acute rejection has decreased, yet other factors now account for more of the longer term morbidity and mortality (Lines 86-95). We suggest the addition of ***additional organ specific risk factors*** that may have a negative impact on clinical outcome, from the UNOS ECD criteria, be added to the listing here. (EFPIA). Please add to the 4th bullet, line 248: *'Organ specific risk factors, e.g. cold ischemic time, complicated transplant vascular anatomy; organ atherosclerosis, left ventricular hypertrophy or ventricular dysfunction in heart transplantation; liver steatosis for liver transplantation*; **elevated creatinine; history of stroke; history of hypertension.'**	Extension of non-specific risk factors is not considered to be essential.
Line 224	(RISET). "number of HLA mismatches » ; it would be good to specify the level of resolution of the typing. ***Proposal***: "number of HLA mismatches ***and level of resolution of the typing considered***"	Accepted and extended to both recipient and donor typing.
Line 256 – 257	(RISET). « region-related imbalances, e.g. as regards global transplantation risk to be taken into account in the analysis of treatment results". It would be good to suggest validated sources of such information and to indicate that detailed methodology in the description of the protocol should be given on those aspects in order to allow to actually take this into account.	This level of detailing is not foreseen to be given in this guideline.
Line 262	(RISET). "The ultimate aims of solid organ transplantation are improved survival and improved quality of life while the goals of development of new immunosuppressants are"… **The quality of life is being also influenced by immunosuppression ; it is suggested to underline more the quality of life issue.**	Considered already.
Line 272	This should be changed to reflect graft failure/**graft loss** (Roche and EFPIA).	Graft loss is part of graft failure.
Line 275	As the draft guideline acknowledges the role of evaluation of acute rejection in immunosuppressive therapy (Lines 282-286), in certain instances, it may be appropriate to qualify acute rejection in terms of ***severity of outcome***, treatment or ***refractory to treatment***. It might also be useful to define the ***grading system*** to be used for the BCAR diagnoses in a particular organ transplant study, as 1) different grading systems and criteria are used for different solid organ transplants,	Clarity is useful. Accepted in modified version (including pathologic grading scheme to be used for the specific type of organ transplant, severity of outcome, treatment, response to treatment, **as appropriate**).

	2) even for one type of organ, there may be differences in the histological criteria or systems used. (EFPIA). Revise Line 275 to read: c) *biopsy confirmed acute rejection BCAR* **<u>(including pathologic grading scheme to be used for the specific type of organ transplant, severity of outcome, treatment, response to treatment)</u>.**	
Lines 276-279	It is acknowledged that graft function is an important efficacy endpoint in solid organ transplantation, and that graft dysfunction should be considered in the evaluation of the efficacy failure rate. However ***flexibility*** should be provided about the appropriate statistical analysis for such endpoint. The galready noted that incorporation of this variable as a component of a composite primary endpoint may not be appropriate (e.g. to avoid mixing categorical and continuous components in the composite endpoint) and that separate co-primary endpoints may be used. This may imply that the study would have to be powered for both co-primary endpoints. For some organs, e.g. lungs and hearts, there may not be sufficient experience on "clear-cut and discrete criteria" that predicts long-term outcomes and ensure assay sensitivity for a co-primary endpoint (e.g. when superiority could have been demonstrated on the primary composite endpoint (patient/graft survival and BCAR). Therefore, we are suggesting a possible rewording. (EFPIA). Please **amend** as follows: *d) graft dysfunction* ~~*(defined by*~~ **<u>if</u>** *clear-cut and discrete criteria*~~*) for at least kidneys, lungs and hearts*~~ **<u>exist.</u>** ~~*Alternatively, and in order to increase the sensitivity of clinical studies, co-primary endpoints may be used: the composite of a) to c) plus d) as a continuous variable.*~~ **<u>Alternatively, graft function may be assessed separately from the composite primary endpoint of a) to c), as a key efficacy endpoint assessed through the appropriate categorical or continuous variable. It is recommended to seek Scientific Advice in case of uncertainties on the most appropriate variables and analytical methods to assess graft dysfunction in a specific development program.</u>**	More clarity is useful. Categorical variable of (dys)-function seems reasonable. Acceptable. Accepted in modified version: d) graft (dys)-function (defined by **<u>best available</u>** clear-cut and discrete criteria) for at least kidneys, lungs and hearts. Alternatively, and in order to increase the sensitivity of clinical studies, co-primary endpoints may be used: the composite of a) to c) plus d) as a continuous **<u>or categorical</u>** variable, **<u>as appropriate.</u>**
279	If a composite endpoint consists of a) patient death, b) graft failure, c) BCAR, and d) graft dysfunction (defined by clear cut and discrete criteria), as defined in the draft text, then graft ***dysfunction must be expressed as a categorical variable*** (e.g. %) like the other variables of the composite endpoint. When co-primary endpoints are used rather than the 4-part composite endpoint cited above, there is no reason to limit graft function (or graft dysfunction as currently written) to a	Accepted in modified version: d) graft (dys)-function (defined by **<u>best available</u>** clear-cut and discrete criteria) for at least kidneys, lungs and hearts Alternatively, and in order to increase the

	continuous variable as proposed in the draft text. For instance in renal transplantation, categorical renal function variables have been reported to be predictive of long-term graft survival (ref. Hariharan S et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int*; 2002: 62:311-318). In addition, the way the text is written *"…plus d) as a continuous variable."* does not seem correct as d) in line 276 refers to graft dysfunction. Where a continuous variable is permitted, we propose that the term graft function rather than graft dysfunction be used. (Wyeth). Modify end of sentence to read: *"(…) plus ~~d/ as a continuous variable~~ graft function as a continuous or categorical variable."*	sensitivity of clinical studies, co-primary endpoints may be used: the composite of a) to c) plus d) as a continuous **or categorical** variable, **as appropriate.**
Line 283, paragraph 4.3.1	'patient graft survival and patient survival' should be written in the reverse order given the relative importance of the two. (EKHA). 'patient survival and patient graft survival'	Accepted
Line 286	(RISET): "These endpoints are applicable to both treatment naïve cases and to cases resistant to rejection therapy." The sentence reads strange! ***Proposal: These endpoints are applicable to both treatment of naïve cases and of cases resistant to rejection therapy.***	Accepted in version: "These endpoints are applicable to both treatments of naïve cases and of cases resistant to rejection therapy.".
Line 287	In an effort to assure consistency within the guideline (see also Section 4.1, Lines 197-198) and to maintain the inclusion of 'prophylaxis" language when referring to CAD, we suggest the addition of "and/or prophylaxis" in the following context. (EFPIA). Please amend as follows: "*The primary efficacy endpoint for CAD treatment* **and/ or prophylaxis** *should capture preservation of transplant organ function, graft and patient survival*."	Accepted
Line 288 paragraph 4.3.1	'graft and patient survival' should be written in the reverse order given the relative importance of the two. (EKHA). 'patient and graft survival'	Accepted
Lines 289-312	Secondary endpoints: The list describes current practice, but the evidence base and relevance of each is variable and potentially controversial. Similarly, relevance for some is organ specific. Please provide specific guidance as to ***flexibility*** for specific trials and specific organs. Clarity should reflect evidence base and relevance for each potential secondary endpoint. (EFPIA).	The details of non-specific examples are not essential.
291	Section 4.4.3.b (lines 413-4), states that the primary endpoint should be a minimum of 12 months. While it is reasonable to collect data for another 12 months (***24 months*** after randomization), it is not reasonable to impose a mandatory collection of graft function, graft	More clarity is given distinguishing CAD from AR.

	survival, and patient survival at 3 years (or at 5 years) as secondary endpoints in all solid organ transplantation trials (and this includes in our opinion confirmatory phase 3 pivotal trials). First, all currently EU-approved agents are approved for the treatment or prevention of acute organ rejection. No agents are approved for the prevention of chronic allograft dysfunction (***CAD)*** which would indeed require longer periods of evaluation. Second, it is very difficult to keep patients on ***blinded therapy beyond 2 years***, or to keep them in an open trial more than 12 months after reaching the primary endpoint, and the outcomes become public. Interpreting trials beyond the point when a majority of patients remain on assigned therapy is difficult. Finally, making all confirmatory registration trials a mandatory 5 years in duration would discourage research in transplantation therapy and the discovery of new immunosuppressive agents in this field. At present, we believe that a mandatory 2-year follow-up would be the best compromise. (Wyeth) Modify bullet point to read: *"(…) e.g. 6, 12 and 24 months ~~and 3, 5 years~~."*	Modified as: …e.g. 6, 12, **and 24** months; **for CAD:** 3, 5 years.
292	See the previous point. (Wyeth) Modify bullet point to read: "(…) e.g. 6, 12 and 24 months ~~*and 3, 5 years*~~, with (…)"	More clarity is given distinguishing CAD from AR. Modified as: …e.g. 6, 12, **and 24** months; **for CAD:** 3, 5 years.
294	See the previous point. (Wyeth) Modify bullet point to read: "(…) e.g. 6, 12 and 24 months ~~*and 3, 5 years*~~, with (…)"	More clarity is given distinguishing CAD from AR. Modified as: …e.g. 6, 12, **and 24** months; **for CAD:** 3, 5 years.
296	In line with our suggestions above to limit mandatory reporting of graft function, graft survival, and patient survival to 24 months following randomization, later time points should be added as "other frequently reported endpoints". Regarding proteinuria, this is increasingly recognized as an independent predictor of allograft survival in renal transplantation (ref. Halimi JM et al. Respective predictive role of urinary albumin excretion and nonalbumin proteinuria on graft loss and death in renal transplantation. *Am J Transplant* 2007; 7: 2775-81.) Additionally, renal dysfunction is problematic even in nonrenal solid organ transplantation (Ojo AO et al. Chronic renal failure after transplantation	Issue solved in different way. For the time being, proteinuria is still under way to be validated for specificity and sensitivity as a new BM/surrogate marker.

	of a nonrenal organ. N Eng J Med. 2003; 349:931-40). (Wyeth) Add the following bullets to the section *"Other frequently reported endpoints include:"* - ***"Graft function at additional time points e.g. 3 and 5 years*** - ***Graft survival at various time points e.g. 3 and 5 years, with reasons for graft failure*** - ***Patient survival at various time points e.g. 3 and 5 years, with reasons for death*** ***Proteinuria"***	
Line 329	How are the '*main immunosuppressives*" to be defined? Those planned for use in the clinical trials with the sponsor's drug? Or the combination regimens that will be approved? Or other? Please clarify. (Roche and EFPIA).	All inclusive.
Line 321	(RISET): "The pharmacokinetics of the experimental medicinal product should be documented in accordance with relevant guidelines » **It would be valuable to indicate some sources of such guidelines if available** ***Proposal:*** "...with relevant guidelines, **such as…**"	Other than mentioned in Section 3 "Legal basis" seems redundant.
Line 329	There is no rationale for conducting interaction studies if there is not much chance of such an interaction. Suggest that this is deleted. (Roche) *…..even if PK interactions are considered unlikely'*	To be deleted part … *even if PK interactions are considered unlikely'*.
Line 330	(RISET). "...population PK studies may be informative **It was not found very clear what kind of population studies were meant here. Could this be specified or an example given?**	None is for exclusion.
Line 335	(RISET). "Future developments, such as immunotolerance induction, may generate a need for new valid biomarkers". **This is a reality already today (the consortium Riset is largely engaged in such work) and should not by left as "may".** ***Proposal:*** "Future developments, such as immunotolerance induction, ~~***may already***~~ generate a need for new valid biomarkers".	Accepted.
Line 340-344	(RISET). "….Currently tests predictive of over- and under- immunosuppression are under development and when reasonably validated, their inclusion at least in exploratory studies is encouraged." **This is important and the definition of "reasonably validated" could be further documented, as it is a major concern in exploratory studies to decide what tests are sufficiently validated to be used, not yet at large but for such studies.**	This is general area of qualification of biomarkers that is under preparation in separate EMEA documents. As this is not specific to transplantation, proposal is to leave it open in this guideline.
Line 345	In addition to prospective trials to evaluate the need for PK and/or PD monitoring strategies, it would be useful to have guidance around the value of retrospective PK-Clinical Outcome analysis from randomized dose controlled studies to determine the need for randomized	This general requirement is covered in Section "Legal basis" of guideline.

	concentration controlled studies in Phase 3 development. Simulation studies suggest that exposure-response information derived from dose controlled studies are often likely to be more useful in identifying optimal therapeutic concentrations than prospective concentration controlled studies [Br J Clin Pharmacol. 2007 Sep;64(3):266-77]. Since PK/PD modelling analysis can serve to support Therapeutic Drug Monitoring guidance it is proposed to include this in the guideline. (EFPIA). Please add the following sentence to the last paragraph of section 4.4.2: **'PK/PD modelling analysis could also serve to support clinical practice monitoring.'**	
Line 363-364	The guideline states "*Parallel group, randomised, placebo-controlled (when feasible) add-on trials are recommended, where background therapy should be a transplantation regimen acceptable from a clinical perspective"*. This statement seems to imply that those regimens do not necessarily need to be ***approved*** from a regulatory perspective, but should be well accepted from a clinical perspective – is that a correct interpretation? (Roche and EFPIA).	This issue is covered in section "Choice of comparator".
Line 388-393	*Most clinical trials are designed to compare the efficacy or safety of a new regimen with a well established standard therapy. Comparative trials should be designed as randomised, parallel group studies according to the aims of product development: (A) to substitute one or several therapeutic components of well-established immunosuppressive regimens to improve efficacy, safety or compliance or (B) as add-on to improve efficacy of an approved regimen, or (C) to introduce new concepts of treatment replacing current well established therapy regimen.* In the cited paragraph - new regimen, well established standard therapy & approved regimen are mentioned, and for each of the situations A, B & C you could compare the "new regimen" with the "well-established standard therapy". Is it correctly understood that the "well-established standard therapy" does not necessarily need to be ***approved from*** a regulatory perspective but should be the current therapy used in clinical practice, provided there is enough evidence to support the use of this regimen? If this is a correct interpretation – how to justify that a certain therapy is the current standard therapy? Suggest a clarification to the text. (Roche).	This issue is covered in section "Choice if comparator". This sections relates to standards (they should reflect well established versions of comparators, may cover several approved versions, etc).
Line 392	Please clarify how an add-on trial to improve efficacy of an approved regimen might impact claims for additional labelling. For example claims using multiple drug regimens, reducing drug(s) in an approved regimen, etc. (EFPIA).	No examples specific to transplantation area are reasonable to highlight.
Lines 398-405	We acknowledge that the choice of the comparator is a company's decision and it's an area where approved and non-approved regimens coexist...If the strategy is discussed with regulators prior to initiating the early studies, it will ensure the data generated will be viewed	Certain clarity is useful (remaining is not excluded):

	as relevant for justification of the Phase 3 design. It is assumed that this paragraph about a "non-approved comparator" only refers to a medicinal product, not to a regimen? (See further comment on line 388-389 regarding justification required to confirm that a regimen/drug is the current standard of care in the transplant indications). (Roche and EFPIA). It is suggested to revise the text for better clarity. *"……it is advisable ~~to reach~~* **to seek** *European regulatory advice with respect to the choice of comparator prior to the initiation of confirmatory studies.* **Such advice may also be useful prior to initiation of earlier dose finding studies.**"	*"……it is advisable ~~to reach~~* **to seek** *European regulatory*
Line 400	(RISET). "that regiment" ***Proposal:*** "that ***regimen***"	Accepted
Line 400	We suggest the addition of a statement to reflect that use of standard of care may also be appropriate when the evidence-based practice of immunosuppressive therapy has advanced ahead of regulatory evaluation/approvals. For example, the combination of tacrolimus and mycophenolate mofetil is the most commonly used immunosuppressive regimen in renal and liver transplantation, and has become the standard of care despite lacking regulatory approval. Its use is supported by safety and efficacy data from many multi-center trials. As such, trials incorporating other comparators are less informative to clinicians and also operationally less feasible. (EFPIA). A rewording is thus proposed. "*If an approved regimen already exists, active ~~a~~ comparison with that regiment is ~~necessary~~* **recommended**. I*n the absence of* ***an*** *approved regimen for a given indication* **or where the standard clinical practice is use of a non-approved regimen,** *best standard practice should be employed."*	Certain amendment is useful: *"If an approved regimen already exists, active ~~a~~ comparison with that regiment is ~~necessary~~* ***strongly*** **recommended**. I*n the absence of* ***an*** *approved regimen for a given indication* **or where the standard clinical practice is use of a non-approved regimen,** *best standard practice should be employed,* ***if justified****.".*
Line 402-405	*With respect to the choice of non-approved comparator****(s)****, it is advisable to reach European regulatory advice with respect to the choice of comparator****(s)*** *prior to the initiation of confirmatory studies.* (Roche).	Accepted
Line 405	The use of an ***external control group*** may be possible in certain cases and the guideline should reflect this possibility. (EFPIA). Add the following at end of line 405: "**The use of an external control group (i.e. historical controls) can be explored in special cases where the endpoints are objective and the impact of baseline and treatment**	This should be left for scientific advice.

	variables on the endpoint is well characterized thereby controlling the introduction of selection bias. The acceptance of an historical control will require adequate justification and prior discussion".	
Line 407-408,	It is understood that in general 12-month data are required for an "induction prophylaxis study". However, there should be the possibility to submit an application with ***6- month*** results if the data are ***very convincing*** and provide longer-term data as a follow-up submission. This should be reflected in the guideline. (EFPIA). Please add the following after line 408: **"The use of 6m data would require demonstration of a clinically relevant and statistically significant difference in efficacy or safety over existing therapy".**	This should be left for scientific advice.
Line 421	In heart transplantation also "renal function at baseline" is considered a risk factor for study outcome. (EFPIA). Please add '**stratification for renal function at baseline**' to the list in heart transplantation	The list that is mentioned encounters just procedure-related and treatment related RFs. Baseline factors are given in line 430.
Line 424	In liver transplantation also "hepatic artery thrombosis" is considered a risk factor for study outcome. (EFPIA). Please add '**hepatic artery thrombosis**' to the list in 424	Accepted
Line 470	(RISET). "...during a time period of not less than 10 years. This period is needed for safety studies regarding claim of comparative clinical carcinogenic potential." **This period of surveillance should also be notified to the patient at time of information.** ***Proposal:*** "…"...during a time period of not less than 10 years. This period is needed for safety studies regarding claim of comparative clinical carcinogenic potential. ***Patients should be informed of this time period before consenting."***	The practicalities of Informed consent are already covered in other relevant legal documents and guidelines.
470-471	Whereas it is recognized that malignancy is complex and that a long period of observation along with careful control of risk factors is necessary to make conclusions on overall oncogenic potential as well as the risk of many de novo cancers, there are recurrent cancers that could be studied in periods much shorter than 10 years. For instance, basal cell and squamous cell carcinomas are often recurrent with some patients having many in a single year. Also, patients undergoing liver transplantation in the presence of hepatocelluar carcinoma have a considerable risk of recurrence. Furthermore, it is considered highly unlikely that ITT follow-up could be maintained in a population of solid organ transplant recipients for a 10 year period. It is therefore suggested to revise this paragraph. (Wyeth)	Not endorsed for broad spectrum comparison that is of real relevance.

	Revise last sentence to read *"(…) 10 years. Any comparative claim for reducing the incidence or recurrence of malignancy should be adequately powered based on the incidence of occurrence or recurrence. Additionally, the patient population should be well characterized for the principal risk factors of the malignancy studied. ~~This period is needed for safety studies regarding claim of comparative clinical carcinogenic potential~~."*	
5. DEFINITIONS		
Line 479	The definition of "Biopsy-confirmed acute rejection (BCAR)" should be expanded by mentioning also the well established rating system for heart transplantation (ISHLT Grade). (EFPIA). Please add '...definition and rating system (such as Banff Grade >1 for renal transplantation **and ISHLT Grade >3A for heart transplantation**) and confirmed....'	Extension of examples is acceptable.
Line 500-502	The draft guideline states: *"**Triple therapy:** Immune suppression regimen with three immunosuppressants, usually a calcineurin inhibitor, an antiproliferative agent plus a corticosteroid.* ***Dual therapy**: Usually a calcineurin inhibitor or an antiproliferative agent plus a corticosteroid".* In 1.2 the term "antiproliferative agents is not included. Please use consistent terminology. (Roche and EFPIA). **'Triple therapy:** *Immune suppression regimen with three immunosuppressants, usually a calcineurin inhibitor, an antiproliferative agent* **(such as mycofenolate mofetil, azathioprine and/or sirolimus)** *plus a corticosteroid.* **Dual therapy***: Usually a calcineurin inhibitor or an antiproliferative* **(such as mycofenolate mofetil, azathioprine and/and sirolimus)** *agent plus a corticosteroid.'*	Examples are reasonable to limit to MMF only and in all therapies (including quadruple therapy). ***Triple therapy:** Immune suppression regimen with three immunosuppressants, usually a calcineurin inhibitor, an antiproliferative agent* **(such as MMF)** *plus a corticosteroid.* ***Dual therapy**: Usually a calcineurin inhibitor or an antiproliferative agent* **(such as MMF)** *plus a corticosteroid.* ***Quadruple therapy:** Usually: (1) induction therapy (prophylaxis); (2) calcineurin inhibitor; (3) an antiproliferative agent* **(such as MMF)** *and (4) a corticosteroid.*