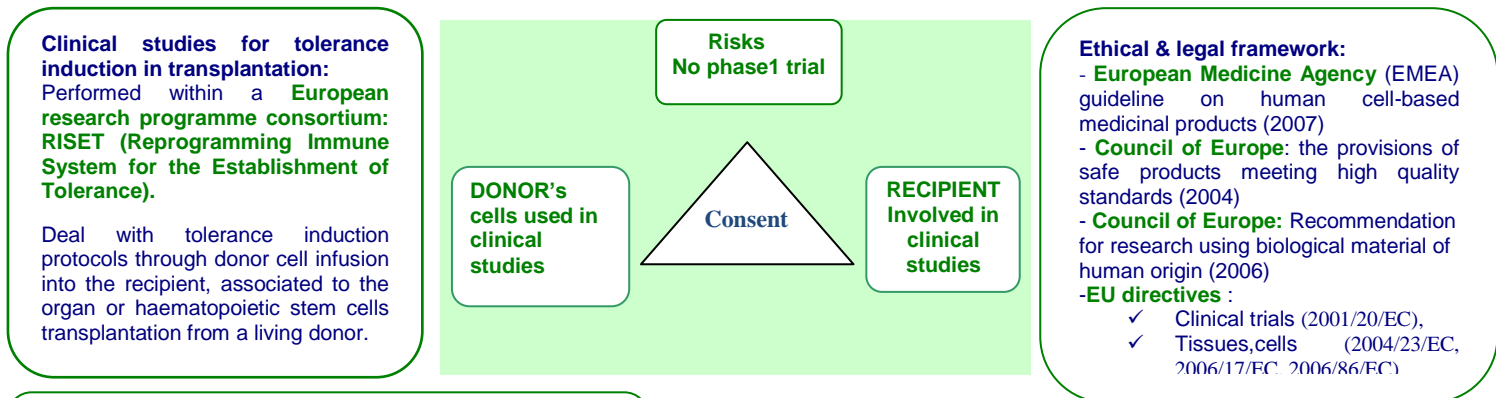


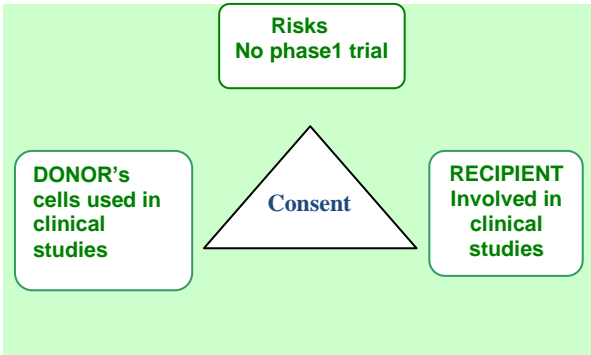
Recommendations proposed by an EU consortium regarding ethical aspects of pilot clinical assays for tolerance induction in transplantation

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Immunosuppression is needed to control rejection. It is efficient on the short term but has drawbacks for long term transplantation outcome and secondary effects. Tolerance induction could be a solution.



Clinical studies for tolerance induction in transplantation:
 Performed within a **European research programme consortium: Riset (Reprogramming Immune System for the Establishment of Tolerance)**.
 Deal with tolerance induction protocols through donor cell infusion into the recipient, associated to the organ or haematopoietic stem cells transplantation from a living donor.



Ethical & legal framework:
 - **European Medicine Agency (EMA)** guideline on human cell-based medicinal products (2007)
 - **Council of Europe:** the provisions of safe products meeting high quality standards (2004)
 - **Council of Europe:** Recommendation for research using biological material of human origin (2006)
 - **EU directives :**
 ✓ Clinical trials (2001/20/EC),
 ✓ Tissues, cells (2004/23/EC, 2006/17/EC, 2006/86/EC)

Specific dimensions are:
 The issues below are not individually new, but their association is unique. On account of the overlap between the therapeutic act and the research protocol it may be difficult for the patient to distinguish between the two acts.

Extract of the handbook of 10 recommendations related to these specific dimensions:
 → clinical researchers, ethics committees, health authorities.

Information and consent related to:

Risks
 Assessment of risks/benefits balance is tricky;
 ✓ Loss of a transplant may happen in a short period whereas the benefits of diminishing immunosuppression are long term.
 ✓ There is no phase I assay on healthy volunteers
How to deal with information about adverse events when assessing risks/benefits balance ?

Both recipient and donor involvement
 These tolerance induction protocols involve both donor and recipient:
 ✓ Need of an adequate information for both of them before beginning the trial
 ✓ Right to withdraw of the donor versus the right to participate of the donor in case of iterative donor cell procurement
How to deal with an adequate information and consent?

Risks/ Benefits balance
 Recommendation 1: That for tolerance pilot studies a **sufficient time period** is maintained between the enrolment of each patient in order that possible adverse events observed can be taken into account before the next patients are enrolled.
Discussion: how to define "sufficient time"? Criteria used may vary but should be explained when asking for ethical approval.
 Recommendation 3: That **specific research for constructing tools for assessing risk/benefit balance** in such protocols should be set up at European level.

Adequate information and consent
 Recommendation 4:
 a. That **independent informed consent** for the research should be given both by donor and recipient
 b. That both donor and recipient should be informed that the other, in addition to consenting to giving (receiving) the transplant, is also asked for consent to participate in the research part of the procedure including cell therapy
 c. That for such protocols an **extensive dialogue** with the donor and the recipient should be required with **specific information** provided about the study **that cannot be or is not included in general hospital information leaflet**
 d. That both donor and recipient should have the possibility of several days of reflection before the consent signature.
 Recommendation 7:
 a. That donor and recipient should be informed of the **peculiarities relating to the right to withdraw** from a tolerance induction study, since it can have an impact on the follow up of the tolerance induction for the transplant recipient
 b. That, for the recipient, information concerning the right to withdraw from the trial at any time should be given, as usual
 c. **That while maintaining the principle of withdrawal, the donor, when relevant to the protocol, should be informed about his/her responsibility towards the recipient who would, as a result no longer be able to continue to participate in the clinical tolerance study in case of donor withdrawal.**
Other recommendations
 Deal especially with information content, education of personnel, return of results, medical and psychological follow up.

This set of specific recommendations for ethics in tolerance induction clinical pilot studies has been validated within the Riset consortium (<http://www.risetfp6.org/>). It is currently being circulated for comments to various experts, committees, institutions and other stakeholders, prior to an open consultation and then its publication.

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