# Safety

## Adverse Events Definitions

*Adverse Event (AE)*

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs whether or not related to the study intervention. This definition includes physical signs, symptoms and laboratory test values. At study enrolment, laboratory values that fall outside the relevant reference range will not be reported as AEs.

*Serious Adverse Event (SAE)*

An adverse event that:

* Led to death
* Resulted in serious deterioration in the health of the subject that:
  + resulted in a life-threatening illness or injury
  + resulted in a permanent impairment of a body structure or a body function
  + required in-patient care or prolongation of hospitalisation
  + resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

This includes device deficiencies that might have led to a serious adverse event if:

1. suitable action had not been taken or
2. intervention had not been made or
3. circumstances had been less fortunate.

These are handled under the SAE reporting system.

Planned hospitalisation for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a SAE.

*Adverse Device Effect (ADE)*

An adverse event related to the use of an investigational medical device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. This definition also includes any event resulting from user error or from intentional misuse of the investigational device.

*Serious Adverse Device Effect (SADE)*

Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above.

*Unanticipated Serious Adverse Device Effects (USADE)*

Any serious adverse device effect which, by its nature, incidence, severity or outcome, has not been identified in section 10.4.

*Device Deficiency*

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling. Device deficiencies resulting in SADEs will be managed as detailed in section 10.5.

Device deficiencies that did not lead to an adverse event, but could have led to a medical occurrence if suitable action had not been taken, or intervention had not been made or if circumstances had been less fortunate will also be managed as detailed in section 10.5.

*Use error*

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.

## Causality of an AE in relation to the intervention

* + - *Highly probable*: Apparent relationship in time between AE and intervention. Relationship between AE and intervention is already known or expected and there is an appropriate temporal relationship between therapy and AE.
    - *Probable*: Known effect of the intervention with no possible other cause and appropriate temporal association.
    - *Possible*: AE likely to be associated with the intervention and no other explanation for the AE, or known effect of intervention that could also be associated with another concomitant therapy, illness or external cause.
    - *Unlikely*: Unlikely to be causally related; e.g. reaction occurred after intervention or is more likely to be due to another concomitant therapy, illness or external cause.
    - *Definitely not*: AE known to be caused by another concomitant therapy, illness or external cause.
    - *Not assessable*: Likelihood of AE not known, or relationship of AE to intervention, another concomitant therapy, illness or external cause is not clear. This category should be used very scarcely.

## Grade of severity

* *Mild (grade 1)*: patient is aware of symptoms but tolerates them easily. Symptoms do not interfere with daily activity.
* *Moderate (grade 2)*: patient experiences discomfort that interferes with normal activity. No treatment is required except acetaminophen.
* *Severe (grade 3):* patient is unable to carry out normal activity. Treatment is required.
* *Life-threatening (grade 4)*: emergency room visit , disabling or hospitalization.

## Adverse Events to be reported

* All adverse events as per the definitions in the Safety section (11.1)
* The following anticipated adverse events need to be reported within one week after becoming aware of the event irrespective of seriousness criteria:
  + Venous or arterial thrombosis
  + Rejection
  + Graft loss

The investigator will exercise his/her medical judgment in deciding whether a postoperative laboratory finding falling outside the relevant reference range or other abnormal assessment is clinically significant. However, if in the opinion of the investigator, the frequency or severity of the event is greater than would be expected then it must be reported.

## Adverse Events that do not require reporting

* The following adverse events are very common features in kidney transplant recipients and are not considered adverse events for the purpose of the trial:
  + Gastrointestinal problems (nausea, constipation and/or diarrhoea) related to the use of immunosuppression (such as mycophenolate acid derivatives)
  + Hypertension as a pre existing disease or induced by immunosuppression
  + Headaches related to immunosuppression
  + Anaemia, Leukopenia or thrombocytopenia related to immunosuppression
  + Transient hyper/hypocalcemia, hyper/hyponatremia, hyper/hypokalaemia, hyper/hypophosphataemia, hypomagnesemia are expected during the peri-operative period after kidney transplantation
  + Transient abnormal liver function tests induced by medication given to a kidney transplant patient
  + Peripheral oedema and hypoalbuminemia in the peri-operative period related to filling status and peri-operative management (until first 3 months after kidney transplantation)

## Recording adverse events and device deficiencies

It is the responsibility of the Local Investigator to ensure that all adverse events (including ADEs) and device deficiencies occurring during the course of the study are recorded. This will include but not be limited to:

* A description of the event
* The dates of the onset and resolution
* Action taken
* Outcome
* Assessment of relatedness to the device
* Whether the AE is serious or not
* Whether the AE arises from device deficiency
* Whether the AE arises from user error

Adverse events that occur during the course of the study should be treated by established standards of care that will protect the life and health of the study subjects.

It is the responsibility of the Local Investigator to collect all directly observed adverse events and all adverse events spontaneously reported by the subject. In addition each subject should be questioned about adverse events at each visit. Adverse events should be recorded on provided adverse event data collection forms within the eCFR.

## Reporting procedures for all serious adverse events

Reporting of all Serious Adverse Events will be done in accordance with the European Commission Guidelines on Medical Devices Serious Adverse Event Reporting (MEDDEV 2.7/3; December 2010).

It is the responsibility of the local investigator to ensure that all adverse events which fall in to the category of Serious Adverse Events (SAEs) and any device deficiencies (including Serious Adverse Device Effects (SADEs)) are reported to the coordinating centre, chief investigator, principle investigator, national investigators as soon as possible after becoming aware of the event but no later than 24 hours. Details to be included in the report are as Section 10.5.

Adverse event and serious adverse event reporting will be via the electronic data collection tool using the COPE SAE form, with SAEs being automatically forwarded to the Trial Coordinator and clinical reviewers by the reporting tool. The clinical reviewers are the Chief Investigator, Principle Investigator and Central Investigator and National Investigators. Reporting by Fax will provide a backup system (+32 (0)16 34 87 43) in the event that the online data collection tool is unavailable. The Fax machine is located in the central coordinating centre and is manned during normal office hours only.

Within the following 5 working days, the Local Investigator should provide any additional information on the initial SAE or device deficiency in the form of a written narrative using the same SAE form submitted initially – do not create a new form for follow up information. This should include a copy of the completed SAE form, and any other diagnostic or relevant information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the coordinating centre and clinical reviewers using the same electronic COPE SAE form.

On submission of an electronic SAE form, the co-ordinating centre and all of the clinical reviewers will be immediately notified by email. They will review SAEs and, if they feel they pose an immediate risk to patient health or safety, then they will report them to the DMC immediately and to the device manufacturer and research ethics committees within 2 calendar days of the principle Investigator becoming aware of the event.

All other reported SAEs will be reported to the DMC within 7 calendar days of notification, if appropriate. This will not include SAEs that may be expected as part of the risks of kidney transplant surgery. Adverse device events (SADEs, USADEs) and device deficiencies will also be reported to the device manufacturer. All SAEs will be followed up to resolution. The DMC will review the accumulating data at regular intervals.

The Principle Investigator will also inform all investigators concerned and the device manufacturer of relevant information about USADEs that could adversely affect the safety of participants.