Official Title: Safety and Efficacy of Kidney Transplantation in Patients with Aortoiliac Stenosis

Brief Title: Aortoiliac Stenosis in Kidney Transplantation (TASC)

NCT number: NCT06020534

RESEARCH PROTOCOL

(30 November 2022)

PROTOCOL TITLE 'Safety and Efficacy of Kidney Transplantation in Patients with Aortoiliac Stenosis'

Protocol ID	MEC-2017-1039
Short title	Kidney transplantation & aortoiliac stenosis
EudraCT number	***N.A.***
Version	**3.0**
Date	**30-11-2022**
Coordinating investigator/project leader	***Y. Fang*** ***y.fang.1@erasmusmc.nl*** Erasmus MC University Medical Center Rotterdam Department of Surgery Dr. Molewaterplein 40, 3015GD Rotterdam The Netherlands
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) ***<Multicenter research: per site>***	***Dr. R.C. Minnee*** ***r.minnee@erasmusmc.nl*** Erasmus MC University Medical Center Rotterdam Department of Surgery Dr. Molewaterplein 40, 3015GD Rotterdam The Netherlands N.A.
Sponsor (in Dutch: verrichter/opdrachtgever)	Erasmus MC, University Medical Center Rotterdam Department of Surgery Dr. Molewaterplein 40 3015 GD Rotterdam, The Netherlands
Subsidising party	***N.A.***
Independent expert (s)	***N.A.***
Laboratory sites <*if applicable*>	***N.A.***
Pharmacy <*if applicable*>	***N.A.***

PROTOCOL SIGNATURE SHEET

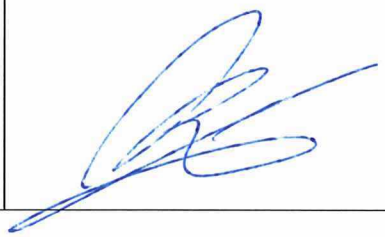
Name	Signature	Date
Sponsor or legal representative: ***Prof. dr. J.M. Hendriks*** **Head of Department of Surgery**		22/12/22
Principal Investigator: ***Dr. R.C. Minnee*** ***Surgeon***		14/12/22

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Kidney transplantation is the standard treatment for end stage renal disease (ESRD). Patients with aortoiliac stenosis are often ineligible for kidney transplantation due to the high risk of vascular complications.
Objective: To assess the impact of pre-transplant aorto-iliac stenosis on short and long term outcomes of kidney transplant patients.
Study design: Single-centre retrospective cohort study
Study population: Patients who underwent kidney transplantation in Erasmus MC between January 2010 and December 2020.
Intervention (if applicable): NA
Main study parameters/endpoints: Primary outcome measures are patient survival and death-censored graft survival and secondary outcome measures are renal function (such as eGFR) and the incidence rate of vascular complications.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This is a retrospective cohort study and no additional burden or risks will be applied to the patients.

1. INTRODUCTION AND RATIONALE

Kidney transplantation has been recognized as the paramount therapy for end stage renal disease. It increases the quality of life and survival rate of patients when compared with long-term hemodialysis(1). For patients who are ineligible for kidney transplantation, peritoneal dialysis or hemodialysis is the only alternative option. According to the annual data report of 2016 from the United States Renal Data System, the overall 5 year survival of hemodialysis patients is 41,6% and for peritoneal dialysis 59,4% (2). In comparison to those survival rates, the survival rate in patients receiving a deceased-donor kidney transplant was 75,7% and for patients receiving a living-donor kidney transplant 84,6%(2). Therefore, kidney transplantation should be the first choice of therapy in patients with end stage renal disease. There is little known about the proportion of renal transplant candidates who are considered ineligible by the transplant center. Kianda et al. investigated that 8% of the referred patients were considered ineligible and he described in 44% of the patients aorto-iliac atherosclerosis as the only reason (3). Other less frequent reasons for ineligibility in this study were severe ischemic heart disease, advanced age, metastatic neoplasia and severe impairment of general status or a combination of these factors. This shows that aorto-iliac atherosclerosis is the most frequent reason why patients are considered ineligible for kidney transplantation.

There are a number of concerns when considering kidney transplantation in patients with aortoiliac atherosclerosis. At first, it may complicate a vascular anastomosis between donor renal artery and recipient iliac artery during transplantation, sometimes even requiring a vascular procedure. Secondly, ‘steal syndrome’ can occur whereby the transplanted organ results in redirection of blood flow from an already vulnerable limb leading to distal ischemia. This syndrome has been showed in children undergoing renal transplantation(4). However, Northcutt et al. investigated this syndrome in adults and he did not show significantly deterioration of ischemia(5). The third concern is the physiologic impact of a complex operation on these critically ill patients(6, 7). Finally, a recent study concluded that aortic calcification index can progress after transplantation and represent a post-transplant cardiovascular event risk factor(8). As a result of these concerns, aorto-iliac atherosclerosis is a relative contraindication for kidney transplantation.

Over the years, a few case series and case reports have been published about aorto-iliac calcifications in renal transplant patients requiring a vascular procedure(6, 7, 9-18). Those case series report very successful short term survival and graft function. However, the impact of aorto-iliac calcifications on long term survival in kidney transplant patients remains unclear. Because of the poor survival of patients requiring dialysis, broader patient selection for kidney transplantation is desirable. The present study aims to assess the impact of pre-transplant aorto-iliac stenosis on short and long term outcomes of the kidney transplant patients.

2. OBJECTIVES

Primary Objective: This study aims to assess the impact of pre-transplant aorto-iliac stenosis on short and long term outcomes of kidney transplant patients.

3. STUDY DESIGN

This single-center retrospective study includes all kidney transplant patients who underwent kidney transplantation in Erasmus MC between 2010 and 2020. Data of patient characteristics, operation details and long-term outcomes will be collected. All patients will be divided into non-stenosis group and stenosis group based on the existence of pre-transplant aortoiliac stenosis. Propensity score matching will be used to make the baseline characteristics comparable between two groups. Patient survival, graft survival and long-term renal function of the two groups will be compared to indicate if the aortoiliac stenosis has an impact on the survival of transplant patients.

4. STUDY POPULATION

4.1 Population (base)

The research population are patients (n= ~2000) who underwent kidney transplantation in Erasmus MC between Jan 2010 and December 2020. Based on the pre-transplant existence of aortoiliac stenosis, all patients will be divided into non-stenosis group (n=~1800) and stenosis group (n=~120).

4.2 Inclusion criteria

Patients who underwent kidney transplantation in Erasmus MC between Jan 2010 and December 2020 will be included in the study.

4.3 Exclusion criteria

Patients under 18 years old and who underwent combined kidney and liver transplantation will be excluded from the study.

4.4 Sample size calculation

Sample size calculation is performed by G*Power for future use of t test. Both the accepted false positive and negative rate is 5%. The results indicate the sample size should be at least 105 in each group to reach a reliable answer, which is feasible based on the current patient population.

The protocol of power analyses are as follows:

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	0,5
	α err prob	=	0,05
	Power (1-β err prob)	=	0,95
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	3,6228442
	Critical t	=	1,9714347
	Df	=	208
	Sample size group 1	=	105
	Sample size group 2	=	105
	Total sample size	=	210
	Actual power	=	0,9501287

5. TREATMENT OF SUBJECTS

NA

5.1 Investigational product/treatment

<Please give a description of the intervention (medicinal product, medical device, food supplement, radiation, surgery, behavioural interventions, etcetera). Also use of comparator or placebo should be described.>

5.2 Use of co-intervention (if applicable)

< Please describe what subjects should do and not do (e.g. use co-medication, adequate contraception, diet). If it is allowed to use co-medication or other kind of intervention, it should be specified on forehand what is allowed.)>

5.3 Escape medication (if applicable)

<Please describe type, dose per unit and maximum dose allowed.>

6. INVESTIGATIONAL PRODUCT

NA

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

<One may refer to the Investigator's Brochure (IB), Investigational Medicinal Product Dossier (IMPD), Summary of Product Characteristics (SPC) or a similar document (if applicable), by mentioning the relevant pages in that document. Be sure that the information is up to date and references to peer reviewed papers in (biomedical/scientific) journals should be given where appropriate.>

6.3 Summary of findings from clinical studies

<See explanatory text of chapter 6.2, including remark>

6.4 Summary of known and potential risks and benefits

<See explanatory text of chapter 6.2, including remark>

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

<Please describe the p*rocedures for the shipment, receipt, disposition, return and destruction of the investigational medicinal products.>*

7. NON-INVESTIGATIONAL PRODUCT

NA

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

<One may refer to the Investigator's Brochure (IB), Investigational Medicinal Product Dossier (IMPD), Summary of Product Characteristics (SPC) or a similar document (if applicable), by mentioning the relevant pages in that document. Be sure that the information is up to date and references to peer reviewed papers in (biomedical/scientific) journals should be given where appropriate.>

7.3 Summary of findings from clinical studies

<See explanatory text of chapter 7.2, including remark>

7.4 Summary of known and potential risks and benefits

<See explanatory text of chapter 7.2, including remark>

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

<Please describe the procedures for the shipment, receipt, disposition, return and destruction of the non-investigational medicinal products.>

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Primary outcome measures are patient survival and death-censored graft survival.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcome measures are renal function (such as eGFR) and vascular complications.

8.1.3 Other study parameters (if applicable)

NA

8.2 Randomisation, blinding and treatment allocation

NA

8.3 Study procedures

Since this study is a retrospective study, no additional procedures/tests will be performed.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

8.5 Replacement of individual subjects after withdrawal

8.6 Follow-up of subjects withdrawn from treatment

8.7 Premature termination of the study

< Please describe the criteria for terminating the study prematurely and the procedures in case the study will be terminated prematurely.>

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

< Please describe the procedures for handling the serious adverse events. If certain SAEs do not require immediate reporting by the investigator to the sponsor, please specify.>

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: <*specify which*

SAEs do not require immediate reporting by the investigator to the sponsor, if applicable> .

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

< If certain SAEs do not require(expedited) reporting to the accredited METC, please specify these SAEs as well as the frequency of reporting of these SAEs in line listings, or in a annual safety report or otherwise.>

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

<This c*hapter is only applicable for studies with an investigational medicinal product*>
Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC <*reporting via webportalToetsingOnline is only applicable for investigator initiated studies*>:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;

- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

< For multicentre studies the responsibilities of investigators in participating centres as well as of the coordinating investigator should be clearly defined>

<Please describe also the method of breaking the code for SUSAR reporting.>

9.3 Annual safety report

<This c*hapter is only applicable for studies with an investigational medicinal product*>
< The annual safety report may be combined with the annual progress report (see chapter 12.4).>

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;

- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

<In case a DSMB is established to perform ongoing safety surveillance and to perform interim analyses on the safety data, this committee should be an independent committee. The composition of the DSMB should be described and it should be clear that each member has no conflict of interest with the sponsor of the study.
The task and responsibility of the DSMB should be described (see chapter 10.4 for interim analyses either for safety or for futility or positive efficacy) >

<Criteria on which the DSMB may decide to terminate the trial prematurely should be clearly defined before the trial has started.>

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

< In case a DSMB is not needed, but some safety review is deemed appropriate, information on this safety committee should be given here. Information should be provided on the composition of the committee and (in)dependence of the members, the reason to establish this committee, type of data that will be reviewed and moment of review, possible measures to be taken>

10. STATISTICAL ANALYSIS

Patient survival, death-censored graft survival and eGFR will be reported as mean ± standard deviation (SD) if normally distributed or median with interquartile range (IQR) if data is skewed. Categorical variables such as the incidence rate of vascular complications will be described as numbers and percentages. Continuous variables will be compared using student's t-test or Mann–Whitney U test. Categorical variables will be compared using $\chi 2$ test or Fisher's exact test. Kaplan-Meier curves and log-rank test will be used to compare patient and graft survival. The data will be analyzed is SPSS. A p-value of < 0.05 is considered statistically significant.

10.1 Primary study parameter(s)

Patient survival is defined as the time from transplantation to death or the last follow-up. Death-censored graft survival is defined as the time from transplantation to graft failure or the last follow-up with a functioning graft, with censoring death with a functioning graft.

10.2 Secondary study parameter(s)

Data of eGFR will be extracted from Clinical Chemistry department of Erasmus MC. Vascular complications are defined as the occurrence of steal syndrome, renal artery haemorrhage and thrombosis.

10.3 Other study parameters

10.4 Interim analysis (if applicable)

< Please describe when the interim analysis will be done, which statistical methods will be used, who will perform the interim analysis and the stopping rules (if applicable). Also refer to the DSMB Charter in case a Data Safety Monitoring Board will be established to advice on stopping, see also chapter 9.5>

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

11.2 Recruitment and consent

Gathering the express consent of test subjects is only possible by exerting disproportionate effort or would lead to unacceptable selection bias. All allogeneic kidney transplantation recipients from 2010 to 2020 are included in this study. The study population concerns patients that have been treated 10 years ago; A substantial amount of the study population is expected to have passed away and/or has no records available about current whereabouts. Asking express consent could result in an unacceptable selection bias and therefore produce unreliable data. Recovering addresses would involve a disproportionate effort for gathering the express consent of test subjects. The Form exception informed consent is attached as a separate document.

11.3 Objection by minors or incapacitated subjects (if applicable)

<Please specify which code of conduct is applicable for minors and/or incapacitated adults participating in non-therapeutic research. This should also be specified in the informed consent letter.>

11.4 Benefits and risks assessment, group relatedness

<*Please give a justification of the proposed study.*>

11.5 Compensation for injury

<*Please give information about the liability insurance and the insurance for the subjects participating in the study*.>
<*The sponsor or investigator should also have a liability insurance.*>

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

<*Please describe any special incentives, compensation or treatment that subjects will receive through participation in the study*.>

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The research data will be pseudonymised by the research coordinator as soon as the first record of the participant is created in the research database. The data that is entered in the database does not contain any directly identifying data. This way, the identity of the subject is only to be re-identified by using the pseudonymisation key. This key is stored separately from the data and is managed by the principal investigator. After the project is completed, only the principal investigator will have access to the pseudonymisation key file.

12.2 Monitoring and Quality Assurance

< If monitoring of the conduct of the study takes place, please describe who will monitor, what will be monitored, frequencies etc. One can refer to a monitoring plan for details >

12.3 Amendments

<*The following text is applicable for studies without an investigational medicinal product*.>
Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

<*The following text is applicable for studies with an investigational medicinal product.*>
A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.
< Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.>

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

<*The following text is applicable for studies without an investigational medicinal product*.>
The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

<*The following text is applicable for studies with an investigational medicinal product.*>
The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

<In case the final study report will not be available within one year, another term should be defined including the reasons.>

12.6 Public disclosure and publication policy

The participants of this study have no conflicts of interest to disclose.

13. STRUCTURED RISK ANALYSIS

NA

13.1 Potential issues of concern

< In this final paragraph of the research protocol a structured risk analysis which consists of a number of steps is required. The analysis should result in a comprehensive overall synthesis of the direct risks for the research subjects in this study in chapter 13.2. The risk considerations on the various issues listed below should be supported by up to date information and should be clearly described to allow a thorough review by the METC. For details one may refer to the previous chapters, the Investigator's Brochure (IB) or a similar document (if applicable), peer reviewed papers in (biomedical/scientific) journals. The issues below are provided to structure your considerations and allows an efficient communication with the METC when questions arise as a result of the review of your research protocol. The remarks per item are provided as a guidance for describing your considerations. Should issues not be applicable, please indicate so.
*For registered products to be used within the indication and **not** in combination with other products chapter 13.1 can be skipped; explain in chapter 13.2 why 13.1 is skipped >*

a. Level of knowledge about mechanism of action

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

d. Selectivity of the mechanism to target tissue in animals and/or human beings

e. Analysis of potential effect

f. Pharmacokinetic considerations

g. Study population

h. Interaction with other products

i. Predictability of effect

j. Can effects be managed?

13.2 Synthesis

<should include uncertainties and the unknown and the overall risk:
Make clear what measures have been taken to reduce what risks
Make clear why in your opinion the remaining risks are acceptable for the subjects participating in the study>

14. REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999 Dec 02;341(23):1725-30.
2. https://www.usrds.org/reference.aspx UADRRTU.
3. Kianda MN, Wissing KM, Broeders NE, Lemy A, Ghisdal L, Hoang AD, et al. Ineligibility for renal transplantation: prevalence, causes and survival in a consecutive cohort of 445 patients. Clin Transplant. 2011 Jul-Aug;25(4):576-83.
4. Goldsmith PJ, Fraser SM, Fitzpatrick M, Scott DJ, Ahmad N. Acute lower limb ischemia following pediatric renal transplantation. Pediatr Transplant. 2010 Nov;14(7):E93-5.
5. Northcutt A, Zibari G, Tan TW, Coulter AH, Zhang WW. Does kidney transplantation to iliac artery deteriorate ischemia in the ipsilateral lower extremity with peripheral arterial disease? Vascular. 2015 Oct;23(5):490-3.
6. Gouny P, Lenot B, Decaix B, Rondeau E, Kitzis M, Lacave R, et al. Aortoiliac surgery and kidney transplantation. Ann Vasc Surg. 1991 Jan;5(1):26-31.
7. Piquet P, Berland Y, Coulange C, Olmer M, Mercier C, Rampal M. Aortoiliac reconstruction and renal transplantation: staged or simultaneous. Ann Vasc Surg. 1989 Jul;3(3):251-6.
8. Imanishi K, Hatakeyama S, Yamamoto H, Okamoto A, Imai A, Yoneyama T, et al. Posttransplant renal function and cardiovascular events are closely associated with the aortic calcification index in renal transplant recipients. Transplant Proc. 2014;46(2):484-8.

9. Adamec M, Janouoek L, Tooenovsky P, Lacha J. Renal transplantation combined with aortofemoral bypass using a fresh arterial allograft. Transpl Int. 2000;13 Suppl 1:S56-9.
10. Ozcelik A, Treckmann J, Paul A, Witzke O, Sotiropoulos G, Nadalin S, et al. Results of kidney transplantation with simultaneous implantation of vascular graft. Transplant Proc. 2007 Mar;39(2):509-10.
11. Galazka Z, Grochowiecki T, Jakimowicz T, Kowalczewski M, Szmidt J. Is severe atherosclerosis in the aortoiliac region a contraindication for kidney transplantation? Transplant Proc. 2011 Oct;43(8):2908-10.
12. Coosemans W, Nevelsteen A, Pirenne J, Vanrenterghem Y. Renal transplantation in patients with a vascular aortoiliac prosthesis. Transplant Proc. 1999 Jun;31(4):1925-7.
13. Wright JG, Tesi RJ, Massop DW, Henry ML, Durham JR, Ferguson RM, et al. Safety of simultaneous aortic reconstruction and renal transplantation. Am J Surg. 1991 Aug;162(2):126-30.
14. Ahlmen J, Henriksson C, Claes G, Gelin LE, Thoren O. Successful kidney transplantation in a man with Dacron "trouser" prosthesis. Scand J Urol Nephrol. 1979;13(1):133-5.
15. Gill R, Shapiro R, Kayler LK. Management of peripheral vascular disease compromising renal allograft placement and function: review of the literature with an illustrative case. Clin Transplant. 2011 May-Jun;25(3):337-44.
16. Lacombe M. Aortoiliac surgery in renal transplant patients. J Vasc Surg. 1991 May;13(5):712- 8.
17. Sterioff S, Jr., Zachary JB, Williams GM. Dacron vascular grafts in renal transplant patients. Am J Surg. 1974 May;127(5):525-8.
18. Turunc V, Eroglu A, Tabandeh B, Sarkislali K, Sener T, Aydin A, et al. Femoro-femoral Bypass for Graft Salvage in a Renal Transplant Patient With Aorto-iliac Occlusion: A Case Report. Transplant Proc. 2015 Jun;47(5):1511-4.