AMC / VUMC
Erasmus MC
LUMC
RadboudUMC
UMCG
UMCU
UZ Leuven

GGG Grote Trials

ZonMw

Chiesi

NOVARTIS

Wat is de Optimize studie

Waarom

Doel

Hypothese

Protocol

Waar staan we nu

OPTIMIZE

- **OP**en label multicenter randomized **T**rial comparing standard **IM**munosuppression with tacrolimus and mycophenolate mofetil with a low exposure tacrolimus regimen **I**n combination with everolimus in *de novo* renal transplantation in **E**lderly patients

Waarom de Optimize?

Steeds meer ouderen getransplanteerd
Orgaanoverleving wordt door sterfte bepaald
sterfte in ouderen door infecties en kanker
Oudere ontvangers ontvangen vaak oudere organen, dus slechtere nierfunctie, dus gevoeliger voor schadelijke invloeden TAC
Daarom zoeken naar optimale IS regime voor de oudere ontvanger, dus voorkomen van over-IS

Doel van de Optimize:

Immuunsuppressie aanpassen aan de leeftijd,

dus gereduceerd TAC en EVR, en vanaf start reductie MMF

samen met Txlines

Bloedonderzoek,

Vragenlijsten en grip strength

Biobank Txlines

+ biobank verouderings-studie

Minder infecties, betere nierfunctie en minder sterfte

Transform:

Reductie van TAC, in combinatie met EVR, vergeleken met standaard TAC en MMF, alle leeftijden >18,
even effectief in voorkomen rejecties dan standaard regime,
EVR vermindert aantal virale infecties

Optimize

Een fase 4 multicenter studie met bijna alle UMC's in NL, + UZ Leuven.

PI: Jan Stephan Sanders (SPB)

2 strata: **A**: 65+ ontvanger met donor 65+, DBD of DCD
B: 65+ ontvanger met donor DBD, DCD of living, alle leeftijden

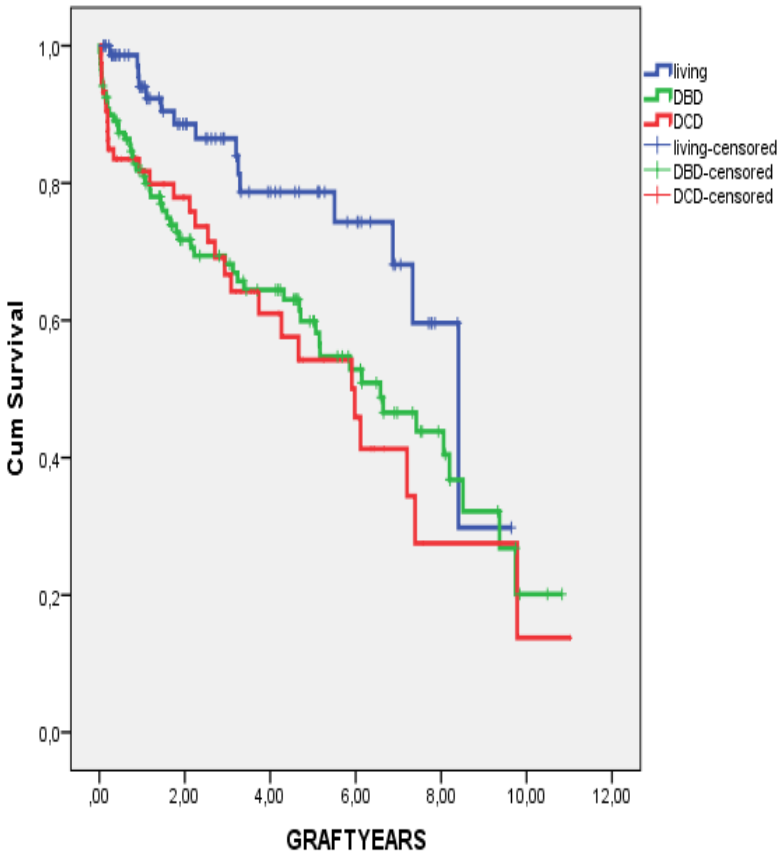
Worden toegewezen aan behandeling met:
Arm 1: Envarsus, MMF en pred
Arm 2: Envarsus, Everolimus en pred

In Groningen plm 100 patiënten, in alle centra plm 400.

Hypothese Optimize:

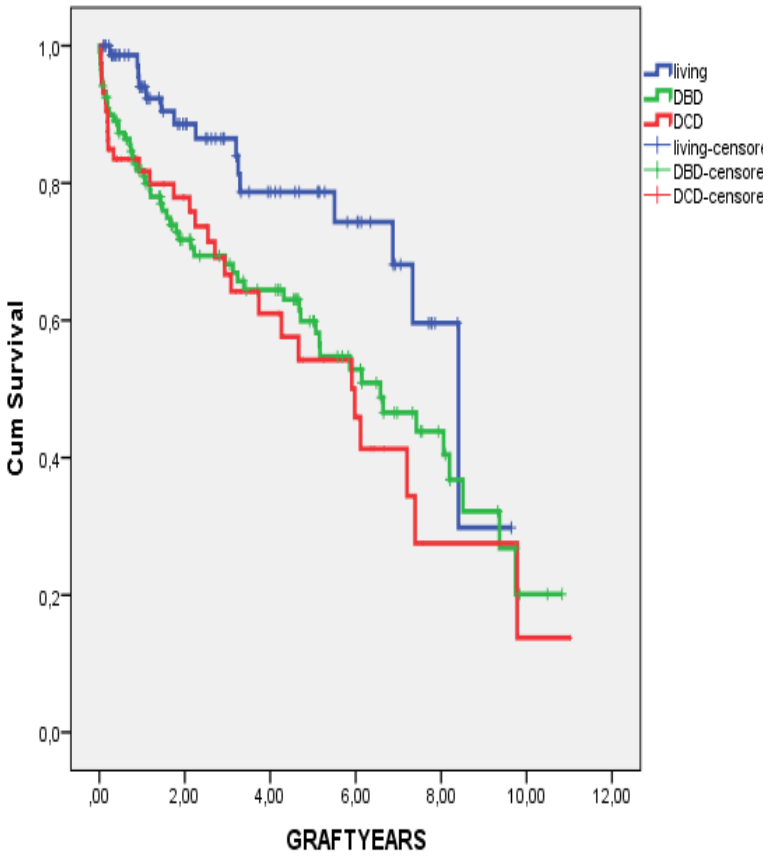
Oudere patiënten zijn meer gebaat bij behandeling gericht op voorkomen schadelijke bijwerkingen en sterfte dan voorkomen van rejectie

Transplantatie bij 65+

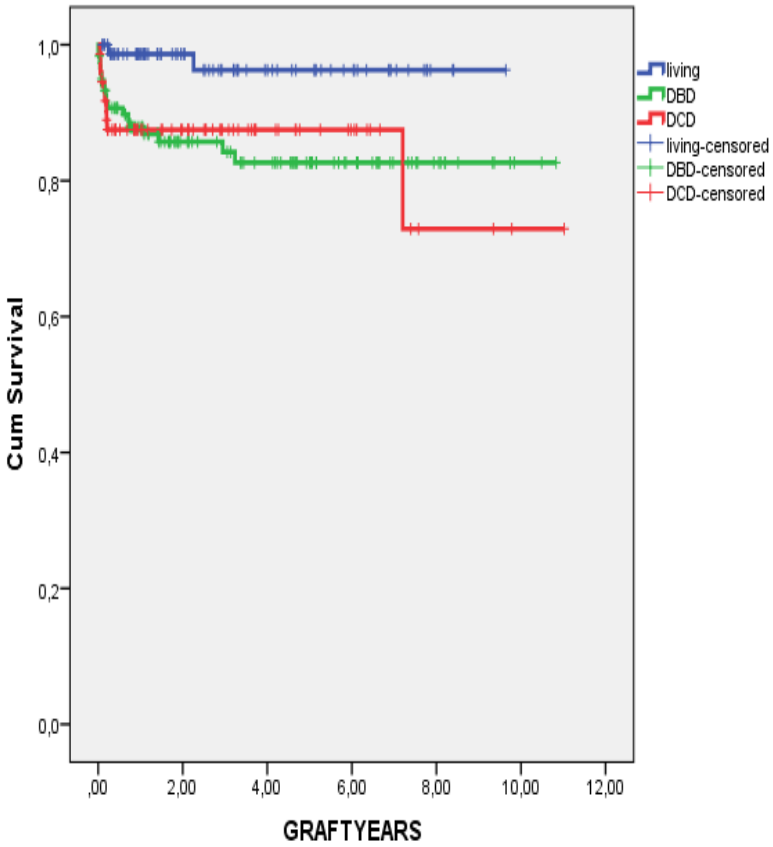


Graft Survival

Transplantatie bij 65+



Graft Survival



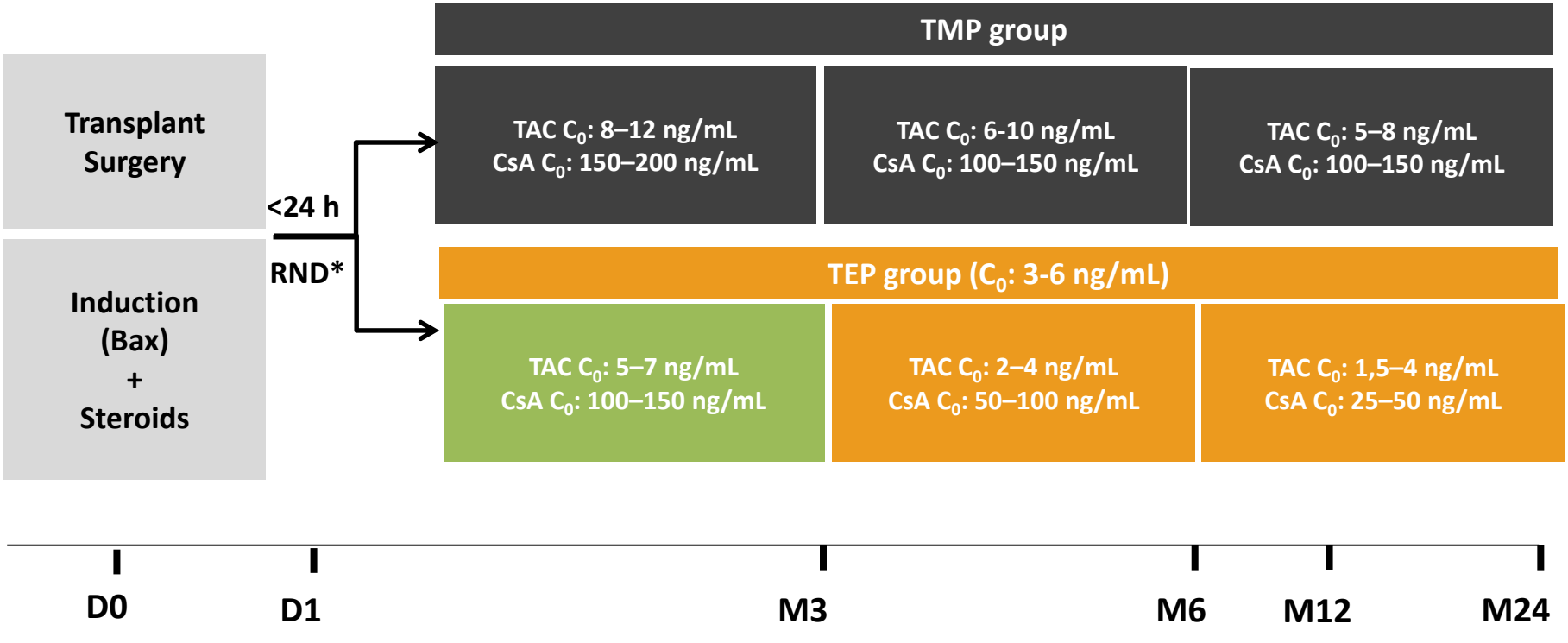
Death Censored Graft Survival

OPTIMIZE TRIAL

PROTOCOL

- Stratum A: old-for-old
- Stratum B: oudere ontvangers van een
  - Nier van postmortale donor < 65 jaar
  - Nier van levende donor

  - Patiëntenvereniging meegekeken



Immuunsuppressie, spiegels in ug/l:

Arm 1: Dag 0 en 4 Basiliximab 20 mg

TAC BL t/m M 6 visite: 8-12

TAC M 6 t/m M 24 visite: 5-8

MMF 2 x 500 mg

Prednisolon BL tot M 3: 20 mg, afbouwen naar

Prednisolon M 3 tot M 24: 5 mg.

Arm 2: Dag 0 en 4 Basiliximab 20 mg

TAC BL t/m M 3 visite: 5-7

TAC M 3 t/m M 6 visite: 2-4

TAC M 6 t/m M 24 vistie : 1.5-4

EVL vanaf BL t/m M 24 visite : 3-6

Prednisolon BL tot M 3: 20 mg, afbouwen naar

Prednisolon M 3 tot M 24: 5 mg.

Primaire eindpunt: geslaagde niertransplantatie

- In leven met functionerend graft

- Functie
  - Stratum A -> 30 ml/min*1,73m2
  - Stratum B -> 45 ml/min*1,73m2

Inclusie

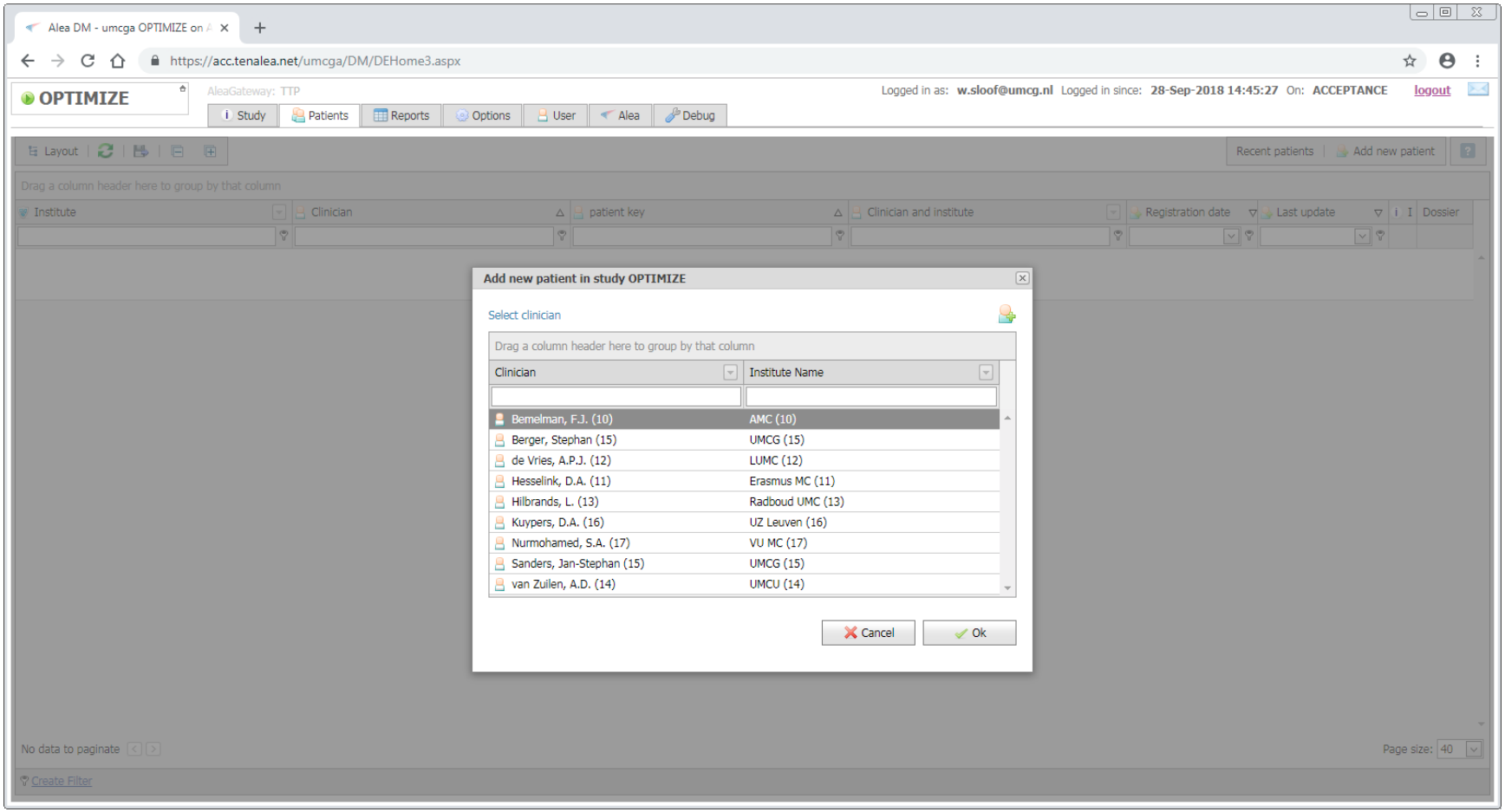
- Written informed consent must be obtained before any assessment is performed
- Male or female subject ≥65 years old
- Subject randomized within 24 hours of completion of transplant surgery
- Stratum A: Recipient of a primary (or secondary, if first graft is not lost due to immunological reasons) renal transplant from a deceased donor aged 65 years or older
- Stratum B: Recipient of a primary (or secondary, if first graft is not lost due to immunological reasons) renal transplant from a deceased donor aged below 65 years or a living donor of any age

exclusie

- Subject is a multi-organ transplant recipient
- Recipient of bloodgroup ABO incompatible allograft or CDC cross-match positive transplant
- Subject at high immunological risk for rejection as determined by local practice for assessment of anti-donor reactivity
- Recipient of a kidney with a cold ischaemia time (CIT) >24 hr
- Recipients of a kidney from an HLA-identical related living donor
- Known intolerability for one or more of the study drugs
- Subject who is HIV positiveHBsAg and/or a HCV positive subject with evidence of elevated liver function tests (ALT/AST levels ≥2.5 times ULN). Viral serology results obtained within 6 months prior to randomization are acceptable
- Recipient of a kidney from a donor who tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV)
- Subject with severe systemic infections, current or within the two weeks prior to
- randomization
- Subject requiring systemic anticoagulation that cannot be temporarily interrupted and which would preclude renal biopsy
- Subject with previous trombo-embolic events not receiving systemic anticoagulation
- History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
- Subject with severe restrictive or obstructive pulmonary disorders
- Subject with severe hypercholesterolemia or hypertriglyceridemia that cannot be controlled
- Subject with white blood cell (WBC) count ≤ 2,000/mm^3 or with platelet count ≤ 50,000/mm^3

ALEA - OPTIMIZE

patiënt toevoegen



Visits and Assessments

	SCR/BL	Day 7	Week 4	Mo 3	Mo 6	Mo 9	Mo 12	Mo 18	Mo 24
Day	0	7	28	90	180	270	360	540	720
Visit number	1	2	3	4	5	6	7	8	9
Time window (days)	-	+/-2	+/-7	+/-7	+/-7	+/-14	+/-14	+/-21	+/-21
Randomization, IC	X								
Demographics	X								
In- and Exclusion criteria	X								
Medical History (Renal Disease Risk Factors, Other Current and Past diseases)	X								
Vital signs	X	X	X	X	X	X	X	X	X
Haematology	X		X	X	X	X	X	X	X
Biochemistry	X		X	X	X	X	X	X	X
Lipid Profile	X			X	X	X	X	X	X
Urine biochemistry: Spot urine	X		X	X	X	X	X	X	X
Urine biochemistry: 24 H			X	X	X	X	X	X	X
Dialysis information	X	X	X	X					
Donor information	X								
Ischemia	X								
Anatomy donor kidney	X								
Trough levels (LCMS) CNI/EVR		X	X	X	X	X	X	X	X
Virology PCR				X	X		X		X
Biobanking	X				X		X		X
Donor Specific Antibodies (DSA)	X						X		X
Creatinine clearance			X	X	X	X	X	X	X
Secondary endpoint status		X	X	X	X	X	X	X	X
Study medication status		X	X	X	X	X	X	X	X
Grip strength	X						X		X
Forms 1	X						X		X
Forms 2							X		X
MOCA							X		X

- **Caption of flowchart**
- Vital Signs: (Height only at SCR/BL), Blood pressure, Weight, Heart rate
- Haematology: Hb, MCV, Ht, leucocytes with differentiation, platelets
- Serum biochemistry: urea, creatinine, sodium, potassium, albumin, calcium, phosphate, fasting glucose, HbA1c
- Lipid profile: fasting cholesterol (Total, HDL and LDL) and triglycerides
- Urine biochemistry spot: urea, creatinine, sodium, protein, albumin
- Urine biochemistry 24 H: protein, albumin
- Virology plasma: CMV PCR, BKV PCR
- Biobanking: plasma, serum, urine,
- 1 x EDTA 10 ml (4 x 1,5 ml) 1 x serum 10 ml (4 x 1,5 ml) 1 x spot urine (4 x 2 ml); 1 x Paxgene 2,5 ml (RNA)
- 3 x lithium heparin 10 ml (PBMC isolation)
- Forms 1: EQ-5D, Clinical Frailty Scale, G8 Geriatric Assessments
- Forms 2: Short Physical Performance Battery, Fried
- MOCA: Montreal Cognitive Assessment

Follow-up (incl. lab-biobank-geriatrische tests)

- Lab
- Biobank
- Geriatrische tests (Clinical frailty scale, MOCA, SPPB, FRIED)

Appendix 1: Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status
Shrinking	**Frailty cut point:** **Baseline:** Self reported unintentional weight loss ≥10lb in previous year **Follow-up:** Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2
Physical endurance/energy	*Geriatric Depression Scale:* 1. *Do you feel full of energy?* 2. *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. **Frailty cut point:** No to 1 and every day or every week to 2.
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Frailty cut point:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. **Frailty cut point:** **Grip strength:** lowest 20% (by gender, body mass index) *Men* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21
Slow walking speed	Walking time in seconds (usual pace) over 15 feet **Frailty cut point:** Slowest 20%, stratified by gender and median standing height. *Men* Height ≤173 cm ≥7 seconds Height >173 cm ≥6 seconds *Women* Height ≤159 cm ≥7 seconds Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) **Frailty cut point:** TUG time ≥19 seconds

Frail: ≥3 criteria present; **Intermediate or Pre-Frail:**1 or 2 criteria present; **Robust :** 0 criteria present

Adapted from Fried et al, Cardiovascular Health Study Collaborative Research G. Frailty in older adults: Evidence for a phenotype. The Journals of Gerontology. Series A, Biological sciences and medical sciences. 2001;56:M146-156.

EQ-5D=3L (kwaliteit van leven)

SF12 (gezondheid)

B-IPQ (hoe denkt u over de Niertx)

MTSOSD-59 (klachten)

BAASIS(inname van IS)

Bij start studie algemene vragen

(burgerlijke staat, opleiding, roken en alcohol)

Waar staan we nu?

Allereerste patiënt 22 Jul 2019

Universitair Medisch Centrum Groningen	75	92	J.S.F. Sanders
Erasmus MC, Universitair Medisch Centrum Rotterdam	98	61	D.A. Hesselink
Academisch Medisch Centrum	43	32	F.J. Bemelman
Vrije Universiteit Medisch Centrum	18		S.A. Nurmohamed
Leids Universitair Medisch Centrum	57	27	A.P.J. de Vries
Radboud Universitair Medisch Centrum	38	11	L. Hilbrands
Universitair Medisch Centrum Utrecht	22	25	A.D. van Zuilen
UZ Leuven	23	24	D. Kuypers

DSMB vergadering 02 Juni:

Inclusiesnelheid boven verwachting (COVID)

Spiegels beter in range naarmate de tijd vordert

Vroegtijdig stoppen:
in de MMF groep 29/135
in de EVR groep 28/133
waarvan 12/12=24 overleden
3/7= 10 graft loss

SAE’s
MMF groep 72
EVR groep 75
meest infecties

Rejecties
MMF groep 25
EVR groep 24

Bootcongres


THANK
YOU!

Studievisites

Study visit	Tacrolimus ranges		Cyclosporine ranges		EVR ranges
	EVR arm	MMF arm	EVR arm	MMF arm	
D1 - M3	5-7 µg/l	8-12 µg/l	100-150 µg/l	150-200 µg/l	3-6 µg/l
M3 - M6	2-4 µg/l	6-10 µg/l	50-100 µg/l	150-200 µg/l	3-6 µg/l
M6 - M24	1,5-4 µg/l	5-8 µg/l	25-50 µg/l	100-150 µg/l	3-6 µg/l
Beide armen: prednisolon BL 20 mg; afbouwen tot 5 mg op M3. M3-M-24: 5 mg.