Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**Tacrolimus als behandeling bij COVID-19**
Projecttaal / Project language	:	**Nederlands / Dutch**
Geplande startdatum / Planned start date	:	**01-07-2020**
Geplande duur / Planned duration	:	**6 maanden / months**
Datum indienen / Date of application	:	**13-05-2020**
Projecttype / Project type	:	**Toegepast onderzoek**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

Dr. (10)(2e) **PhD (Hoofdaanvrager)**
Functie / Position: ziekenhuisapotheker/klinisch farmacoloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@umcutrecht.nl

Universitair Medisch Centrum Utrecht
Apotheek
Postbus 85500
3508 GA UTRECHT

Dr. (10)(2e) **PhD (Projectleider en penvoerder)**
Functie / Position: ziekenhuisapotheker/klinisch farmacoloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@umcutrecht.nl

Universitair Medisch Centrum Utrecht
Apotheek
Postbus 85500
3508 GA UTRECHT

Dr. (10)(2e) **PhD (Bestuurlijk verantwoordelijke)**
Functie / Position: ziekenhuisapotheker/klinisch farmacoloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@umcutrecht.nl

Universitair Medisch Centrum Utrecht
Apotheek
Postbus 85500
3508 GA UTRECHT

Dr. (10)(2e) **(Mede aanvrager)**
Functie / Position: arts-microbioloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@umcutrecht.nl

Universitair Medisch Centrum Utrecht
Postbus 85500
3508 GA UTRECHT

Prof. dr. H. Heijerman (Mede aanvrager)
Functie / Position: longarts | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@umcutrecht.nl

Universitair Medisch Centrum Utrecht
Postbus 85500

3508 GA UTRECHT

Dr. (10)(2e) **(Mede aanvrager)**
Functie / Position: ziekenhuisapotheker/klinisch farmacoloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e) @umcutrecht.nl

Universitair Medisch Centrum Utrecht
Postbus 85500
3508 GA UTRECHT

Prof. dr. D. de Lange (Mede aanvrager)
Functie / Position: intensivist | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e) @umcutrecht.nl

Universitair Medisch Centrum Utrecht
Postbus 85500
3508 GA UTRECHT

Dr. (10)(2e) **(Mede aanvrager)**
Functie / Position: longarts | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e) @umcutrecht.nl

Universitair Medisch Centrum Utrecht
Postbus 85500
3508 GA UTRECHT

Dr. (10)(2e) **(Mede aanvrager)**
Functie / Position: medisch immunoloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e) @umcutrecht.nl

Universitair Medisch Centrum Utrecht
Postbus 85500
3508 GA UTRECHT

Dr. (10)(2e) **(Mede aanvrager)**
Functie / Position: internist-nefroloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e) @umcutrecht.nl

Universitair Medisch Centrum Utrecht
Postbus 85500
3508 GA UTRECHT

Projectgegevens / Project information

Aandachtsgebieden / Focus

1.1 Thema's aandachtsgebied 1
- Behandeling
- Virus, immuniteit, immuunrespons en pathogenese

1.2 Subthema aandachtsgebied 1
- RCT studie via REMAP-CAP

1.3 Setting
- Ziekenhuiszorg

Samenvatting / Summary

We propose to include tacrolimus as a treatment arm in the REMAP-COVID platform given the rationale included in the pre-proposal. It will be integrated into the COVID-19 immune modulation domain, for which ethical committee approval has already been granted in a number of countries, including the Netherlands..

Trefwoorden / Keywords

tacrolimus, COVID-19, adaptive immune response

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:
Nee / No

Inhoud / Content

Disciplines / Disciplines

- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Immunologie, serologie / Immunology, serology
- Biofarmaceutische wetenschappen, toxicologie / Biopharmaceutical sciences, toxicology
- Longziekten / Pulmonology

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	(10)(1c)								
Materieel									
Implementatie									
Apparatuur									
Overig									
Totaal / Total									

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X				X
DEC		X			
WBO		X			

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity			X
Code openheid dierproeven / Code Transparency of Animal Testing			X

Andere vergunningen / Other permits

AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE "TOELICHTING INDIENING PROJECTIDEE" VAN DE OPROEPTEKST ZORGVULDIG!

Wanneer u het formulier heeft ingevuld:

1. **Zet het formulier om naar een PDF file en controleer de details**
2. **Upload het complete formulier als een bijlage bij uw indiening in Projectnet (Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)**

ProjectNet: Aandachtsgebied 1 (voorspellende diagnostiek en behandeling)
ProjectNet: Aandachtsgebied 2 (zorg en preventie)

NAAM VAN DE HOOFDAANVRAGER:

Dr (10)(2e)

ORGANISATIE:

UMC Utrecht

PROJECTTITEL:

Tacrolimus als behandeling bij COVID-19

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de ZonMw website om de datastewards te informeren en ondersteunen.

☐ Ik betrek een datasteward bij mijn project:
Naam: Klik of tik om tekst in te voeren.
Instituut: Klik of tik om tekst in te voeren.
E-mail: Klik of tik om tekst in te voeren.
Was aanwezig bij de webinar: ☐ Ja ☒ Nee

☒ Ik heb nog geen datasteward.

ONDERZOEKSVOORSTEL max 3 pagina's A4 (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

A novel coronavirus, SARS-CoV-2, causing a severe acute respiratory syndrome, emerged from its epicenter in Wuhan China in December 2019 and is now a global pandemic (1). There is an urgent need for effective treatment. Current focus has been on the development of novel therapeutics, including antivirals and vaccines. Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a hyperinflammation syndrome including pulmonary involvement with acute respiratory distress syndrome (ARDS) as one of the symptoms in approximately 50% of patients (2). In other hyperinflammation syndromes, such as macrophage activation syndrome, immunosuppression is beneficial. The majority of studies attribute a dysregulated/exuberant innate response as a leading contributor to SARS-CoV-2-mediated pathology. Nevertheless, the number of T cells, playing a critical role in antiviral immunity, dramatically drop in the blood of COVID-19 patients, especially among the elderly and patients admitted to the ICU, while the remaining T cells show functional exhaustion markers. T cell cytokines have been reported to be increased during the cytokine release syndrome (CRS) (2,3), however whether T cell activation represents a driving force for severe clinical outcomes has not been confirmed. There is, on the other hand, clinical evidence that acute respiratory distress syndrome (ARDS) could be intervened by inhibition of CD8 T-cells (4).

The focus of most therapies is currently on Il-1 and 6-blocking strategies which are suggested to have a beneficial effect on patient outcomes and/or are under investigation (5). As hyperinflammation is one of the major challenges in COVID-19 treatment and a dysregulated response of the adaptive immune system may play a role, the calcineurin inhibitor tacrolimus is a therapeutic option that should not be overlooked. Tacrolimus is a strong and broad T-cell activation and proliferation blocker. It acts primarily on T regulatory (CD4) cells and T cytotoxic (CD8) cells and attenuates *B cell* stimulatory cytokine mRNA levels in T *cells*. Such a broad and strong T-cell blockade can prevent progression to lung fibrosis which might also be caused by deregulated CD4+ cell responses (6). For instance, clinical evidence exists, of successful tacrolimus therapy to prevent lung fibrosis in the treatment of acute exacerbation of idiopathic lung fibrosis (IPF), although based on a retrospective analysis (8). In addition, the decision to pharmacologically immunosuppress a moderately to severely ill patient with COVID-19 remains a difficult one. Possible beneficial effects of reducing inflammation should be carefully weighed up against the potential for deleterious impairment of anti-microbial immunity (6). In this respect, cyclosporine, also a calcineurin inhibitor, has also been used to successfully treat lymphohistiocytosis (HLH) by a reduction of cell proliferation and the concomitant production of other cytokines, although it remains to be seen if calcineurin inhibitors (CNI) at the therapeutic range would be capable of inhibiting the SARS-CoV-2 CRS. This does, however, suggest that CNIs may not be harmful in the hyperinflammatory phase of SARS-CoV-2 infection, which may also justify their continued usage in recipients of transplants (9).

Regarding this delicate balance, the strong benefit of tacrolimus compared to other immunosuppressive agents including biologicals is fourfold; First, tacrolimus therapy is guided by therapeutic drug monitoring. As such, over immune suppression can be corrected based on tacrolimus whole blood levels as a marker for drug exposure. Second and related to the first concerns tacrolimus pharmacokinetics, it has a relative short half-life and within 2 days after withdrawal most of the drug will be cleared from the body in case of any overexposure. Also, tacrolimus is rapidly and readily distributed to the site of action in the case of COVID-19, the lungs. The third benefit is its pharmacodynamics. Tacrolimus attains its maximal immunosuppressive effect within minutes after administration and the effect is abrogated within 1-2 days after withdrawal. The fourth benefit are the costs. At 5 to 10,- EURO/day tacrolimus is a very cheap drug compared to other bio-based immunomodulators. And more important, the drug is produced at large scale by numerous pharmaceutical companies and is readily available worldwide.

Current evidence of associations between immunosuppressive and stimulating drugs and novel COVID-19 suggests that tacrolimus may have beneficial impacts on COVID-19 (9,10). Overall, the small amount of literature available suggests a potential role of tacrolimus as a potent antiviral in the treatment of human coronaviruses (9). The administration of this drug could not only decrease mortality secondary to lung involvement by COVID-19, but also decrease the excessive burden of care that intensive care units are bearing. It is important to take note, that a study group from Spain will initiate a small scale randomized trial of low-to-medium dose tacrolimus and steroid pulse therapy in COVID-19 patients (11).

Tacrolimus side effects are well known and reversible in almost all cases. Nefro- and neurotoxicity are the most predominate side effects of tacrolimus. However, these side effects can be considered transient in case of short term

use (<1 month). To counteract and alleviate possible tacrolimus side effects we refer to the UMC Utrecht lung transplantation protocol (12).
The risk of the development of tacrolimus-associated thrombotic microangiopathy (TMA) should also be mentioned. Firstly, this risk is low e.g. in transplant populations and the therapy consist of withdrawal of the calcineurin inhibitor, which leads to reversal of TMA in almost all cases.
To conclude, we propose to include tacrolimus as a treatment arm in the REMAP-COVID platform given the above rationale. It will be integrated into the COVID-19 immune modulation domain, for which ethical committee approval has already been granted in a number of countries, including the Netherlands..

2. PLAN VAN AANPAK:

Tacrolimus can be included in the REMAP-COVID or REMAP-CAP as a comparator to other immunomodulators of the innate immune response (within the immune modulatory domain). Also, we aim to include a pharmacokinetic-pharmacodynamic (PKPD) and immunomonitoring substudy in the tacrolimus treatment arm. Length of therapy is three weeks or withdrawal at hospital discharge, whichever comes first, for both moderate and severely ill patients. Dosing of the oral formulation and monitoring of tacrolimus will be according to the UMC Utrecht lung transplantation protocol (12), targeting levels of 10-15 ng/mL. Differences in drug absorption and clearance can be corrected for using therapeutic drug monitoring. Pre-set exposure targets are identical to those strived for directly post-transplant. Drug monitoring of tacrolimus is common in EU and is routinely available in every clinic.
Participation in this intervention of the immune modulation domain will only be offered to sites able to perform drug monitoring as described. In case of over immune suppression or toxicity, drug tapering or withdrawal is at the discretion of the treating physician. Guidance will be offered to clinicians for dose increases and reductions.
Furthermore, the effect of tacrolimus exposure on the (clearance of) COVID-19 infection is unknown, also in respect to the concomitant exposure to the other agents in REMAP-COVID. There are no specific consideration regarding subpopulations, timing or interaction with other agents. We provide guidance on interactions in the working documents for the trial already, and will include information on tacrolimus where necessary.

3. HAALBAARHEID VAN HET PROJECT:

TIJDSSCHEMA
Volgens en gebruikmakend van REMAP-COVID platform.
MOTIVATIE HAALBAARHEID
Because the overarching protocol of REMAP-CAP has already been approved, including the pandemic appendix to the core protocol, and approval for the "COVID-19 immune modulation domain" has also already been granted, the addition of tacrolimus is just another substantial amendment to the protocol. Writing of this addition to the approved protocol and submission to IRBs can be instantaneously. The start date of this intervention will mainly depend on the speed of IRB approval.
The data collection tool for this study has already been set up and is functioning. Minor adaptations will be made to facilitate this study. A trained project management team is helping sites get set up. Working documents and training materials have already been developed.
In the Netherlands, 4 sites already participate in the study (UMCU, RadboudUMC, Canisius Wilhelmina hospital, Leiden UMC), 4 are advanced in the start-up process and recruitment for another 22 is ongoing. Globally, to date, 168 sites are active and over 420 patients with COVID-19 have been included.
Completion of this study highly depends on the number of COVID-19 patients in The Netherlands and globally, but the REMAP-CAP approach represents the most efficient mechanism for recruitment, and has a higher chance of obtaining definitive conclusions compared to traditional, 2-arm, RCTs (14).

4. RELEVANTIE VOOR DE PRAKTIJK:

Onderbouw de relevantie aan de hand van de in de subsidieoproep benoemde
Ronde specifieke criteria
1. Bij een positieve risk-benefit balans van de toepassing van tacrolimus bij COVID-19 kan de ernst van de symptomen verminderen, ziekenhuis- en IC-opnames verkorten en de overleving doen toenemen. Tacrolimus is wereldwijd goed beschikbaar en zeer betaalbaar (5-10,- euro/dag). Het kan daarmee snel in de kliniek worden ingezet.
2. Het REMAP-COVID platform met een 'adaptive trial design' is bij uitstek het geschikte platform om deze interventie te onderzoeken. Tacrolimus wordt hierbij direct vergeleken met andere immuunmodulerende middelen als tocilizumab.
3. De interventie met monotherapie van hoog-gedoseerd tacrolimus wordt nog niet elders ter wereld uitgevoerd (clinicaltrials.gov , bezocht op dd 13 mei 2020 met zoektermen 'tacrolimus' EN 'COVID-19').

4. Tacolimus is generiek beschikbaar/uit patent. Er zijn daarmee geen commerciële partijen betrokken.
5. De alhier omschreven interventie met tacrolimus is eenvoudig uitvoerbaar in iedere Nederlandse kliniek. Het doseer- en monitoringprotocol zal worden vastgelegd, worden geborgd en is daarmee overdraagbaar.
6. Tacrolimus als mede de therapeutic drug monitoring (TDM) van dit middel zijn landelijk goed beschikbaar en zeer betaalbaar/goedkoop in vergelijking met andere immuunmodulerende behandelingen bij COVID-19.
7. Dit voorstel wordt gesteund en is mede-opgesteld door een breed spectrum aan (medische) specialisten, onder andere zijn betrokken: longartsen, immunologen, farmacologen, intensive-care artsen, artsen-microbioloog en nefrologen. Daarnaast is gebleken uit de eerder studies dat patiënten graag hun medewerking verlenen aan een Adaptive Trial Design. Hiertoe refereren we naar het PREPARE platform (zie https://www.prepare-europe.eu/News/Events/Reaching-out-20-21-September-2018
8. Bij een positieve risk-benefit balans kan de interventie met tacrolimus voor COVID-19 patiënten overlevingswinst, gezondheidswinst en verminderd lijden tot effect hebben. Het kan leiden tot minder longschade door remming van de hyperinflammatie, hetgeen de kwaliteit van leven significant zal verbeteren van patiënten die COVID-19 hebben overleefd na een ziekenhuisopname. Tevens kan het de druk op de zorg verlichten door kortere opnameduur en een reductie van het aantal IC-opnames.
9. In geval van een kortere opnameduur en een afname van het aantal IC-opnames is de interventie snel kosteneffectief (naast de gezondheidswinst en verminderd leiden). Als vermeld betreft het een relatief goedkope behandeling van 5 tot 10,- euro/dag , welke snel is terugverdiend door de besparingen die het potentieel oplevert. Hierbij kan ook gedacht worden aan minder intensieve nazorg van de overlevende patiënten in geval van een afname van longschade.

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.):

Dit voorstel wordt gesteund en is mede-opgesteld door een breed spectrum aan (medische) specialisten, onder andere waren betrokken longartsen, immunologen, farmacologen, intensive-care artsen, artsen-microbioloog en nefrologen. Daarnaast is gebleken uit de eerder studies dat patiënten graag hun medewerking verlenen aan een Adaptive Trial Design. Hiertoe refereren we naar het PREPARE platform (zie https://www.prepare-europe.eu/News/Events/Reaching-out-20-21-September-2018)

6. LITERATUURREFERENTIES (optioneel):

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