Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**REMAP clinical pharmacology Platform to accelerate the development of repurposed Immunomodulating agents for COVID-19 treatment [RAPID]**
Projecttaal / Project language	:	**Engels / English**
Geplande startdatum / Planned start date	:	**01-06-2020**
Geplande duur / Planned duration	:	**24 maanden / months**
Datum indienen / Date of application	:	**14-05-2020**
Projecttype / Project type	:	**Strategisch onderzoek**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

Dr. (10)(2e) **(Main applicant)**
Functie / Position: ziekenhuisapotheker-onderzoeker | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* (10)(2e) | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Apotheek Klinische Farmacie
Huispost 864
Postbus 9101
6500 HB NIJMEGEN

(10)(2e) **(Projectleader and secretary)**
Functie / Position: Hospital pharmacist- clinical pharmacologist | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Apotheek Klinische Farmacie
Huispost 864
Postbus 9101
6500 HB NIJMEGEN

Dr. (10)(2e) **(Administrative responsibility)**
Functie / Position: Head Grant Support Office | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Directoraat Valorisatie
huispost 903
Postbus 9101
6500 AB NIJMEGEN

Prof. dr. D.M. Burger (Co-Applicant)
Functie / Position: Hospital pharmacist - clinical pharmacologist | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Apotheek Klinische Farmacie
Huispost 864
Postbus 9101
6500 HB NIJMEGEN

Dr. (10)(2e) **(Co-Applicant)**
Functie / Position: Head of Section Biobank | *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) **(Co-Applicant)**
Functie / Position: Head of the Section Pediatric Infectious Diseases | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Pediatrics
Pediatric Infectious Diseases and Immunology
Postbus 9101
6500 HB NIJMEGEN

Dr. (10)(2e) **(Co-Applicant)**
Functie / Position: Pharmacometrician | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Apotheek Klinische Farmacie
Huispost 864
Postbus 9101
6500 HB NIJMEGEN

Dr. (10)(2e) **(Co-Applicant)**
Functie / Position: Infectious disease physician | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Infectieziekten
Algemene Interne Geneeskunde 463
Postbus 9101
6500 HB Nijmegen

Dr. (10)(2e) **(Co-Applicant)**
Functie / Position: Ass professor Systems Biomedicine and Pharmacology | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@lacdr.leidenuniv.nl

Leiden Academic Center for Drug Research
Systems Biomedicine and Pharmacology
Postbus 9600
2300 RC LEIDEN

Dr. (10)(2e) **(Co-Applicant)**
Functie / Position: Hospital pharmacist - clinical pharmacologist | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@amsterdamumc.nl

Amsterdam UMC
Meibergdreef 9
1105 AZ AMSTERDAM ZUIDOOST

Projectgegevens / Project information

Aandachtsgebieden / Focus

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

1.3 Setting
- Ziekenhuiszorg

Samenvatting / Summary

At the end of 2019, the SARS-CoV-2 virus emerged as a cause of severe respiratory illness beginning in Wuhan, China. The impact of COVID-19 has resulted in a global race to find effective treatments. Due to our inability to design new agents to be deployed against COVID-19 disease in such a short time, we currently have to rely on repurposing established drugs for treatment of COVID-19. However, solid pharmacokinetic and pharmacodynamic data in the relevant populations to support optimal dosing of any agent for this novel indication are completely lacking.
Our group has recently found that adequate antiviral chloroquine concentrations are not reached in COVID-19 patients unless it comes at the costs of extreme toxicity. Should we have known this earlier, it would have been highly unlikely that chloroquine would have been repurposed as first line treatment for COVID-19.
Similar to antiviral drugs, no pharmacological or dose finding studies are available for immune modulating drugs and there is an unmet need to integrate pharmacological knowledge in the experimental treatment of COVID-19 disease.
One of the potential explanations for this mismatch between the hypothesized activity of drugs in COVID-19 patients and the disappointing results in clinical studies, is the fact that a critical step in clinical drug development, i.e. dose-finding and pharmacokinetic-pharmacodynamic (PK/PD) evaluations have been skipped in the global scramble to curb the pandemic.
There is, therefore, an urgent need to add clinical pharmacological evaluation of the repurposed drugs of COVID-19.
Ideally, this is not done through small-scale isolated studies, but integrated in a larger infrastructure for evaluation of repurposed drugs. By doing so we will be able to deliver better directed treatments.
Our aim is to to embed a clinical pharmacological platform in REMAP and to start with to develop optimal and individualized dosing regimens for anakinra and tocilizumab in COVID-19 patients

Trefwoorden / Keywords

pharmacology; pharmacometrics; targeted; drug licensing; repurposing

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:

Nee / No

Inhoud / Content

Disciplines / Disciplines

- Immunologie, serologie / Immunology, serology
- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Biofarmaceutische wetenschappen, toxicologie / Biopharmaceutical sciences, toxicology
- Bioinformatica/biostatistiek, biomathematica, biomechanica / Bioinformatics/biostatistics, biomathematics, biomechanics

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)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

(10)(2e)

ORGANISATIE:

Radboud university medical center (Radboudumc), Nijmegen, The Netherlands

PROJECTTITEL:

REMAP clinical pharmacology Platform to accelerate the development of repurposed Immunomodulating agents for COVID-19 treatment [**RAPID**]

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

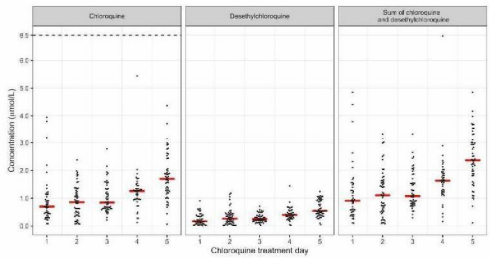
☒ Ik heb nog geen datasteward.
We zullen zsm een datasteward in het project betrekken. Financiën zijn hierop vooruitlopend al gereserveerd.

ORGANISATIE:

Radboud university medical center (Radboudumc), Nijmegen, The Netherlands

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

Background. At the end of 2019, the SARS-CoV-2 virus emerged as a cause of severe respiratory illness beginning in Wuhan, China. Soon thereafter, the World Health Organization declared COVID-19 a pandemic. The clinical features of SARS-CoV-2 infected individuals vary from exhibiting no symptoms to being critically ill. The impact of COVID-19 has resulted in a global race to find effective treatments.
Due to our inability to design new agents to be deployed against COVID-19 disease in such a short time, we currently have to rely on **repurposing established drugs** for treatment of COVID-19. However, solid pharmacokinetic and pharmacodynamic data in the relevant populations to support optimal dosing of any agent for this novel indication **are completely lacking**. Our group has recently found that adequate antiviral chloroquine concentrations as defined by Wang et al [Cell Research volume 30 (2020)] of >6.9 uM **are not reached** in COVID-19 patients unless it comes at the costs of extreme toxicity [figure 1 - unpublished data - confidential]. Should we have known this earlier, it would have been **highly unlikely that chloroquine would have been repurposed** as first line treatment for COVID-19. Besides antiviral therapy, immune modulation is one of the main strategies to overcome severe inflammation and lung damage in COVID-19 patients. Similar to antiviral drugs, no pharmacological or dose finding studies are available for immune modulating drugs and there is an unmet need to integrate pharmacological knowledge in the experimental treatment of COVID-19 disease.



One of the potential explanations for **this mismatch** between the hypothesized activity in COVID-19 patients and the disappointing results in clinical studies, is the fact that a critical step in clinical drug development, i.e. dose-finding and pharmacokinetic-pharmacodynamic (PK/PD) evaluations have been skipped in the global scramble to curb the pandemic. There is, therefore, **an urgent need to add clinical pharmacological evaluation** of the repurposed drugs of COVID-19. Ideally, this is not done through small-scale isolated studies, but integrated in a larger infrastructure for evaluation of repurposed drugs. By doing so we will be able to deliver better directed treatments. We have demonstrated with chloroquine that our group successfully can deploy such a strategy in this very short time frame.
To start, we believe the highest need lies in this field of immunomodulating agents as dosing of these drugs is rather empirical and currently not adjusted to the COVID-19 pathophysiology.
Aims of the project: Primary aim: to develop optimal and individualized dosing regimens for anakinra and tocilizumab in COVID-19 patients
Implementation aim: to support future studies with immunomodulating agents for treatment of COVID-19 by embedding a clinical pharmacology working group within the REMAP consortium to accelerate drug repurposing for COVID-1

2. PLAN VAN AANPAK:
Immunomodulating agents and pharmacology: In a retrospective study, it was demonstrated that high dose anakinra (5 mg/kg twice daily; median treatment duration 9 days) compared to regular dose was associated with improved survival compared to a low dose [Cavalli et al, Lancet Rheumatology, May 3 2020] Anakinra blocks the activity of IL-1 by competitive inhibition of IL-1 binding to IL-1R and thus effects cytokine responses (including IL-1 levels). Since cytokine responses and levels may be highly variable in COVID-19 patients, one may hypothesize that the

administered dose should be adjusted individual biomarkers. Furthermore, anakinra is mainly renally excreted [Yang et al. Clinical Pharmacology & Therapeutics 2003] and renal dysfunction is highly prevalent (as in COVID-19 patients) [Battle et al. J Am Soc Nephrol. 2020]. It may therefore be argued that anakinra dosing should not only be optimized for individual cytokine status, but also for renal function as otherwise it will result in suboptimal treatment. Currently, optimal dosing strategies for anakinra in COVID-19 are lacking.

Tocilizumab is used to target highly elevated IL-6 levels in COVID-19 patients and inhibition of this cytokine seems promising for treatment of severe lung inflammation in COVID-19 patients [Xu et al, Proceedings of the National Academy of Sciences (2020) in press]. Tocilizumab pharmacokinetics are highly variable and – because it is an antibody - dependent on IL-6 levels. [Frey et al. J Clin Pharmacol. 2010]. Furthermore, it is known that tocilizumab exposure may also vary due to variability of CRP (as is the case in COVID19) and bodyweight [Br J Clin Pharmacol. 2018]. Lastly, monoclonal antibodies such as tocilizumab distribute mainly over the extracellular water in the human body [Keizer et al. Clin Pharmacokinet. 2010], hence it can be postulated that in COVID-19-patients drug leaks from the body, i.e. a leaky lung phenomenon, similar to the leaky gut phenomenon with biologic agents for treatment of Crohn's disease [Dalal et al. Gastroenterol Hepatol (N Y). 2015 Oct]. The consequence is an insufficient clinical effect. Tocilizumab exposure correlates well with its clinical efficacy [Clin Med Insights Arthritis Musculoskelet Disord. 2012]. There is, therefore, an urgent need to verify whether current tocilizumab dosing regimens are sufficient for COVID-19 patients and whether these should be adjusted individually.

Workpackage 1 - The pharmacokinetics of anakinra and tocilizumab in patients with COVID 19 (PK analysis)
Hypothesis: Treatment of covid-19 with immunomodulating drugs like anakinra or tocilizumab can be further optimized with evidence based knowledge on the PK of these drugs..
Patients: Adult patients suspected or proven to have COVID-19, receiving anakinra or tocilizumab as allocated interventions in REMAP-CAP who consent to sampling. There are no exclusion criteria for this study as it involves only blood sampling.
Setting: REMAP-CAP hospitals in the Netherlands will recruit patients, for this pharmacology substudy we aim to include 40 patients per agent.
Sample size justification: no formal sample size calculation was conducted. Typically 40 individuals with intensive sampling schemes are sufficient to predict clearance and volume of distribution with an CV% accuracy and precision of <15%.
Analysis and outcome: The pharmacokinetics of anakinra of tocilizumab will be assessed using non-linear mixed effects modelling. Analytical infrastructure is safeguarded by the lab of immunology [Dr. de Jonge]. Physiologically plausible covariates for the pharmacokinetics will be investigated for the clearance and disposition of anakinra and tocilizumab.

Workpackage 2 - The pharmacodynamics of anakinra, tocilizumab in patients with COVID-19 (PK-PD analysis).
Hypothesis: optimal dosing schedules can be defined based on a pharmacokinetic/pharmacodynamic analysis.
Setting: In the samples collected in WP 1, analysis will be performed to determine the impact of immunomodulating agents on the immune system. For this purpose, we will measure the following markers: serum IL-1b, CRP, serum IL-6, IL18, serum TNFα differentiation in B-cell population during treatment, overall survival, oxygen requirement, partial pressure of oxygen in the blood, time until cessation of mechanical ventilation.
Analysis and outcome: We will investigate the pharmacokinetics and dynamics of anakinra and tocilizumab and their effect on cytokine responses and clinical parameters.

IMPLEMENTATION AIM. One of the largest international consortia currently investigating COVID-19 treatments is the REMAP-CAP consortium (https://www.remapcap.org/coronavirus). This consortium was set up from its inception, in 2014, to adapt and respond rapidly in the event of a pandemic, like the current novel 2019 coronavirus (COVID-19). All adaptations are combined in the REMAP-COVID subcore, and described in a Pandemic Appendix to the Core protocol. The here proposed pharmacology platform will be nested in the overall REMAP-CAP consortium and will provide the infrastructure, personnel, and expertise to optimize designs in the current and future proof-of-concept and phase-II studies that will be initiated. Currently available interventions include (amongst others)

anakinra. An amendment for the use of tocilizumab and sarilumab is under ethical review in the Netherlands. If successfully implemented, our pharmacological approach can be directly translated to other immunomodulating drugs but obviously also to other classes of drugs. To realize a pharmacology domain within the multinational REMAP consortium to implement personalized dosing for patients with COVID-19 we have asked the help of Dr. Lennie Derde and Prof. Marc (10)(2e). With their aid and if we are capable of demonstrating the added value of a pharmacological knowledge group to accelerate drug development in REMAP, the Netherlands can play a leading role in this global initiative. A pharmacological approach using innovative model-informed precision dosing of repurposed drugs for treatment of COVID-19 would truly aid in better treatment outcomes.

3. HAALBAARHEID VAN HET PROJECT:

TIMELINE: Total duration of the project will be 24 months. Four months have been allocated for drafting and approval of the study protocol. Twelve months have been allocated for the WP1 and WP2. For international implementation we are not dependent on the national inclusion of patients in WP1 and WP2. Four months will be allocated for the analysis and another 4 months for report/manuscript writing and dissemination.

MOTIVATION FEASIBILITY: The REMAP-CAP is the largest worldwide platform, with over 160 participating sites across 14 countries, where drug repurposing for treatment of COVID-19 can be performed rapidly and on a large scale. The project group and participants have collaborated previously on a wide variety of infectious disease topics. We have involved key players in the application: (i) the REMAP consortium, which can facilitate the recruitment of patients, coordinate sampling infrastructure and storage (biobanking), collection of data and epidemiological expertise, and is also instrumental in translating the outcomes of the study into public health measures and National treatment guidelines (SWAB); and (ii) the necessary expertise in pharmacology of infectious diseases through international renowned experts from Radboudumc, (iii) immunology expertise and lab infrastructure is performed by the Radboudumc (Dr. van de Veerdonk and Dr. de Jonge), (iv) The Radboud Applied Pharmacometrics group as well as LACDR Leiden and Amsterdam Medical Center are involved for advanced pharmacometric modelling and simulation integrated within the clinical pharmacology working group which will be embedded within the REMAP consortium and which will ensure vast and sound data collection, data analysis and implementation of personalized dosing of immunomodulatory drugs. Pop-PKPD models can be visualized such as already done by the group in Leiden (http://covid19pkpd.eu/). The implementation into international REMAP-CAP is feasible through Prof. Marc (10)(2e) and Dr. Lennie Derde who have expressed they will be assisting in achieving this goal.

4. RELEVANTIE VOOR DE PRAKTIJK:

This proposal will focus on the area "Aandachtsgebied 1: thema's: behandeling en pathogenese" of the ZonMW call for COVID-19. Our proposal has the capacity to identify a relevant treatment strategy in COVID-19 and by repurposing personalized dosing of immunomodulating agents for COVID-19 can be rapidly implemented in a large randomized adaptive trial through the REMAP consortium. If proven effective, this would have far-reaching consequences, also for health utilization and the society at large:

- It would improve the therapeutic effects of immunomodulating agents and likely thereby reduce COVID-19 associated morbidity and mortality
- it would reduce health utilization (e.g. occupation of hospital and ICU beds)
- it would reduce the need for a 'lock down' or other restrictive measures
- This project is well aligned with the national research agenda of the NFU on personalized medicine (https://www.nfu.nl/img/pdf/18.2847_NFU_Kennisagenda_Personalised_Medicine_def_online.pdf)

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.): This project is discussed with NVZA, SWAB, NIV, REMAP