

**Algemene gegevens / General Information**

Programma / Programme : **COVID-19 Programma**
 Subsidiëronde / Subsidy round : **Bottom-up ronde COVID-19 aandachtsgebied 1**
 Projecttitel / Project title : **Outcomes of treatment of COVID-19 with hydroxychloroquine, chloroquine and azithromycin in secondary and tertiary care hospitals in the Netherlands**
 Projecttaal / Project language : **Engels / English**
 Geplande startdatum / Planned start date : **01-06-2020**
 Geplande duur / Planned duration : **6 maanden / months**
 Datum indienen / Date of application : **14-05-2020**
 Projecttype / Project type : **Toegepast onderzoek**
 Vervolg eerder ZonMw-project / Continuation previously funded project : **Nee / No**
 ZonMw

Projectleden / Project members**Dr. (10)(2e) (Main applicant)**

Functie / Position: internist-infectioloog-acute geneeskundige | *Opleiding / Education:*

Studierichting / Subject:

T: (10)(2e) | F: | E: (10)(2e) @amsterdamumc.nl

Amsterdam UMC
De Boelelaan 1117
1081 HV Amsterdam

Dr. (10)(2e) (Projectleader and secretary)

Functie / Position: internist en infectioloog in opleiding | *Opleiding / Education:*

Studierichting / Subject:

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Amsterdam UMC
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1081 HV Amsterdam

Prof. dr. J.M. Prins (Administrative responsibility)

Functie / Position: afdelingshoofd interne geneeskunde | *Opleiding / Education:*

Studierichting / Subject:

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Amsterdam UMC
Meibergdreef 9
1105 AZ AMSTERDAM ZUIDOOST

Dr. (10)(2e) (Co-Applicant)

Functie / Position: neuroloog | *Opleiding / Education:*

Studierichting / Subject:

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Amsterdam UMC
Meibergdreef 9
1105 AZ AMSTERDAM ZUIDOOST

Dr. (10)(2e) (Co-Applicant)

Functie / Position: internist-infectioloog | *Opleiding / Education:*

Studierichting / Subject:

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Amsterdam UMC
De Boelelaan 1117

Aanvraagformulier GGG_digitaal / Applicationform GGG_digital

Dossier nummer / Dossier number: (10)(2g)

1081 HV Amsterdam

Dr. (10)(2e) **(Co-Applicant)***Functie / Position:* anaesthesioloog-intensivist | *Opleiding / Education:**Studierichting / Subject:*

T: (10)(2e) | F: | E: (10)(2e) @amsterdamumc.nl

Amsterdam UMC

De Boelelaan 1117

1081 HV Amsterdam

Dr. (10)(2e) **(Co-Applicant)***Functie / Position:* internist-infectioloog | *Opleiding / Education:**Studierichting / Subject:*

T: (10)(2e) | F: | E: (10)(2e) @isala.nl

Isala

Dokter van Heesweg 2

8000 GK ZWOLLE

Projectgegevens / Project information**Aandachtsgebieden / Focus**

1.1 Thema's aandachtsgebied 1

- Behandeling

1.3 Setting

- Ziekenhuiszorg

Samenvatting / Summary

Research question:

The objective of this study is to observe differences in outcome in persons with COVID-19 treated with or without (hydroxy)chloroquine alone or in combination with azithromycin.

Urgency:

Urgent insights are needed to the efficacy of treatment of COVID-19 with (hydroxy)chloroquine with or without azithromycin until more definite answers become available from randomized controlled trials. These insights will have a direct and profound effect on how patients are treated globally with these medications, now and in possible future waves. Several preliminary studies have reported that the antimalarial agents hydroxychloroquine and chloroquine alone or in combination with the antibiotic azithromycin might have an effect on the viral replication and can decrease the mortality of COVID-19. The use of the medication, however, is not undisputed. The clinical studies so far have been hampered by (indication) bias, monocenter setup, and by small numbers of included subjects.

Hypothesis:

We hypothesize that (hydroxy)chloroquine with or without azithromycin does not lead to better clinical outcomes.

Method:

In this application, we intend to merge two large databases that include subjects with COVID-19 in thirty secondary and tertiary care hospitals in the Netherlands. These include hospitals that do and do not routinely use (hydroxy)chloroquine with or without azithromycin. We will study all subjects available in the databases (approximately 3,400). We will use a multivariable Cox model with inverse probability weighting according to the propensity score to determine the relative hazard of death between groups over the study period. We will analyse the (dichotomous) outcomes with chi-square statistics. With help of the merged databases, we hope to eliminate most sources of bias to contribute to the safe and effect treatment of patients with COVID-19.

Trefwoorden / Keywords

covid-19
hydroxychloroquine
chloroquine
azithromycin
hospital
mortality

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

Ja / Yes

Aanvraagformulier GGG_digitaal / Applicationform GGG_digital

Dossier nummer / Dossier number: (10)(2g)

Organisaties

Amsterdam UMC

Amsterdam UMC

Isala

Inhoud / Content**Disciplines / Disciplines**

- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Longziekten / Pulmonology
- Microbiologie / Microbiology

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
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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:

Dr. (10)(2e)

ORGANISATIE:

Amsterdam UMC, locatie VUmc

PROJECTTITEL:

Outcomes of treatment of COVID-19 with hydroxychloroquine, chloroquine and azithromycin in secondary and tertiary care hospitals in the Netherlands

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: (10)(2e)

Instituut: Amsterdam UMC, locatie VUmc

E-mail: (10)(2e)@amsterdamumc.nl

Was aanwezig bij de webinar: ☒ Ja ☐ Nee

ONDERZOEKSVORSTEL max 3 pagina's A4 (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)
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1. PROBLEEMSTELLING EN DOELSTELLING(EN):

The spread of SARS-CoV-2, leading to the current pandemic of COVID-19, has a profound global impact on daily life, morbidity and mortality. The disease course is heterogeneous. The majority of patients experience only mild symptoms, but a substantial percentage develops severe disease ranging from increasing hypoxia up to the acute respiratory distress syndrome (ARDS)^{1,2}. Supportive measures are key in the treatment of COVID-19. Several preliminary studies have reported that the antimalarial agents hydroxychloroquine and chloroquine alone or in combination with the antibiotic azithromycin can have an effect on the viral replication and might decrease the mortality of COVID-19^{3,4,5}. It has even lead to a public announcement by the president of the USA to take the medication regardless of study results. The use of the medication, however, is not undisputed. The clinical studies so far have been hampered by (indication) bias^{3,4}, monocenter setup^{4,5}, and by small numbers of included subjects⁵. In-vitro data suggests that high (toxic) levels of (hydroxy)chloroquine are needed to stop viral replication. Side effects of both (hydroxy)chloroquine and azithromycin include neurological, gastro-intestinal, psychological and dermatological effects, but also fever, cardiac conduction abnormalities and blood cell disorders. The side effects could be enhanced by co-administration of medication. Randomised controlled clinical trials (RCTs) are currently being deployed to investigate the effect of the medication on outcome of COVID-19. RCTs, however, cost time to conduct. There is a global need for fast advice on the effectiveness of (hydroxy)chloroquine and azithromycin. A cohort study with low chance of bias could well give quick but reliable answers while we are awaiting definite results from RCTs. The CovidPredict database and a database initiated by Isala Clinic, can help to give such quick answers. The CovidPredict database is a consortium of 22 hospitals in the Netherlands that, so far, have included over 2,500 individuals admitted with COVID-19. The project started as collaboration of the Dutch Association for Intensive Care and the National Intensive Care Evaluation Foundation (NICE), with doctors and researchers from Amsterdam UMC and Maastricht UMC+ to centralize the collection of data of COVID-19 patients. The consortium has grown rapidly since the start of the project, with numerous new hospitals, clinicians, and researchers joining the team every week. Some of these hospitals routinely have used hydroxychloroquine, chloroquine and/or azithromycin, while a few others (including Amsterdam UMC) have not. The Isala database includes 900 subjects. The large number of included subjects in both databases and the routine use or not-use of the medication tackles the issues of low number of inclusions, monocenter setup and indication bias from previous cohort studies.

Objectives

1. the objective of this study is to observe differences in outcome in persons with COVID-19 treated with or without (hydroxy)chloroquine alone or in combination with azithromycin.

2. PLAN VAN AANPAK:

Design

Prospective cohort study of subjects admitted to hospital in one of the hospitals that are included in the CovidPredict and the Isala databases.

Population

1. Exposure group: subjects treated in a hospital that routinely prescribes (hydroxy)chloroquine alone or in combination with azithromycin to patients with COVID-19
2. Control group: subjects treated in a hospital that routinely does not prescribe (hydroxy)chloroquine alone or in combination with azithromycin to patients with COVID-19

Procedure

The data are currently being gathered in the Netherlands in each of the hospitals linked to the CovidPredict database. The database is set up by a consortium at the initiative of Amsterdam UMC and MUMC+. Separate funding will be sought for the complete sophisticated (with help of artificial intelligence) analysis and setup of that database. This application is intended for the merger of part of the CovidPredict database with a database of another research group in the Netherlands that currently collects data on the initiative of Isala Clinics, Zwolle. Data include demographical data (including gender and socioeconomic status), data

on treatment and outcome data (e.g., mortality, intensive care unit admission, intubation, hospital admission days).

Primary outcomes

The primary outcome will be comparison of clinical outcomes in hospitals that routinely prescribe (hydroxy)chloroquine alone or in combination with azithromycin to patients with COVID-19, compared to hospitals that do not.

Outcomes include mortality, intensive care unit admission, intubation and mechanical ventilation, hospital admission days.

Data handling

We will store the data on the ICT data platform of Amsterdam UMC for the period required by law. To maximize sharing and reuse of data between project partners and with the wider research community, we will develop a data management plan according to the FAIR data principles. Any ethical aspects with respects to the sharing and publication of patient data both within and outside the project will be addressed by the data steward.

Statistics

We will analyse baseline characteristics and demographical data with descriptive statistics. We will use a multivariable Cox model with inverse probability weighting according to the propensity score to determine the relative hazard of death between groups over the study period. We will analyse dichotomous outcomes with chi-square statistics. We will attempt to perform a propensity score to correct for covariates including premorbid health of the subjects among the different hospitals. Most important covariates include gender, body mass index, age, Charlson comorbidity index, history of COPD, diabetes mellitus, cardiovascular disease, socio-economic status and smoking history.

Sample size

The sample size is a convenience sample. We will study all subjects available in the database until May 13th. Total number of included subjects will be approximately 3,400.

3. HAALBAARHEID VAN HET PROJECT:

The inclusion of data of the subjects in the has already been approved by the METc of the participating hospitals. Data of most subjects are currently being entered in the database. We hope to analyse the data in June 2020, and report the results before the end of July 2020.

4. RELEVANTIE VOOR DE PRAKTIJK:

The results of this study will give important scientific insights to the clinical effect of (hydroxy)chloroquine alone or in combination with azithromycin to patients with COVID-19. Outcomes will have a direct effect on the participating and future patients with COVID-19, now and in any future waves of the pandemic. The database of Isala clinics contains approximately 900 subjects, the CovidPredict data approximately 2,500 subjects. The data is generated in 30 secondary and tertiary care hospitals in the Netherlands. The data collection started early in the pandemic. The data collection is setup prospectively and includes data on consecutive subjects admitted on the general medicine and pulmonology wards and to intensive care units. The database is setup according to the WHO standards, which enables data comparison and uniformity of data among the different participating centres.

Within the databases, Amsterdam UMC is unique because it is one of the few centres in the Netherlands that has chosen not to treat patients with (hydroxy)chloroquine alone or in combination with azithromycin according to national standards, because of the paucity of efficacy data early in the pandemic. It makes selection or indication bias less likely because we can compare the outcome data with other hospitals in the same insurance/hospital care setting in the Netherlands who did choose to treat patients with (hydroxy)chloroquine and/or azithromycin. With help of propensity scoring, we hope to correct for any influence of population selection and hospital circumstances on outcomes.

We believe that the gained insights will give quick answers to the questions that remained after earlier studies on the treatment while awaiting more definite answers from RCTs. The clinical observational studies so far were marred by (indication) bias^{3,4}, monocenter setup^{4,5}, and by small numbers of included subjects⁵. We will share the gained knowledge with the aim to improve local, national and international

treatment protocols. The large cohort will allow to differentiate outcomes stratified by diversity parameters e.g., gender and socio-economic background. We are committed to work together with our data steward to ensure that research findings and data relevant to this outbreak are shared rapidly and openly, including data sharing according to FAIR principles. We aim to publish the research in open access journals. This project is initiated by Infectious Diseases Specialists, Acute Medicine Specialists, intensivists and other clinicians, Epidemiologists, and data managers of all participating centers.

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

Hoofdaanvrager: dr. (10)(2e) internist-infectioloog-acute geneeskundige¹
 Projectleider/penvoerder: dr. (10)(2e) internist-infectioloog in opleiding, klinisch epidemioloog¹
 Bestuurlijk verantwoordelijke: prof. dr. J. Prins, afdelingshoofd Interne Geneeskunde^{1,2}
 Overige leden researchteam: dr. (10)(2e), neuroloog,² dr. (10)(2e), internist-infectioloog,¹ dr. (10)(2e), anaesthesioloog-intensivist,¹ dr. (10)(2e), internist-infectioloog.³
 Deelnemers (artsen, onderzoekers, patiënten) aan de CovidPredict database en Isala database.

1. Amsterdam UMC, locatie VUmc, Amsterdam
2. Amsterdam UMC, locatie AMC, Amsterdam
3. Isala, Zwolle

6. LITERATUURREFERENTIES (optioneel):

1. Yang, X. *et al.*, Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China. *Lancet Respir Med* 2020 **8**, 475–481
2. Petrilli, C. M., *et al.*, Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. *medrxiv.org* 2020
3. Rosenberg ES, *et al.*, Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA*. 2020 May 11.
4. Geleris J, *et al.*, Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020 May 7. [Epub ahead of print]
5. Gautret P, *et al.*, Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020 Mar 20:105949

DAEB Format

Organisation	Type of organisation	Quoted costs	Quoted co-funding	Requested budget
VU Medisch Centrum	Knowledge institution	-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
	Total	-	-	-

Staff costs[illegible]

Material, equipment & consumer goods (itemised)

[illegible]

[illegible]

Specification staff

1.a Staff costs (based on salary scale)

nr	Function / Name	NFU / VSNU member / other staff ruling	Function/Scale	Months	Gross salary - based on table / 1 FTE	Monthly Gross salary (for Other	% fee (for the project)	Salary costs	Gross salary, 40% increment (for Other ruling only)	Overhead % (for Other ruling only)	Total
1	Phd Student	NFU	PostDoc	3	€ 19.877		80%	€ 15.901,60	€ -	-	€ 15.901,60
2	Co Assistant	NFU	NWP-H	3	€ 16.587		80%	€ 9.952,20	€ -	-	€ 9.952,20
4	to be specified				€ 0		100%	€ -	€ -	-	€ -
4	to be specified				€ 0		100%	€ -	€ -	-	€ -
5	to be specified				€ 0		100%	€ -	€ -	-	€ -
6	to be specified				€ 0		100%	€ -	€ -	-	€ -
7	to be specified				€ 0		100%	€ -	€ -	-	€ -
8	to be specified				€ 0		100%	€ -	€ -	-	€ -
9	to be specified				€ 0		100%	€ -	€ -	-	€ -
10	to be specified				€ 0		100%	€ -	€ -	-	€ -
11	to be specified				€ 0		100%	€ -	€ -	-	€ -
12	to be specified				€ 0		100%	€ -	€ -	-	€ -
13	to be specified				€ 0		100%	€ -	€ -	-	€ -
14	to be specified				€ 0		100%	€ -	€ -	-	€ -
15	to be specified				€ 0		100%	€ -	€ -	-	€ -

1.b Staff costs (based on hourly rate)

The hourly rate should be acceptable, reasonable and fair

Nr	Function	Activity / Actions
1	to be specified	
2	to be specified	
3	to be specified	
4	to be specified	
5	to be specified	
6	to be specified	
7	to be specified	
8	to be specified	
9	to be specified	
10	to be specified	
11	to be specified	
12	to be specified	
13	to be specified	
14	to be specified	
15	to be specified	

[illegible]