Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 3**
Projecttitel / Project title	:	**Long-term mental health trajectories in recovered Covid-19 patients: exploring the interplay of psychosocial and biological factors affecting health-related quality of life**
Projecttaal / Project language	:	**Nederlands / Dutch**
Geplande startdatum / Planned start date	:	**01-09-2020**
Geplande duur / Planned duration	:	**24 maanden / months**
Datum indienen / Date of application	:	**14-07-2020**
Projecttype / Project type	:	**Toegepast onderzoek / Applied research**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

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Projectgegevens / Project information

Aandachtsgebieden / Focus

3.1 Thema's aandachtsgebied 3
- Onderzoek naar de effectiviteit en impact van maatregelen/strategieën rondom het coronavirus

3.3 Subthema's Onderzoek naar de veerkracht van de samenleving
- Psychologische effecten en emotioneel welbevinden

Samenvatting / Summary

ONDERZOEKSVRAAG

- To determine long-term mental health and health-related quality of life (HRQL) trajectories in recovered COVID-19 patients exploring the interplay of biomedical- and psychosocial factors.
- To determine which individuals are at risk of trajectories characterized by persistently or recurrently reduced mental health and HRQL and design guidance for identifying individuals at risk.

URGENTIE

The current outbreak of COVID-19 is expected to have long-term impact on mental health and health-related quality of life (HRQL) of recovered patients based on experience with previous infectious diseases outbreaks. To reduce potential long-term sequelae, individuals at risk need to be identified and linked to appropriate additional support and /or intervention. Moreover, insights into mechanisms of long-term sequelae should lead to targets for new interventions.

HYPOTHESIS

We hypothesize that persistent long-term sequelae among patients recovered from COVID-19 will be caused by a dynamic interaction of biomedical and psychosocial factors.

PLAN VAN AANPAK

To unravel the expected dynamic interaction of biomedical and psychosocial factors we will follow patients from the onset of the infection and assessing the contribution of biomedical and psychosocial factors. The recently formed cohort of patients recovered from COVID-19 (RECOVERED/ VIS cohort) with mild to severe illness give us the unique possibility to study the course of mental health and HRQL. In addition to the biomedical data collected in the cohort, longitudinal data on mental health, HRQL and psychosocial factors are collected using self-report questionnaires at enrolment, and after 1, 3, 6, 9 and 12 months. State-of-the art computational modeling will be used to determine trajectories in mental health and HRQL and biomedical and psychosocial factors and their interactions influencing trajectories.

Trefwoorden / Keywords

mental health, health-related quality of life, COVID-19, psychosocial

Samenwerking / Collaboration

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

Nee / No

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	65.137	65.136	0	0	0	0	0	0	130.273
Materieel	25.247	25.247	0	0	0	0	0	0	50.494
Implementatie	0	5.000	0	0	0	0	0	0	5.000
Apparatuur	0	0	0	0	0	0	0	0	0
Overig	20.000	20.000	0	0	0	0	0	0	40.000
Totaal / Total	**110.384**	**115.383**	**0**	**0**	**0**	**0**	**0**	**0**	**225.767**

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 UITGEWERKTE SUBSIDIEAANVRAAG – BOTTOM-UP RONDE

COVID 19 programma

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

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE ''TOELICHTING INDIENING SUBSIDIEAANVRAAG" 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**

ProjectNet: Aandachtsgebied 3 (Maatschappelijke dynamiek)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

Pythia Nieuwkerk

ORGANISATIE:

Amsterdam UMC/ location AMC, University of Amsterdam

ENGELSE PROJECTTITEL:

Long-term mental health trajectories in recovered Covid-19 patients: exploring the interplay of psychosocial and biological factors affecting health-related quality of life

NEDERLANDSE PROJECTTITEL:

Mentale gezondheid en kwaliteit van leven van coronavirus patiënten: de invloed van psychosociale en biologische factoren op het lange termijn herstel.

ONDERZOEKSVOORSTEL **max 8 pagina's A4** (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING, URGENTIE EN DOELSTELLING(EN)

Onderbouw probleemstelling, urgentie en doelstelling. Maak doelstelling SMART (specifiek, meetbaar, acceptabel, realistisch en tijdsgebonden)

The current SARS-CoV-2 (COVID)-19 pandemic is expected to have significant impact on mental health and health-related quality of life (HRQL) of recovered COVID-19 patients. Past epidemics caused by similar viruses (MERS/SARS) show that the impact on mental health and HRQL can last more than a decade following infection (1, 2).

Factors possibly influencing the long-term impact of COVID-19 are expected to include disease severity (hospitalized or non-hospitalized for COVID-19), initial psychiatric symptoms- and psychological responses, psychological mechanisms, social factors and post-infectious symptoms. In this proposed study, we will follow patients from the onset of the infection to assess their mental health and HRQL trajectories and assess the role of each of the aforementioned factors, especially psychological and social factors, and their interaction in influencing COVID-19 related mental health and HRQL.

We will gain insight in why and when some individuals are vulnerable and develop mental health problems and lower HRQL, including persistent fatigue, and others not. Importantly, the insights into mechanisms underlying mental health and HRQL following COVID-19 infection would enable health care professionals and policy makers to target persons in most need of intervention and to tailor evidence-based health care services to address this appropriately.

Thus far, the aforementioned factors and their interactions have not been studied longitudinally following COVID-19 or other serious infections. The newly established cohort of non-hospitalized and hospitalized patients recovered from COVID-19 (ZonMW grant 10150062010002) gives us the unique possibility to study the full course of mental health and HRQL following COVID-19 infection and to explore the interplay of psychosocial and biological factors affecting HRQL. Moreover, we will be able to study the impact of fear of re-infection and possibly actual re-infection on mental health and HRQL. By identifying mental health and HRQL trajectories of individuals at risk, strategies for early detection and tailored interventions can be developed.

Our overall aim is: to determine long-term mental health and HRQL trajectories in recovered Covid-19 patients and exploring the interplay of psychosocial and biological factors affecting these trajectories.

Specific objectives are:

- To determine mental health and HRQL trajectories of patients who recovered from COVID-19 with different levels of disease severity (i.e., non-hospitalized and hospitalized patients).
- To explore how biomedical-, psychological and social- factors contribute to mental health and HRQL trajectories and interact with each other, with an emphasis on psychological- and social factors.
- To determine which individuals are at risk of trajectories characterized by persistently or recurrently reduced mental health and HRQL and design strategies for early detection and tailored interventions.

2. LOPEND ONDERZOEK

Beschrijf beknopt gepubliceerd onderzoek EN lopend nationaal (en waar mogelijk internationaal) onderzoek op dit gebied en wat uw project daaraan toevoegt. Zie hier een lijst met mogelijke portals.

The additional value of the proposed study is that we focus on the mental health and HRQL of COVID-19 patients and potential influencing psychosocial factors and their interaction with biomedical factors.

To the best of our knowledge, ongoing and published research among COVID-19 patients has so far focused on biomedical aspects, but not on mental health, health-related quality of life and potentially influencing psychosocial factors. Research on mental health, health-related quality of life and psychosocial aspects in the context of COVID-19 that we identified was exclusively directed at uninfected populations such as the general population, vulnerable uninfected populations (e.g., elderly, pregnant women, youth, ethnic and sexual minority groups) and patients with medical conditions other than COVID-19 (e.g., cancer patients, inflammatory bowel disease patients) (https://osf.io/us3pk).

We searched “Databronnen COVID-19” from the RIVM and research projects that are captured under WHO priority research area 9 “Social sciences in the outbreak response” via the COVID-19 Research Project Tracker (https://www.ukcdr.org.uk/funding-landscape/covid-19-research-project-tracker/). We also searched the OSF registries and PubMed using combinations of the terms “COVID-19”, “depression”, “anxiety”, “mental health”, “quality of life”, “health-related quality of life” and “psychosocial”. All searches were performed on July 1, 2020.

3. PLAN VAN AANPAK (ONDERBOUW KEUZES)

THEORETISCHE EN/OF EMPIRISCHE ONDERBOUWING

On the short term it is likely that mental health and HRQL of COVID-19 patients will be mainly determined by the level of disease severity (non-hospitalized or hospitalized for COVID-19) and treatment related factors, e.g. length of ICU stay. However, long-term mental health and HRQL are often not consistently associated with biomedical indicators of disease severity assessed in the early phase of disease (1, 3) and often relate to 1) initial psychiatric symptoms and psychological responses 2) psychological mechanisms 3) social factors and 4) persistent post-infectious symptoms.

Each of these potentially influencing factors are described below.

Level of disease severity of COVID 19: Level of disease severity ranges from asymptomatic or mild to severe, the latter requiring hospitalization with or without admittance to an Intensive Care Unit (ICU). Admittance to a hospital and being dependent on a ventilator at ICU are risk factors for a temporarily impaired mental health and HRQL in itself (4).

Initial psychiatric symptoms and psychological responses: In the acute phase, concerns about the outcome of illness and traumatic memories of being severely ill may have significant mental health impacts. Following this early phase, recovered COVID-19 patients may fear potential re-infection and recurrence of disease and may even actually experience re-infection which may have significant impacts on mental health and HRQL (5). Research among patients recovered from previous infectious diseases outbreaks (i.e., Q fever, Legionnaires disease, SARS-CoV and MERS-CoV) showed that patients may experience post-traumatic stress and increased symptoms of depression and anxiety long after the early phase of the illness and remission (3, 6, 7).

Psychological mechanisms: Illness-related cognitions (i.e., patients’ views or beliefs about their illness) are key determinants of behavior directed at managing illness and of psychological well-being across diseases (8). Illness-related cognitions are potentially amenable to intervention which could reduce disability and improve functioning. The cognitive emotion regulation strategies, .i.e., coping styles, that people use, play an important role in the relationship between the experience of negative life events and the reporting of symptoms of anxiety and depression or onset of disorders (9). Psychological resilience, a personality characteristic that is defined as the ability to adapt positively to adversity, can mitigate the negative effects of illness on subjective well-being (10).

Social factors: Social support can protect patients from the negative consequences of illnesses. Social isolation after infection and in general COVID-19 lockdown restrictions are likely to reduce social support and lead to feelings of loneliness, both negatively influencing health outcomes. Hospitalized COVID-19 patients are not allowed to receive visits from relatives/ family members and only have contact with health care workers wearing protective clothing. Patients with mild COVID-19 have to self-isolate themselves at home, which had a profound negative mental health impact in previous infectious diseases outbreaks (11). Both patients with severe and mild disease are thus severely deprived of social support in the early phase of illness. Unlike previous infectious diseases outbreaks, recovered COVID-19 patients return to a society were lockdown restrictions might still be active and where many people are facing continuous social restrictions, uncertain job prospects and financial difficulties which are expected to add to the impact of COVID-19 disease.

Post-infectious symptoms: Persistent (low-grade) inflammation (PLGI) is believed to play a role in the persistence of reduced mental health and HRQL among patients in remission after infectious diseases (12). PLGI is characterized by an increase in the level of circulating pro-inflammatory compounds, such as acute phase proteins [e.g., C-reactive protein (CRP)] and cytokines [e.g., interleukin (IL)-6], and/or by a pro-inflammatory activity of circulating or tissue resident immune cells PLGI is common in people with obesity, is associated with the development of atherosclerosis, type 2 diabetes, and hypertension, well known comorbidities that adversely affect the outcomes of patients with COVID-19 and could thus be expected to influence long term mental health and HRQL. Moreover, PLGI by itself is associated with subsequent

depression (13) and anxiety (14). Transient increases in systemic inflammation are observed in response to acute psychosocial stress, with larger responses among individuals reporting adverse psychosocial states or conditions. Also, PLGI can lead to chronic fatigue (15). Post-infectious chronic fatigue, defined as severe fatigue persisting for more than 6 months after infection, is one of the most common symptoms following infectious diseases, e.g. more than 40 percent of patients following SARS and 20 percent of patients following Q-fever reported chronic fatigue. In patients with COVID-19, post-infectious chronic fatigue is a major concern, with fatigue during the acute phase being one of the most common symptoms (16). A substantial subgroup is expected to develop persistent fatigue. Post-infectious fatigue is most likely multi-factorial determined.

The unique feature of the proposed study is that we will investigate the above mentioned factors and their interactions longitudinally among patients who were recently infected with COVID-19. Psychosocial- and biological risk factors often partially overlap and mental health problems and reduced HRQL are believed to be caused by a dynamic interaction of ***psychosocial and biological factors***. Illness-related cognitions, cognitive emotion regulation strategies, resilience and social factors could both serve as risk factors as well as protective factors for long-term mental health and HRQL.

DESIGN

We will study mental health and HRQL following COVID-19 infection longitudinally in the recently established prospective RECOVERED/VIS-cohort of patients recovered from COVID-19 (ZonMW grant 10150062010002).

STUDIE POPULATIE/DATABRONNEN

In the RECOVERED/ VIS cohort, non-hospitalized and hospitalized individuals with COVID-19 infection, aged 16 years and older, are invited to participate. Non-hospitalized patients with mild disease are recruited after case notification at the GGD Amsterdam. Hospitalized COVID-19 patients are recruited at Amsterdam UMC (AMC and VUMC). Enrolment started in May, 2020 and by July 1, over 100 participants were included, and recruitment will continue until 300 participants are in follow-up. A biobank with specimens including sera of COVID-19 patients from the cohort is in place. At enrolment, and day 7 data on COVID-19 related symptoms and disease, and comorbidity including psychiatric comorbidity, and specimens are collected, followed by monthly study visits including clinical data and specimen collection at GGD or Amsterdam UMC. At the follow-up visits at months 1, 3, 6, 9 and 12, participants are also asked to complete validated self-administered questionnaires. The following concepts are measured:

Outcome measures:

-**Health-related quality of life** (short form 36-item health survey (SF36))
-**Mental health** (depression, anxiety (Patient Health Questionnaire (PHQ-SADS), post-traumatic stress (Post-Traumatic Stress Disorder Test (PTSD-5) (PCL-5)).
-**Fatigue** (Checklist Individual Strength (CIS), Short Fatigue Questionnaire (VVV)

HRQL is the overarching outcome measure. We will more specifically focus on the domains mental health and fatigue because we anticipate these will be most relevant for long-term HRQL based on previous research.

Potential influencing factors:

-**Psychological mechanisms and responses** (illness and symptoms related beliefs (brief illness perceptions questionnaire (B-IPQ), Cognitive Behavioural Responses to Symptoms Questionnaire *(*CBRSQ**)** coping style *(*cognitive emotion regulation questionnaire (CERQ-10)), resilience (brief resilience scale (BRS-6), negative life events (adapted version NEMESIS))
-**Social factors** loneliness (De Jong Gierveld CBS), quantity of social contacts and social distancing (CRF RECOVERED/VIS cohort, in line with questions of national behavioral survey/panel of GGD/RIVM).
-**Biological and medical factors**, (inflammation profiles **(**cytokines IL-6 and TNF-alpha and CRP), determined on specimens that are stored in the biobank), disease severity (i.e., hospitalized or non-hospitalized for COVID-19) , length of hospitalization and ICU stay, having received mechanical ventilation, physical symptoms, comorbidity (e.g. obesity, diabetes), history of psychiatric illness (derived from the CRF RECOVERED/ VIS cohort).

Sociodemographic factors:
Age, gender, ethnicity and educational level (CRF RECOVERED/ VIS cohort). We will describe the diversity of our sample in terms of these demographics and explore the extent to which demographics are related to outcomes and influencing factors.

VERWACHTE UITKOMST (in parameters of beschrijvend)

At the end of the study we expect to have:

- A characterization of the mental health and HRQL trajectories of patients who recovered from COVID-19 with different levels of disease severity.
- Insight in the psychological- social- and biomedical factors that contribute to mental health and HRQL trajectories and how these factors interact with each other, with an emphasis on psychological- and social factors.
- Determined the profile of individuals at risk of trajectories characterized by persistently or recurrently reduced mental health and/ or HRQL. In addition, we have designed strategies for early detection of these individuals at risk (who and when) and have designed strategies for tailored referral to additional support and/ or intervention.

DATA-ANALYSE

We will use state-of-the-art computational modeling methods, such as latent class analysis, to determine mental health trajectories and HRQL to gain a better understanding of the multi-faceted psychosocial and biomedical factors and their potential interactions contributing to these trajectories.
A novel modelling method, stable specification search for longitudinal data [S3L], based on Structural Equation modelling and allowing modelling of causal relationships between longitudinal data, will be applied (17). A separate analysis will be conducted for trajectories of each outcome measure, i.e., HRQL, fatigue, mental health (depression, anxiety, PTSS). Trajectories of outcome measures and the potential psychological mechanisms (illness cognitions, coping style, resilience, cognitive behavioral responses to symptoms and negative life events), the social factors (loneliness, social distancing, social contacts) and biomedical- factors (inflammation profile, disease severity, length of ICU stay, duration of mechanical ventilation, comorbidity e. g. obesity, diabetes) and socio-demographic factors (age, gender, ethnicity, educational level) as assessed at the different time-points will be entered simultaneously into the model. Relationships between variables will be identified by analyzing the data repeatedly, for different data-subsets. The results from the repeated analyses will be integrated and model-fit determined in order to arrive at a final optimal model that includes stable causal relationships.
For each association between variables, a reliability score and an estimated total causal effect, are given. A high reliability score (> 0.6) indicates a high likelihood that the relationship is part of the causal mechanism. The estimated total causal effect indicates the size and direction (positive/negative) that the cause has on its effect. All analyses will be conducted in the R-package stablespec.
A main advantage of S3L is that it can test a large number of relationships between variables in longitudinal data. S3L will allow us to investigate the dynamic interplay between potential influencing psycho-social, biomedical and outcomes over time. Compared to other, constraint-based, approaches to causal discovery, S3L has the advantage that it directly searches through Structural Equation Models. This makes the analysis and results easier to understand and to reproduce for other researchers in the field.

POWERBEREKENING (indien van toepassing)

Since our analyses are intrinsically quite complex and sometimes more exploratory than confirmatory, it is difficult to provide a precise power analysis. Effect size measures and power curves to predict power for the bootstrap likelihood ratio test (BLRT) in latent class analysis have been studied extensively (18). For medium effects sizes and more or less uniform distributions over the classes, on the order of 100 individuals are needed for the BLRT to achieve a power of 80% for distinguishing between a model with three versus two classes. Exploratory studies using S3L have been successfully conducted with samples of about 150 individuals with (on average) three longitudinal measurements [S3L]. As the RECOVERED/VIS cohort aims to enroll 300 patients, this number will be sufficient to conduct the planned analyses.

4. PLAN VAN AANPAK (ONDERBOUW KEUZES)

TIJDSSCHEMA (maak daarbij duidelijk wanneer de eerste resultaten worden verwacht)

The project will be conducted within 24 months and will start not later than not later than September, 2020.

September 2020 – September 2021: The recruitment and follow-up of participants in the COVID-19 RECOVERED/VIS cohort is already ongoing. In the first 2 months, we will organize a stakeholders meeting for which patient representatives (from RECOVERED/VIS cohort and Q-support), representatives of Home Care organizations (i.e., Sigra), general practitioners, pulmonary- and rehabilitation physicians and infectious diseases specialists will be invited as they are all involved in the aftercare of COVID-19 patients. Patient representatives and representatives of home care organizations and general practitioners will also be invited to join the advisory board of the project. Within the proposed add- on study the first year will be used to collect additional data from the cohort participants on persistent physical symptoms, mental functioning, illness related beliefs and coping style. In the first year a systematic review will be conducted to select the biomarkers which are likely candidates to be related to mental health and HRQL, both directly as indirectly, e.g. as determinants of post-infectious fatigue. These biomarkers will be determined on stored specimens in the biobank. We will perform preliminary statistical analyses to determine the mental health and HRQL trajectories.

September 2021 – September 2022: During the second year, the last patients are expected to have their final assessment of mental health, HRQL and potentially influencing psychosocial and biomedical factors The second year will be used to analyze the complete data set and prepare the manuscripts reporting the results, which will be submitted to peer-reviewed journals. We will organize a second stakeholders meeting with the patient representatives, and representatives of home care organizations, general practitioners, pulmonary- and rehabilitation physicians and infectious diseases specialists to interpret and discuss our findings and implications for clinical practice. We will draft guidance on how and when to identify vulnerable patients since the start of infection and on appropriate referral for additional support and/or intervention.

MOTIVATIE HAALBAARHEID

The instruments to assess mental health, HRQL and their possible determinants are already selected and permission for their use is already given by the Medical Ethical Committee of the Amsterdam UMC when reviewing the RECOVERED/ VIS study. A biobank with specimens including sera of COVID-19 cohort patients is in place. The recruitment of patients is ongoing with over 100 patients enrolled by July 1, 2020. The proposed project is an add-on study of the RECOVERED/ VIS cohort consisting of an in-depth analysis of psychosocial factors and their interaction with biomedical factors that contribute to mental health and HRQL trajectories. Results will be translated into strategies for tailored referral to additional support/ intervention. This ad-on study will not be possible without additional funding. The mental health and HRQL research group formed by experts in mental health and psychiatry (dr.Anja Lok), health related quality of life (dr Pythia Nieuwkerk), social and behavioral factors in health outcomes (dr. Udi Davidovich), infectious diseases epidemiology (Prof Maria Prins), medical microbiology (Prof. Menno de Jong), general practice and family medicine (Dr Eric Moll van Charante), persistent post-infectious symptoms (Prof Hans Knoop) and analyses of longitudinal data and other modern computational methods including machine learning (Prof. Tom Heskes) is well equipped to answer the research questions.

RECRUTERINGSSTRATEGIE (indien van toepassing)
Recruitment will be via the ongoing COVID-19 RECOVERED/VIS cohort

5. RELEVANTIE

OPROEP SPECIFIEKE RELEVANTIE CRITERIA

The proposed study will contribute to alleviating the negative long-term impact of the COVID-19 pandemic by identifying psychosocial risk factors for long-term mental health problems and impaired health-related quality of life among COVID-19 patients, and provide guidance for identifying vulnerable patients at risk. The results of the proposed project will enable health care professionals and policy makers to target persons most in need of intervention and to tailor their evidence-based health care services to address these appropriately.
To the best of our knowledge, ongoing research among COVID-19 patients currently focusses primarily on biomedical aspects but not on psychosocial aspects. The focus on longitudinal psychosocial aspects, mental health and health-related quality in a dynamic model is thus a unique feature of the proposed study.

The knowledge that will be acquired in the proposed study will be available for future regional and national applications in health care strategies/ policies. We will draft guidance on how and when to identify vulnerable patients and for appropriate referral of these patients to additional support and/or intervention. At the start of the project, representatives of patients (RECOVERED/ VIS cohort and Q support), and home care organizations (i.e., Sigra, Amsterdam) and general practitioners are invited to join the advisory board of the project. A general practitioner and a psychiatrist are members of the project team. Other relevant

stakeholders (pulmonary- and rehabilitation physicians and infectious diseases specialists) are invited to participate in stakeholders meetings at the beginning and end of the project.

ZONMW ALGEMENE RELEVANTIE CRITERIA

Diversity: potential differences between males and females, various age-groups and ethnic groups in mental health, health-related quality of life and possible influencing psychosocial factors are taken into account in our analysis and results. Guidance for identifying persons at risk and referral to additional support/intervention (primary and/or secondary care) will be made by sex, age and ethnicity specific if indicated.

Education of relevant health care providers: The main findings of the project will be sought to be integrated into the education of infectious diseases specialists and general practitioners as they are the primary entry point for COVID-19 patients into health care and also in the training of psychiatrists and psychologists working in primary and secondary care as COVID-19 patients with most severe mental health problems are expected to be referred to them.

Participation of patients/ end users: Representatives of patients (RECOVERED/ VIS cohort and Q support) and home care organizations (i.e., Sigra, Amsterdam) and general practitioners are invited to join the advisory board of the project. We will ask their advice in all phases of the project (e.g., data collection, interpretation of findings, dissemination). A general practitioner and a psychiatrist are members of the project team. Other relevant stakeholders (pulmonary- and rehabilitation physicians and infectious diseases specialists) are invited to participate in stakeholders meetings at the beginning and end of the project.

6. PROJECTGROEPLEDEN EN HUN ROLLEN

Onderbouw dat in de projectgroep relevante disciplines met de juiste expertise en beoogde einddoelgroep(en) zijn vertegenwoordigd. Maak helder welke deelnemers aan de projectgroep welke rol hebben. Geef bij voorkeur werkpakketten aan.

The project team members, their respective disciplines and roles are listed below:
Prof Tom Heskes, discipline Data Science, will supervise the statistical analyses
Prof Maria Prins, discipline Infectious Diseases Epidemiology and Prof. Menno de Jong, discipline Medical Microbiology are the principal investigators of the RECOVERED/VIS cohort and will oversee the entire project and provide epidemiological and biomedical expertise.
Dr Eric Moll van Charante, discipline General Practice/ Family Medicine, will provide expertise from the perspective of general practitioners, provide input on guidelines for identifying patients at risk and appropriate referral, implementation and dissemination
Dr. Anja Lok, discipline Psychiatry and somatic comorbidity, dr Pythia Nieuwkerk, discipline Medical Psychology, Prof Hans Knoop, discipline Medical Psychology, and dr. Udi Davidovich, discipline Social Psychology/ Behavioural Science will provide expertise on mental health, health-related quality of life and psychosocial risk factors post-infectious symptoms.
Pythia Nieuwkerk is the project leader and is responsible for the daily management of the project and the supervision of the junior researcher and post-doc (part-time) (requested personnel)

7. KENNISOVERDRACHT, IMPLEMENTATIE, BESTENDIGING

Beschrijf hoe u de kennis opgedaan in uw project gaat delen, en hoe u de resultaten en/of producten verder gaat brengen richting implementatie, bijvoorbeeld door toepassing in de praktijk, of bij het vormen van beleid.

In the project we will determine which individuals are at risk of trajectories characterized by persistently or recurrently reduced mental health and HRQL and design guidance for identifying these individuals at risk (how and when). These individuals may benefit from timely and appropriate referral and from existing evidence-based support and/or interventions (e.g. peer-support, counselling, cognitive behavioral therapy, further psychiatric examination, depending on the severity and duration of their symptoms and/or reductions in HRQL) and possibly need new interventions.

This knowledge will be shared with health care professionals involved in the long-term care of recovered COVID-19 patients, i.e., general practitioners, home care/ primary care, pulmonary- rehabilitation physicians and infectious diseases specialists. Representatives of these health care professionals are invited to participate in stakeholders meetings and/ or are invited to participate in an external advisory board. We will share our (interim) results with our colleague researchers and professionals through presentations at (inter) national conferences (e.g. NHG- conference, meetings of patient organizations), and write and publish our findings in (inter) national peer-reviewed (open access) journals.

At the end of the project we will organize a symposium in collaboration with our stakeholders for which patients, health care professionals and researchers will be invited to present our findings and to discuss the implications. We expect the project will create awareness of the long-term mental health and HRQL impacts of serious infectious diseases outbreaks. This will enable health care professionals to be prepared for current and potential future needs COVID-19 patients and/or future infectious diseases pandemics.

8. DEELNAME VAN DE STAKEHOLDER(S)/EINDDOELGROEPEN

Beschrijf welke partijen (die mogelijk geen mede-aanvrager zijn, bijvoorbeeld patiënten, zorgprofessionals) op welke manier bij uw project worden betrokken.

Patients and health care workers are important stakeholders in this project. Patient representatives (from RECOVERED/ VIS cohort and Q-support, an organization that is active in the support of COVID patients), representatives of home care organizations and general practitioners are invited to join the project in the advisory board. Pulmonary- and rehabilitation physicians and infectious diseases specialists are health care professionals involved in the aftercare of COVID-19 patients. They are invited to participate in a stakeholders meeting at the beginning and at the end of the project. A general practitioner and a psychiatrist are members of the project team. Involving these stakeholders from the start of the project is key for the appropriate design, interpretation, future implementation of study findings and the wider dissemination of study results.

9. LITERATUURREFERENTIES:

Vermeld hier de referenties die uw aanvraag inhoudelijk onderbouwen en vermijd opsommingen van publicaties van uw projectgroep(leden).

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ZonMw Budget Format

	Name organisation	Type of organisation	Quoted costs	Quoted co-funding	Requested budget
1	AMC	Research Organistion	225.765,64	-	225.765,64
2			-	-	-
3			-	-	-
4			-	-	-
5			-	-	-
6			-	-	-
7			-	-	-
8			-	-	-
9			-	-	-
10			-	-	-
		Total	225.765,64	-	225.765,64

Staff costs					
			Costs	Own contribution / 3rd party co-funding	Requested budget ZonMw
Position / Name (will be filled based on "staff"sheet)	Description of activities within project	Organisation (dropdown menu)			
AMC		AMC	€ 112.851,00	€ -	€ 112.851,00
AMC		AMC	€ 17.421,30	€ -	€ 17.421,30
to be specified			€ -	€ -	€ -
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			€ 130.272,30	**€ -**	**€ 130.272,30**

Material, equipment & consumer goods (itemised)					
			Costs	Own contribution / 3rd party co-funding	Requested budget ZonMw
	What item(s)	Used for	Organisation (dropdown menu)		
1	Open Acces Publication		AMC	€ 5.000,00	€ -	€ 5.000,00
2	Cytokine bepalingen		AMC	€ 30.000,00	€ -	€ 30.000,00
3	Vacatiegelden		AMC	€ 2.160,00	€ -	€ 2.160,00
4	Data stewardship		AMC	€ 10.000,00	€ -	€ 10.000,00
5	Implementatiekosten		AMC	€ 5.000,00	€ -	€ 5.000,00
6	Benchfee		AMC	€ 3.333,34	€ -	€ 3.333,34
7	0			€ -	€ -	€ -
8	0			€ -	€ -	€ -
9	0			€ -	€ -	€ -
				€ 55.493,34	**€ -**	**€ 55.493,34**

Other costs (itemised)					
			Costs	Own contribution / 3rd party co-funding	Requested budget ZonMw
	Description	Used for (dropdown menu)	Organisation (dropdown menu)		
1	Statistische analyses (Radboud)		AMC	€ 40.000,00	€ -	€ 40.000,00
2	0			€ -	€ -	€ -
3	0			€ -	€ -	€ -
4	0			€ -	€ -	€ -
5	0			€ -	€ -	€ -
6	0			€ -	€ -	€ -
7	0			€ -	€ -	€ -
8	0			€ -	€ -	€ -
9	0			€ -	€ -	€ -
				€ 40.000,00	**€ -**	**€ 40.000,00**

Total costs project	€ 225.765,64
Own contribution / co-funding	€ -
TOTAL REQUETED BUDGET ZONMW	€ 225.765,64

Additional explanation for budget

Approval financial responsible receiving organisation

Receiving organisation	**AMC**
Name:	**Daniël Wilbords**
Position:	**Project controller**
E-mail adres:	**d.wilbords@amsterdamumc.nl**
Date:	**13-07-2020**

D. Toelichting op de begroting

Personeelskosten: wij vragen 1.0 fte junior onderzoeker/OIO en 0.1 fte post doc voor 24 maanden.

De junior onderzoeker is verantwoordelijk voor de coördinatie van de uitvoering van het onderzoek v.w.b dit project (vragenlijsten worden volgens planning ingevuld, actie ondernemen bij non-response, meehelpen met dataverzameling), organiseert de bijeenkomsten met de adviesraad/stakeholders meetings en het eindsymposium, voert de systematische review uit, draagt zoveel mogelijk bij aan statistische analyses (interim en definitieve analyses) onder begeleiding van de Data Science groep van het Radboud Nijmegen, presenteert onderzoeksresultaten op (inter) nationale congressen, schijft artikelen (inter) nationale peer-reviewed tijdschriften en voor de doelgroep.

De post –doc ondersteunt de junior onderzoeker. Dit is nodig omdat de junior onderzoeker snel zal worden ingezet voor de lopende dataverzameling en de relatief korte duur van het project.

Materiaal kosten: Dit zijn de kosten voor(1) het bepalen van het cytokine profiel van 300 patiënten. Dit profiel zal worden bepaald vanuit materiaal dat is opgeslagen in de biobank die is opgericht ten behoeve van het cohort. (2) kosten tbv data management voor dit project

Implementatie kosten: Kosten voor het organiseren van het eindsymposium voor patiënten, stakeholders en wetenschappers.

Statistische analyse/ methodologische ondersteuning: Dit zal worden gedaan door de Data Science groep van de Radboud Universiteit in Nijmegen volgens een door hen ontwikkelde statistische methode.

Kosten voor data steward/ open access publiceren

Vacatiegelden: Een patiënten vertegenwoordiger vanuit het RECOVERED/ VIS cohort en vanuit Q-support, en een vertegenwoordiger vanuit thuiszorg en huisartsen worden gevraagd om deel te nemen aan een adviesraad. Met deze adviesraad zal overleg zijn het begin en aan de eind van het project. Zij ontvangen een vergoeding per vergadering.

Bijlage E. Reactie opmerkingen e-mail positief advies

Dossiernummer: 50-56300-98-913

Graag reageren wij hierbij op de opmerkingen van de commissie bij ons positief advies.

De commissie noemde de volgende punten:

- De commissie vindt uw projectvoorstel erg relevant en is positief over de aansluiting bij het RECOVERED/VIS cohort. In de uitwerking van het projectidee ziet de commissie graag dat het socio-psychologische aspect sterker naar voren komt dan het medische aspect van het onderzoek.

Wij zijn verheugd dat de commissie het projectvoorstel erg relevant noemt en positief is over de aansluiting bij het RECOVERED/VIS cohort. Wij denken dat de aansluiting bij dit cohort een unieke kans biedt om het beloop van de mentale gezondheid en kwaliteit van leven op de langere termijn in kaart te brengen en na te gaan hoe deze wordt beïnvloed door psychosociale factoren.

Door duidelijk te maken welke patiënten risico lopen op een minder goede lange termijn mentale gezondheid en kwaliteit van leven, hoe en wanneer deze patiënten het beste geïdentificeerd kunnen worden, en het beste kunnen worden doorverwezen naar bestaande evidence-based ondersteuning en interventies hopen wij een bijdrage te leveren aan het verbeteren van de zorg aan deze patiënten.

Wij hebben bij de uitwerking van het projectidee de psychosociale factoren sterker naar voren gebracht dan de biomedische factoren door de sociale factoren verder uit te werken en de psychologische factoren verder onder te verdelen in psychologische reacties en psychologische mechanismen. Voor zover wij kijken naar medische factoren, bekijken wij deze steeds in de interactie met psychosociale factoren. Wij denken dat juist het kijken naar deze interactie tussen psychosociale- en biomedische factoren binnen dit cohort uniek is en een toegevoegde waarde heeft ten opzichte van het afzonderlijk bekijken van psychosociale en medische factoren.

- De commissie mist samenwerking met huisartsen en thuiszorg in het onderzoek. Zij vraagt in de uitgewerkte aanvraag inzicht te geven in hoe huisartsen en thuiszorg betrokken worden bij het onderzoek.

Wij zijn de commissie erkentelijk voor het attenderen op het belang van de samenwerking met huisartsen en thuiszorg binnen het onderzoek. Wij onderschrijven dit van harte. Wij hebben een hoogleraar Huisartsgeneeskunde benaderd om lid te worden van het onderzoeksteam en medeaanvrager te zijn.

Vertegenwoordigers van thuiszorg (Sigra, Amsterdam) en een patiënten organisatie (Q support) en huisartsen zijn benaderd om deel te nemen aan een adviescommissie. Daarnaast zal een patiënten vertegenwoordiger vanuit het RECOVERED/ VIS cohort worden gevraagd om deel te nemen aan de adviesraad. Deze adviescommissie zullen wij raadplegen tijdens de verschillende stappen van het onderzoek. Vertegenwoordigers vanuit longartsen, infectiologen en revalidatieartsen worden uitgenodigd voor een stakeholders meeting bij de start en aan het eind van het project om mee te denken over de opzet van het onderzoek en de betekenis van de resultaten voor de zorgpraktijk. Zij

worden betrokken bij het opstellen van adviezen naar aanleiding van het onderzoek en disseminatie. Bovendien is een psychiater lid van het onderzoeksteam en medeaanvrager.

Checklist

for Open science & FAIR data elements in the COVID-19 research programme

Version 1.1 26 May 2020

This checklist is for the first 4 out of **8 requirements and recommendations** for the **activities for open science and FAIR** data. They relate to the preparation phase of a research project.
The checklists shows a number of options for open science and FAIR data. Please consult **Open science in COVID-19 research** for more information about what you can do, for recent updates on the guidance, new practices, and instructions.

Choose the options that suit your project best!
The purpose of the checklist is to fill in the options that you choose for your project. Discuss with your data steward (or other data expert) the options that suit your project best. If you have options that are not listed below, you may indicate this as well.

Please fill in the form and attach it to your grant application.

Requirements & Recommendations	Applicants must report as follows
The preparation phase: grant application	
Who is the data steward who supports the open science and FAIR data planning in your project? Check the website for ZonMw's webinars to inform and support data stewards.	☒ I involve a data steward: Name: Rudy Scholte Institute: Amsterdam UMC E-mail: r.a.scholte@amsterdamumc.nl ☐ I do not have a data steward yet, because Klik of tik om tekst in te voeren.
Requirement 1: Alignment and reuse Please show the options for reusing data, biological materials, and/or other resources (from research or from practice) in your project. Check whether it is possible to use resources that are made in the context of COVID-19.	Name the existing resources that you plan to use: ☒ Data: **We will integrate our study within an existing cohort study.** ☒ Biological materials: cytokine profielen ☒ Research software: SPSS, R (Studio), Castor ☐ Other resources, i.e. Klik of tik om tekst in te voeren. ☐ No, I will not use existing resources, because Klik of tik om tekst in te voeren. Please mark the resources that you indicated above in **bold** if it is a COVID-19 related resource
Requirement 2: preregistration of all animal studies **(for all other studies, preregistration is strongly recommended)** You are required (for animal studies) and recommended (for all other studies) to preregister your research	☐ In case of preregistration: Provide the link or registration code: Klik of tik om tekst in te voeren. ☐ For animal studies, the code at the Preclinical Trial Register is: Klik of tik om tekst in te voeren. ☐ No, I do not preregister my research proposal.

plan (including the protocols, methods, etc).	
Requirement 3: FAIR data within COVID-19 research community **Choose the options that suit your project best!** Here you can show the COVID-19 specific standards, technology or infrastructure for FAIR data that you have selected to apply during your project. Once your application is granted, you can use these to fill in your data management plan (DMP) (= requirement 5). Read for more information: Open science in COVID-19 research and 3.Creating FAIR data, tailored to COVID-19	Name the COVID-19 specific FAIR data standards, technologies or infrastructure that are applicable in your study, and you plan to use: ☐ eCRF of the WHO (machine actionable) ☐ A COVID-19 related or other FAIR data point ☐ COVID-19 research platform for data sharing ☐ Data will be recorded in RDF format ☐ I plan to use the metadata scheme that will be developed for COVID-19 research (planned in summer 2020) ☒ Other COVID-19 related standards, etc: Data collection within existing COVID-19 cohort. ☐ Collaboration with COVID-19 data collection(s), namely Klik of tik om tekst in te voeren. ☐ A new standard, technology or infrastructure will be developed in the project with the COVID-19 research community, namely Klik of tik om tekst in te voeren. Comment on your choice(s) Klik of tik om tekst in te voeren. ☐ None of the above. Comment: Klik of tik om tekst in te voeren. ☐ I did not decide yet.
Requirement 4: Budget for FAIR data and Open Access Publications You need to plan a budget for open science and research data management during your research project. This budget should include costs for data stewardship, and – if applicable - costs for additional services from data service providers (e.g. from Health-RI or other providers), or extra e-infrastructure.	**Explain how you budgeted for open science and FAIR data in your project:** ☐ I specified the costs in the budget form. ☒ I cannot specify the costs right now, and make a reservation of 5% maximum of my research budget for data stewardship. ☐ I did not budget the costs, because Klik of tik om tekst in te voeren. **When you fill in the budget form, you could consider the following aspects:** ○ Data stewardship ○ Data services providers ○ Additional e-infrastructure, exceeding the regular institutional infrastructure. ○ Other open science and FAIR data related costs. ○ (Optional) Open access publication(s): ZonMw requires researchers within the covid-19 programme to make all publications resulting from scientific research, that is fully or partially subsidised by ZonMw, immediately (without embargo) open access available with an open license. You are allowed to include costs for full gold Open Access publications in the project budget up to a maximum amount of € 5000,- (specify with 'Open

	Access'). Immediate Open Access publishing via other routes is also permitted, but ZonMw does not provide financial resources for this. For the specific conditions we kindly refer to the programme texts.