Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**Identification of COVID-19 patients with high Risk of mortality at ICU admiSsion – IRIS-study**
Projecttaal / Project language	:	**Engels / English**
Geplande startdatum / Planned start date	:	**27-07-2020**
Geplande duur / Planned duration	:	**24 maanden / months**
Datum indienen / Date of application	:	
Projecttype / Project type	:	**Toegepast onderzoek / Applied research**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

Prof. dr. D. de Lange (Main applicant)
Functie / Position: Full professor, secretaris NICE | *Opleiding / Education:*
Studierichting / Subject:
Nationale Intensive Care Evaluatie
Meibergdreef 15
1105 AZ AMSTERDAM ZUIDOOST

Prof. dr. N.F. de Keizer (Projectleader and secretary)
Functie / Position: Full Professor | *Opleiding / Education:*
Studierichting / Subject:
Amsterdam UMC
Meibergdreef 9
1105 AZ AMSTERDAM ZUIDOOST

Dr. D.A. Dongelmans (Administrative responsibility)
Functie / Position: Intensivist, voorzitter NICE | *Opleiding / Education:*
Studierichting / Subject:
Nationale Intensive Care Evaluatie
Meibergdreef 15
1105 AZ AMSTERDAM ZUIDOOST

Prof. dr. A. Abu-Hanna (Co-Applicant)
Functie / Position: Full professor | *Opleiding / Education:*
Studierichting / Subject:
Amsterdam UMC
Meibergdreef 9
1105 AZ AMSTERDAM ZUIDOOST

M.S. Arbous (Co-Applicant)
Functie / Position: Head of education / senior researcher | *Opleiding / Education: Studierichting / Subject:*
Leids Universitair Medisch Centrum
Divisie 1
Intensive Care
Postbus 9600

2300 RC LEIDEN

Dr. P.W.G. Elbers (Co-Applicant)
Functie / Position: Intensivist | *Opleiding / Education:*
Studierichting / Subject:
Amsterdam UMC
De Boelelaan 1117
1081 HV Amsterdam

Prof. dr. M. van der Schaar (Project advisor)
Functie / Position: Full professor Machine learning | *Opleiding / Education:*
Studierichting / Subject:
University of Cambridge
Tennis Court Road 80
CB2 1GA CAMBRIDGE

Dr. M.C. Schut (Co-Applicant)
Functie / Position: Universitair docent | *Opleiding / Education:*
Studierichting / Subject:
Amsterdam UMC
Meibergdreef 9
1105 AZ AMSTERDAM ZUIDOOST

Projectgegevens / Project information

Aandachtsgebieden / Focus

1.1 Thema's aandachtsgebied 1

- Risicoanalyse en prognostiek

1.3 Setting

- Ziekenhuiszorg

Samenvatting / Summary

[ONDERZOEKSVRAAG]
Het doel van dit project is patiënten kenmerken bij IC-opname te identificeren die geassocieerd zijn met ongewenste uitkomst, t.w., extreem lange behandelduur en sterfte (IC en ziekenhuissterfte, als ook 90, 180 dagen sterfte).

[URGENTIE]
Ondanks dat de piek van COVID-19 patiënten op de IC achter ons ligt, worden dagelijks nog nieuwe COVID-19 patiënten opgenomen op de Nederlandse IC's. De zorg voor niet-COVID-19 patiënten start ook weer op, waardoor de druk op de IC capaciteit hoog blijft zeker bij een volgende golf COVID-19 infecties. Het is voor triage uitermate belangrijk om patiënten te identificeren waarvoor IC opname mogelijk niet van toegevoegde waarde is omdat zij een zeer hoge sterftekans of extreem lange behandelduur hebben. Deze prognostische informatie is belangrijk bij het 'samen beslissen'-proces waarin intensivisten en andere specialisten samen met de patiënt en naasten een afweging over IC-opname maken. Bestaande triage protocollen werden onder druk van een mogelijk tekort aan bedden aangescherpt o.b.v. expertkennis en zonder objectieve data te gebruiken m.b.t. uitkomsten van IC patiënten met en zonder COVID-19.

[HYPOTHESE]
Inzicht in determinanten voor ongewenste uitkomst en identificatie van hoog-risico patiënten ondersteunen en verbeteren het triage proces.

[PLAN VAN AANPAK]
In deze observationele studie gebruiken we drie reeds beschikbare en continue geüpdatet datasets: de NICE registratie, CovidPredict.org dataset en Vektis. Tezamen omvat dit alle IC-patiënten in Nederland, inclusief gedetailleerde en lange termijn uitkomstinformatie van COVID-19 patiënten. We passen statistische en machine learning technieken toe om prognostische modellen voor individuele patiënten te ontwikkelen en hoog-risico groepen te identificeren. Hoe deze predictiemodellen in de praktijk gebruikt kunnen worden t.b.v. 'samen beslissen', wordt geëvalueerd met intensivisten, andere specialisten en een panel met ex-IC patiënten met en zonder COVID-19.

Trefwoorden / Keywords

COVID-19; intensive care; machine learning; prognostic model; subgroup discovery; shared decision making; ICU triage

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	127.836	127.836	0	0	0	0	0	0	255.672
Materieel	0	0	0	0	0	0	0	0	0
Implementatie	0	0	0	0	0	0	0	0	0
Apparatuur	10.000	0	0	0	0	0	0	0	10.000
Overig	20.000	0	0	0	0	0	0	0	20.000
Totaal / Total	**157.836**	**127.836**	**0**	**0**	**0**	**0**	**0**	**0**	**285.672**

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

Regarding METC, the Institutional Research Board of the Amsterdam University Medical Centre reviewed the research proposal and waived the need for informed consent (IRB protocol W20_260 # 20.295).

AANVRAAGFORMULIER UITGEWERKTE SUBSIDIEAANVRAAG – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 15 juni 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**

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

Prof dr. Dylan de Lange, secretaris stichting NICE, intensivist in UMCUtrecht

ORGANISATIE:

Stichting NICE – Nationale Intensive Care Evaluatie (NICE) registratie

ENGELSE PROJECTTITEL:

Identification of COVID-19 patients with high Risk of mortality at ICU admiSsion – IRIS-study

NEDERLANDSE PROJECTTITEL:

Identificatie van COVID-19 patiënten met hoog sterfterisico ten tijde van intensive care opname

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)

[PROBLEM STATEMENT]
Although the peak of COVID-19 patients at the ICU is behind us, new COVID-19 patients are admitted to the ICU every day. Care for non-COVID-19 patients has restarted and therefore pressure on ICU capacity will remain high especially when a next peak of COVID-19 cases will occur. Over the last months existing **ICU triage protocols** needed to be adapted because of this pressure and a shortage of ICU beds was feared. So far these protocols are **expert-based and lack evidence-based**, data driven input.

[URGENCY]
New peak(s) of COVID-19 cases are expected to occur according to virologists, intensivists and epidemiologists. It is therefore of **utmost importance to identify COVID-19 and non-COVID-19 patients with high risk of mortality** or extreme long length of stay for whom ICU admission might not be beneficial. This information is important in **shared decision making** between intensivists and other specialists who decide on ICU admission together with patients and their families. A better insight into determinants of outcome and identification of high risk patients will support and improve triage. This allows for better allocation of ICU beds, enable informed recommendations for care trajectories of patients and improved care capacity planning.

Since the first COVID-19 patient was admitted to the ICU end of February, the NICE (National Intensive Care Evaluation) registry has played a central role in outbreak control [1]. Due to its organizational and technical infrastructure, NICE has been able to collect in semi-real time all COVID-19 cases in Dutch ICUs. RIVM used the NICE data to model needed bed capacity, and the LCPS and LNAZ used the NICE data to coordinate an equal distribution of patient load over the country. The task force "acute infectious threats" of NVIC used preliminary reports of NICE on patient characteristics and outcome [2] to update these triage protocols. During the outbreak, NICE collected data about determinants of patients at the time of admission for all COVID-19 and non-COVID-19 patients. Due to its 25 years of experience as a quality registry, NICE data is of high quality [3,4] and includes a linkage to VEKTIS data for long term mortality of ICU patients.

[OBJECTIVE]
The objective of the proposed project is **to identify patient characteristics <u>at ICU admission</u>** that are indicators for undesirable outcomes, most notably a prolonged length of stay (LoS), and mortality (in-ICU, in-hospital and in 90 and 180 days). The developed prognostic models enable us to make **individual predictions** for COVID-19 and non-COVID-19 patients, and we use these models to identify **subgroups of patients** that are at high risk. Usage of the prediction models and subgroups for the purpose of **shared decision making** is examined with the patient panel of COVID-19 and non-COVID-19 patients that have been admitted to the ICU.

[SMART]
The project objective in terms of **SMART** is as follows:
- Specific – we investigate which patient characteristics at ICU admission are indicators for undesirable outcomes. We will do this by applying machine learning techniques to large amounts of observational data, originating from electronic patient records from all Dutch ICUs.
- Measurable – all predictors and outcomes to be analyzed are carefully and precisely defined. For many years, ICUs are used to collect and upload these data to the NICE registry. The quality of the predictions from the prognostic models are measured across a range of criteria including, among others, discrimination, accuracy and calibration. The prognostic models themselves are also measured on interpretability to prevent delivering 'black box' models that perform well but we do not understand.

- Acceptable – there is support for our project in society, among patients, family and healthcare professionals. This is evident from the positive attention in the media and the fact that all Dutch ICUs participate in the NICE registry for decades. All Dutch ICUs additionally collected a small set of data items semi-real time during the recent epidemic.
- Realistic – our project group and the cooperation with many hospitals and experts guarantees sufficient data as well sufficient expertise for analysis and feedback. The data is readily available and is part of a continuous data collection process.
- Timely – the first results of the prognostic analyses are available within the first three months and hence will be available at the time a new peak of COVID-19 cases is expected. More results for short term outcomes will follow within year 1 and the results for the longer term outcomes in year 2. Dissemination of acquired knowledge (webinars, publications, newsletters, press and media) will be throughout the project when results become available.

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 most relevant related project is the CovidPredict study ''Samenwerken tegen corona met intensive care data''. We were specifically asked by the programme committee to explain what is the added value of the IRIS study over CovidPredict and how the projects cooperate.

We explain six aspects of the added value of the IRIS study.
- First, the **main data source** used in IRIS is the continuous, nationwide NICE registration. The NICE registration has existed for 25 years, covers all 80 ICUs, all of which supply ICU data on a regular basis. Through proven measures such as an extensive data dictionary including clear definitions, training for intensivists, local data managers, site visits on data quality, data set control on more than 600 data validation rules, et cetera, the NICE data is highly curated, so that high data quality is guaranteed. Due to the established technical and organizational infrastructure, data collection continues automatically, also in the event of a second or subsequent corona peak. The CovidPredict data is collected and processed more incidentally and not standardized(i.e., it is delivered digitally from the EPD, but not curated), so that afterwards relatively much work has to be done (cleaning, linking, normalizing) to develop models based on this data.
- Second, in addition to the data infrastructure, NICE has a strong **organizational infrastructure** and therefore a high degree of cooperation between intensivists. This network ensures short communication lines between ICUs and the NICE registration where data delivery and interpretation of the data are concerned. The implementation and dissemination of the results from the IRIS project will therefore be relatively easy.
- Third, due to the accumulated experience of the NICE registration, IRIS also has **long-term outcomes** (including mortality after three, six or twelve months) through the existing link between NICE and VEKTIS. This makes it possible to include these outcome measures in the forecast models to be developed during the term of IRIS.
- Fourth, **all Dutch COVID-19 patients** are enrolled in IRIS through the national coverage of the NICE registration, while CovidPredict only has COVID-19 patients from currently 24 hospitals. On top of that, NICE contains all ICU (including non-COVID) patients, so that the objective of IRIS (ICU triage of COVID-19) can be generalized relatively quickly to general ICU triage.
- Fifth, IRIS focuses on **triage at ICU admission** and CovidPredict focuses on the best outcomes of specific IC treatments. Because NICE does not contain detailed treatment data, the CovidPredict questions cannot be answered with NICE data within IRIS.Therefore, there is a clear distinction and additional value of the two projects.
- Finally, **NICE is member of LOGIC** - Linking of Global Intensive Care [13], an independent consortium of ICU databases, networks and national registries with a track record of providing quality improvement, benchmarking and clinical research to improve patients outcomes. This network make collaborations and exchange of research methods and ideas easy to realize.

In addition, there are also three points on which the project is synergistic and there is collaboration.

- Firstly, we will investigate for the limited set of ICUs that participate in NICE as well as in CovidPredict, whether the use of deep, more granular data around ICU admission will further **improve the performance** of our models. As the models need to support all Dutch ICUs, the models based on the continuous NICE quality registry will be our main result.
- Secondly, there is an **overlap of project members**, namely Nicolette de Keizer (Amsterdam UMC location AMC, penvoerder IRIS), Paul Elbers (Amsterdam UMC location VUmc, penvoerder CovidPredict) and Mihaela van der Schaar (Cambridge University, project advisor). This overlap means inherent cooperation and coordination between the projects.
- Thirdly, both projects endorse the importance of **evaluating with patients**, their caregivers and physicians how developed predictive models can best be used in the process of joint decisions between patient and physician. This evaluation is done in collaboration with the FCIC (Family and Patient Centered Intensive Care), among other things, by drawing up patient panels and organizing focus groups. The two projects will work together on this, which will benefit the availability of patients, informal carers and physicians, and will also reduce the burden on them.

3. PLAN VAN AANPAK (ONDERBOUW KEUZES)

[DESIGN]
We propose an **observational study** with data from three available and regularly updated datasets: the NICE registry, CovidPredict.org database and VEKTIS registry.

[DATA SOURCES]
The data comes from **three available and regularly updated datasets**: 1) a broad horizontal dataset originating from the NICE registry, covering **all (at June 12th: 2,903) ICU-admitted COVID-19 as well as non-COVID-19 patients** in the Netherlands which has 100% case coverage and is information rich in terms of baseline patient information such as comorbidities and aggregated patient data; 2) a deep vertical dataset originating from Amsterdam Medical Data Science – Covidpredict.org (coordinator dr Paul Elbers) covering currently 24, potentially 50, ICUs in the Netherlands. This dataset contains detailed patient and treatment data of only COVID-19 patients from which we will use data of the first hours of ICU admission (because of our triage purpose); and 3) a linked dataset between NICE and VEKTIS **for long term patient mortality**.

[DATA-ANALYSIS]
To answer our research question, we will (1) build prognostic models for mortality and extreme LoS of COVID-19 and non-COVID-19 patients at ICU admission and (2) identify subgroups of patients that are at high risk for mortality and extreme LoS based on data available at ICU admission.

As for (1), we will build **parametric (regression) models** and **non-parametric prognostic models** using **machine learning** to cover potentially complex interactions between analyzed variables. Foreseen ML methods to be included are random forests, xgboost, neural networks. In collaboration with University of Cambridge, we apply the AutoPrognosis system [5] which automates the design of ensembles of predictive modeling pipelines tailored for applications related to clinical prognosis. AutoPrognosis includes state-of-the-art imputation and data processing algorithms, feature processing algorithms and classification algorithms. For the classification algorithms, we measure, among others, predictive performance in terms of discrimination (with Area-under-the-Receiver-Operator-Curve (summarized in the c-statistic) and Area-under-the-Precision-Recall-Curve), calibration, positive predictive value and the accuracy of probabilistic predictions (with Brier (skill) scores).

As for (2) with the developed prognostics we perform **subgroup discovery analysis** [6,7] with which we identify subgroups of patients who are at high risks. Such subgroups are expressed as conditions on the features of the patients, e.g., Gender=male and BMI >= 30 and 65 =< Age =< 72. We will use Patient Rule Induction Method (PRIM) [6] that allows for the automated stratification of patients simultaneously over many features and at automatically chosen value thresholds (in contrast to subgroup analysis in e.g. RCTs where a manual process uses predetermined thresholds).

[EXPECTED OUTCOME]
In addition to the proposed model development and subgroup discovery, in the project we also address temporality and interpretability of the developed models. With **temporality** we mean two things. Firstly, in the acuteness of the outbreak, ICU admission criteria changed quickly. For example, when the number of COVID-19 patients grew and the intensity of the treatment, e.g. the long period of mechanical ventilation, became clear in March, age became a more strict criterion for admission. The data may thus have an inclusion bias in that way. Secondly, the SARS-CoV-2 virus itself may also change over time [8], adding even more to the complexity and dynamics of the prognostics that we propose. We will therefore build temporal awareness into the models. As for **interpretability**, we strive for the models to be understandable, explainable and trustworthy by the intensivists as well as patients. While a regression model has understandable covariates and coefficients, the trained features of a neural network are not so easily understood. We spend effort on this interpretability, most notably by using techniques like for example LIME [9] and symbolic metamodels [10] for making more complex models interpretable. Such interpretability, explainability and trustworthiness will allow for better shared decision making, which we will evaluate with both intensivists as well as the **patient panel** in this project.

4. PLAN VAN AANPAK (ONDERBOUW KEUZES)

[TIJDSSCHEMA]
The expected duration of the study is **two years with important milestones in between**. The planned outline of the study is
Year 1: (1) linkage of NICE and CovidPredict datasets, 1 months; (2) development and validation of prognostic models, 6 months; (3) perform subgroup discovery analysis, 5 months;
Year 2: (4) linkage with VEKTIS, for which the data is available about at project-month 12, and perform models updates, 4 months; (5) addressing bias, temporal changes and interpretability, 5 months; and (6) reporting and dissemination, 2 months.
In this outline, the **milestone deliverables** are:
month 3 – individual prognostic models on in-hospital mortality based on regression analyses;
month 7 – individual prognostic models on in-hospital mortality based on machine learning techniques;
month 9 – analysis of inclusion of high granular data (CovidPredict) in prognostic models;
month 12 – high risk patient subgroups for in-hospital mortality;
month 16 – individual prognostic models and high risk patient subgroups for long term mortality;
month 24 – final project report including temporality an interpretability of the models.

[MOTIVATIE HAALBAARHEID]
The project is very feasible within the proposed duration and will deliver first results quickly:
- NICE data on COVID-19 and non-COVID-19 patients is already available and has shown its value in RIVM models
- Preliminary univariate analyses of NICE clinical data on patient determinants for in-hospital mortality are available and promising
- Linkage of NICE data with long term outcome data of Vektis is common practice (yearly updates since 2007)
- Data of CovidPredict is currently available for 24 ICUs although it still needs to be curated. In total 50 ICUs has agreed to deliver data, and collaboration is natural because of overlap in data partners and stakeholders
- NICE provides a strong research and quality improvement collaboration network among all Dutch ICUs
- NICE has a strong research track record together with artificial intelligence researchers of dept Medical Informatics who are included in this project

Proven computational tools are available (University Cambridge) and used in practice (NHS UK).

[RECRUTERINGSSTRATEGIE]
We work with routinely collected observational data, thus a recruitment strategy is not applicable.

5. RELEVANTIE

[OPROEP SPECIFIEKE RELEVANTIE CRITERIA]

1. **Impact on the pandemic** – The results of the project will have immediate impact on the pandemic, since the results of this project will be used by the NVIC task force on infectious threats to update triage protocols. Improving triage as such will positively affect the consequences of the pandemic for the Dutch public and society. Preliminary results with short term outcomes (prolonged length of stay and mortality) are expected within three months and hence expected before a new wave of COVID-19 patients. Within year 1 a complete picture of high risk patient subgroups developed by several advanced statistical and ML analyses will become available. Further results with long term mortality are expected in year 2. The latter is not so much for scientific or technical reasons, but because the long term outcomes are not available earlier (i.e., the 1-year mortality of an ex-COVID-19 patient leaving the ICU in March 2020 can in principle not be determined until March 2021).

2. **Unique position of The Netherlands** – Although some other countries or provinces do have an ICU registration, few of them cover **all** COVID-19 patient of the whole country including an extensive set of well curated and standardized data. The NICE registry is one of the most established and productive national quality registries of the world as shown by the number of scientific publications based on its data. In our collaboration with the CovidPredict project we have additional data of a set of 24 ICUs to investigate the value of this deep, fine-granular data to increase the performance of a ICU triage model.

3. **Research is not done elsewhere** – in section 2 we described the added value of the IRIS study over the CovidPredict study (ZonMw COVID-19 programme, urgent research track), as well as cooperation between these projects. Other related research is in the UK, about which we stay well informed during the project through the involvement of prof. dr. van der Schaar – this research also uses machine learning for planning and managing COVID-19 treatment resources, but specifically looks at predicting demand for intensive care (ICU) beds and ventilators [11]. Through NICE's collaboration in the international LOGIC - Linking of Global Intensive Care project [13] we are well aware of research performed by other national ICU registries.

4. **Public finance required** – The NICE registry is financed by ICUs themselves. The yearly contribution paid is used to process the data of the individual ICUs and transform these data into audit and feedback information in order to monitor and improve quality of care. There is no budget for research and therefore this project is dependent on public funding.

5. **Reusability** – the research structure and knowledge of the project can be reused (e.g., study design, analysis protocols will be published) when more data becomes available over time. Also the study structure and acquired knowledge can be used internationally by other ICU registrations, also allowing for subsequent comparison of results between countries. The NICE registry has become data partner of the EU FAIR initiative OHDSI-EHDEN which will result in a FAIR datastation of NICE data enabling external parties to use the data. Also, in the project we will work together with and contribute to the existing AmsterdamUMC initiatives for making COVID data FAIR.

6.**Scalability** –the involved NICE and NVIC organizations can apply the acquired knowledge on the national level, for analysis of COVID-19 patients in ICU and updating triage protocols, respectively. When we obtain results about which characteristics affect undesirable ICU outcomes (prolonged length of stay and mortality), this knowledge can be applied in all Dutch ICUs.

7. **Cooperation** – the members of the project and involved advisors and experts cover the main stakeholders as the research topic (ICU triage) is concerned. We have included a patient panel of COVID-19 and non-COVID-19 patients that have been admitted to the ICU.

8. **Added value** – the project has significant and long-lasting added value in terms of health gains for patients: better informed admission to ICU; reduced suffering: preventing ICU admission when this is expectedly not effective, and improvement of processes: in particular for the ICU triage process.

9. **Society and economy** – avoiding unnecessary ICU admissions will save inconvenience for patients and their informal care takers as well as avoid costs for society. In-hospital mortality is approximately 30% among COVID-19 cases admitted to the ICU. On average a treatment for surviving COVID-19 patients takes three weeks and for non-survivors two weeks at the ICU, a treatment day in ICU costs approx. €2500. If we can avoid 20% of unsuccessful cases in a new wave of again 3000 patients this will save 0.3 x3000 x 0.2 x 14 x €2500= €6.300.000. But most of all, in case of a new wave of COVID-19 patients the limited amount of ICU beds and ICU nursing capacity need to be used for those patients with the best survival chances. Our project will contribute to this. In a broader societal context, we connect with the Policy Impact Predictor initiative from Cambridge University that assesses the effect of new stringency policies using machine learning [14] to answer "What if?" questions surrounding COVID-19 policy-making.

[ZONMW ALGEMENE RELEVANTIE CRITERIA]
Diversity - This study includes all COVID-19 and non-COVID-19 patients admitted to the ICU, there is no risk of selection bias in the data collection. Our proposed subgroup discovery will unravel whether determinants for outcome will be different for men and women, for young or old patients etc. The research part on temporality will pay attention to shifts in patient population during the epidemic.

Application of ICT and e-Health - The ICT infrastructure for the NICE registry is well established as this quality registry exists for 25 years including ISO 27001 and ISO 9001:2015 and NEN7510 certification. NICE's innovative character is shown by the fact that it is the first quality registry in the Netherlands as well as the first national ICU registry world-wide that is in the process of FAIR-ification, being a data partner of OHDSI-EHDEN. The machine learning methods will be performed by the Autoprognosis tooling developed by the University of Cambridge. This will enable continuous updating of models when new data becomes available.

Training - The Amsterdam UMC department of Medical Informatics, involved as partner in this project, provides courses on AI in Medicine for bachelor, master and post-master students. Results of this project will be disseminated by these programs.

Participation - Data have been collected by all ICUs in the Netherlands. This project will be performed by a strong multi-disciplinary research team of intensivists, data scientists and epidemiologists, building upon the long existing collaboration network of NICE. Recently this group (AMC, NICE) published the report "AI will see you know" [12] in which needs and concerns of ICU-physicians and ICU-patients regarding ML based models for prediction of ICU survival prognosis were identified and transformed into recommendations (supported by Ministry of VWS). These recommendations will also be examined with respect to the specifics of this project with the involved patient panel.

Access to data - All data are readily available. We contribute to **FAIRification** of data – both the NICE registry as well as the CovidPredict.org data of Amsterdam Medical Data Science are in the process of construction with the FAIR implementation by OHDSI open data standards (EHDEN.eu funded for harmonization of COVID-19 datasets). In addition, in the project we will work together with and contribute to the existing AmsterdamUMC initiatives for making COVID data FAIR.

Application - The results of this project will be used by the NVIC task force on infectious threats to update triage protocols. Intensivists will be informed on the results by NICE newsletter, webinars and the annual meeting so that the obtained knowledge can be used in shared decision making with patients. Whereas the **primary aim of our proposal is COVID-19**, the clinical relevance of the study goes beyond the acute situation. As ICU triage is concerned, COVID-19 is a new confounder (in many ways), but effective ICU triage also requires **optimal models for non-COVID-19 patients**. As the NICE dataset includes information about all ICU admitted patients, it is a small step to extend our study beyond COVID-19 and in that way contribute in general to the further development, evaluation and deployment of ICU risk scoring systems like APACHE, improving ICU capacity and care even more.

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 international project group combines research excellence and clinical expertise in **intensive care medicine** (Dr. Dongelmans, Prof. Dr.de Lange, Dr. Arbous, Dr. Elbers), **medical informatics** (Prof. Dr. de Keizer, Prof. Dr, Abu-Hanna) and **machine learning** (Prof. Dr. van der Schaar, Dr. Schut, Prof. Dr, Abu-Hanna). With this group comes a very extensive international network (e.g. LOGIC-Linking of Global Intensive Care [13]) within which comparisons can also be made between international datasets. On the national level, the project is supported by the 80 hospitals that provide data through the National Intensive Care Evaluation Foundation (Prof. Dr. Nicolette de Keizer).

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.

As described in section 5 (Relevance -> Application): The results of this project will be used by the NVIC task force on infectious threats to update triage protocols. Intensivists will be informed on the results by NICE newsletter, webinars and the annual meeting so that the obtained knowledge can be used in shared decision making with patients. Whereas the primary aim of our proposal is COVID-19, the clinical relevance of the study goes beyond the acute situation. As ICU triage is concerned, COVID-19 is a new confounder (in many ways), but effective ICU triage also requires optimal models for non-COVID-19 patients. As the NICE dataset includes information about all ICU admitted patients, it is a small step to extend our study beyond COVID-19 and in that way contribute in general to the further development, evaluation and deployment of ICU risk scoring systems like APACHE, improving ICU capacity and care even more.

As for dissemination of results and scientific output, the results will be published in scientific journals and on ICU conferences as well as Artifical Intelligence and Medical Informatics conferences. As mentioned, NICE webinars and meetings will also be used for publishing achieved results. Additionally, given the recent attention in the media to the involved organisations (NICE, CovidPredict, NVIC), we also expect media coverage of the project, which will inform the general public about the research and results.

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.

The proposal is led by NICE, thus the Dutch intensivists represented in the **NICE** registry participate. Also, the proposal is supported by the Dutch Society of Intensive Care (**NVIC**). In cooperation with **FCIC**, we have a patient panel available with non-COVID-19 patients who were admitted to the ICU and we will extend this panel with COVID-19 patients for the project.

9. LITERATUURREFERENTIES:

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

[1] https://stichting-nice.nl/covid-19-op-de-ic.jsp, accessed May 13, 2020.
[2] https://stichting-nice.nl/COVID_report.pdf, accessed May 13, 2020.
[3] van de Klundert N, Holman R, Dongelmans DA, de Keizer NF. Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol. 2015 Dec;44(6):1850-1850h. doi: 10.1093/ije/dyv291, 2015.
[4] Arts DG, De Keizer NF, Scheffer GJ. Defining and improving data quality in medical registries: a literature review, case study, and generic framework. J Am Med Inform Assoc. 2002; 9(6):600-11.
[5] Alaa A, van der Schaar M, AutoPrognosis: Automated Clinical Prognostic Modeling via Bayesian Optimization with Structured Kernel Learning. In Int. Conf. on Machine Learning (pp. 139-148), 2018.
[6] Nannings B, Abu-Hanna A, de Jonge E. Applying PRIM and logistic regression for selecting high-risk subgroups in very elderly ICU patients. Int. Journal of Medical Informatics. 2008; 77(4):272-9.
[7] Abu-Hanna A, Nannings B, Dongelmans D, Hasman A. PRIM versus CART in subgroup discovery: When patience is harmful. Journal of Biomedical Informatics. 2010; 43(5):701-8.
[8] Korber B, Fischer WM, a.o., Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2, on behalf of the Sheffield COVID-19 Genomics Group, CC LaBranche, DC Montefiori, bioRxiv 2020.04.29.069054, 2020.
[9] Ribeiro, MT, Singh S, and Guestrin C, Why should I trust you? explaining the predictions of any classifier. arXiv:1602.04938, 2016.
[10] Alaa, AM, van der Schaar M. Demystifying Black-box Models with Symbolic Metamodels. In: Advances in Neural Information Processing Systems. 2019. https://www.youtube.com/watch?v=EVl5iMpX1cg.
[11] https://digital.nhs.uk/news-and-events/news/trials-begin-of-machine-learning-system-to-help-hospitals-plan-and-manage-covid-19-treatment-resources-developed-by-nhs-digital-and-university-of-cambridge
[12] Klopotowsk JE, AI will see you now: Het perspectief van de arts en de patiënt op een verantwoorde toepassing van Artificiële Intelligentie (AI) ter ondersteuning van medische beslissingen https://www.datavoorgezondheid.nl/wegwijzer-ai-in-de-zorg/documenten/publicaties/2020/04/03/rapport-ai-will-see-you-now, accessed May 13, 2020.
[13] https://www.icubenchmarking.com/, accessed June 12, 2020.
[14] https://www.vanderschaar-lab.com/new-tool-tackles-the-what-if-questions-of-covid-19/, accessed June 14, 2020.

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	% fte (for the project)	Salary costs	Gross salary, 40% increment (for Other ruling only)	Overhead % (for Other ruling only)	Total
1	PostDoc Kunstmatige Inte	NFU	PostDoc	24	€ 174,213		80%	€ 139,370.40	€ -		€ 139,370.40
2	Arts Onderzoeker Intensiv	NFU	(Arts) onderzoeker	24	€ 145,377		70%	€ 101,763.90	€ -		€ 101,763.90
3	Data stewardship	NFU	NWP-H	24	€ 145,377		10%	€ 14,537.70	€ -		€ 14,537.70
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	Hourly rate	number of hours	Total
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		€ -		€ -

DAEB Format

Organisation	Type of organisation	Quoted costs	Quoted co-funding	Requested budget
AMC	Knowledge institution	285,672.00	-	285,672.00
Vumc	Knowledge institution	-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
	Total	285,672.00	-	285,672.00

Staff costs

Function (will be filled based on "staff"sheet)	Remarks	Organisation (dropdown menu)	Costs	Own contribution / 3rd party co-funding	Requested budget ZonMw
PostDoc Kunstmatige Intelligentie		AMC	€ 139,370.40	€ -	€ 139,370.40
Arts Onderzoeker Intensive Care		AMC	€ 101,763.90	€ -	€ 101,763.90
Data stewardship		AMC	€ 14,537.70	€ -	€ 14,537.70
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
to be specified			€ -	€ -	€ -
			€ 255,672.00	**€ -**	**€ 255,672.00**

Material, equipment & consumer goods (itemised)

Discription	Remarks	Organisation (dropdown menu)	Costs	Own contribution / 3rd party co-funding	Requested budget ZonMw
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -

			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	**€ -**	**€ -**

Other costs (itemised)					
			Costs	**Own contribution / 3rd party co-funding**	**Requested budget ZonMw**
Discription	**cost sort (dropdown menu)**	**Organisation (dropdown menu)**			
Open access		AMC	€ 5,000.00	€ -	€ 5,000.00
High performance computing and network		AMC	€ 10,000.00	€ -	€ 10,000.00
Patient panel		AMC	€ 15,000.00	€ -	€ 15,000.00
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ -	€ -	€ -
			€ 30,000.00	**€ -**	**€ 30,000.00**

Total costs project	€ 285,672.00
Own contribution / co-funding	€ -
TOTAL REQUESTED BUDGET ZONMW	€ 285,672.00

Additional explanation for budget

Approval financial responsible receiving organisation

Receiving organisation	AMC Medical Research bv
Name:	F.J.Gaus
Function:	Projectcontroller
E-mail adres:	20/05/14
Date:	

Subsidieaanvraag 50-56300-98-187
Identification of COVID-19 patients with high Risk of mortality at ICU admiSsion – IRIS-study

---

Bijlage: Toelichting op de begroting

Bij de uitgewerkte subsidieaanvraag is een gedetailleerde begroting ingediend welke wij hieronder onderbouwen.

De gebudgetteerde personele kosten betreffen aanstellingen bij Amsterdam UMC voor een PostDoc Kunstmatige Intelligentie (139keuro) en een arts-onderzoeker Intensive Care (101keuro). Hierbij zal de PostDoc zich richten op de analyse taken en de arts-onderzoeker op de klinische relevantie en embedding van de analyse resultaten.

Voor het uitvoeren van de machine learning algoritmen is er in het budget een bedrag van 10keuro voorzien van high performance computing faciliteiten.

Het uitvoeren van de voorgestelde focusgroepen en het opzetten van het patiëntenpanel wordt in samenwerking gedaan met de stichting FCIC – een samenwerkingsverband tussen ervaringsdeskundigen (patienten/naasten), IC-professionals en wetenschappers op domein van de IC. Binnen deze stichting is IC Connect als patiëntenorganisatie opgericht. De FCIC hanteert een tarief van 100 Euro per uur conform de richtlijnen van de Patiëntenfederatie. De opgenomen budgetpost 'Patient panel' (15keuro) stelt ons in staat om een patiëntenpanel op te zetten en een aantal dagdelen met IC focusgroepen te organiseren.

Voor de volledigheid vermelden wij ook nog ter onderbouwing van de begroting:

- Er zijn geen kosten gemaakt vóór honorering van het project.
- Het bij ZonMw aangevraagde subsidiebedrag is niet veranderd ten opzichte van het gevraagde bedrag in het projectidee.
- Minimaal 5% van het projectbudget is gereserveerd voor communicatie en implementatie.
- Conform instructies is in de projectbegroting 5keuro opgenomen voor Open Access publicaties, gespecificeerd met 'open access'.
- In de begroting zijn de (geschatte) kosten opgenomen voor datastewardship en het gebruik van data services en extra infrastructuur gedurende het project.
- Er worden geen producten en diensten ingekocht.
- Er is geen sprake van cofinanciering.

Subsidieaanvraag 50-56300-98-187
Identification of COVID-19 patients with high Risk of mortality at ICU admiSsion – IRIS-study

---

Bijlage: Reactie op opmerkingen in e-mail met positief advies

Bij de kennisgeving van positief advies van ons projectidee werd ons gevraagd enkel het volgende punt mee te nemen in de uitwerking van de aanvraag.

Vanuit het urgente onderzoeksvragen traject van het covid-programma is financiering beschikbaar gesteld aan de covid-predict studie getiteld ''Samenwerken tegen corona met intensive care data''. De commissie verzoekt u toe te lichten wat de toegevoegde waarde is ten opzichte van dit project en hoe wordt samengewerkt om doublure te voorkomen.

Wij hebben dit punt verwerkt in onze aanvraag en vatten hier onze reactie kort samen.

Wij lichten zes aspecten toe wat de **toegevoegde waarde** is van de IRIS studie.

- Ten eerste is de voornaamste **databron** die in IRIS gebruikt wordt, de continue, landelijk dekkende NICE registratie. De NICE registratie bestaat reeds 25 jaar, beslaat alle 82 IC's die allen op reguliere basis IC gegevens aanleveren. Door in de praktijk bewezen maatregelen zoals een uitgebreide datadictionary inclusief eenduidige definities, trainingen voor intensivisten, lokale datamanagers, site visits t.b.v. audits op datakwaliteit, dataset controle op meer dan 600 datavalidatieregels etc, samenwerking met de EPD-leveranciers is de NICE data in hoge mate gecureerd waardoor een zeer hoge data-kwaliteit is gewaarborgd. Door de jarenlange technische en organisatorische infrastructuur loopt de dataverzameling automatisch door, ook in het geval van een tweede of volgende corona-piek. Bij de CovidPredict data worden de gegevens 'handmatig' verzameld (d.w.z. digitaal aangeleverd uit het EPD, maar niet gecureerd) en verwerkt, waardoor er achteraf relatief veel werk verricht moet worden (opschonen, koppelen, normaliseren) om modellen te ontwikkelen op basis van deze data.
- Naast de data infrastructuur kent NICE een sterke **organisatorische infrastructuur** en dus een grote mate van samenwerking tussen intensivisten. Dit netwerk zorgt voor korte communicatielijnen tussen IC's en de NICE registratie waar het data aanlevering en duiding van de data betreft. De implementatie van de resultaten uit het IRIS project zal daardoor laagdrempelig kunnen verlopen.
- Door de opgebouwde ervaring van de NICE registratie beschikt IRIS tevens over **lange termijn uitkomsten** (onder andere mortaliteit na drie, zes of twaalf maanden) middels de reeds bestaande koppeling tussen NICE en VEKTIS. Hierdoor is het mogelijk om tijdens de looptijd van IRIS deze waarden te kunnen meenemen in de te ontwikkelen voorspelmodellen.
- Ten vierde zijn **alle Nederlandse COVID-19 patiënten geïncludeerd** in IRIS middels de landelijke dekking van de NICE registratie, terwijl CovidPredict enkel beschikt over COVID-19 patiënten uit momenteel 24 ziekenhuizen. Daar nog boven op bevat NICE alle IC (ook niet-COVID) patiënten, waardoor de doelstelling van IRIS (IC triage van COVID-19) relatief snel te generaliseren is tot algemene IC triage.
- Ten vijfde is de **focus van IRIS op triage** en richt CovidPredict zich op beste uitkomsten van specifieke IC behandelingen. Omdat NICE geen gedetailleerde behandelgegevens bevat kunnen deze vragen ook niet met NICE data binnen IRIS beantwoord worden.
- Ten slotte is **NICE lid van LOGIC** - Linking of Global Intensive Care [13], een onafhankelijk consortium van ICU-databases, netwerken en nationale registers met een staat van dienst op het gebied van kwaliteitsverbetering, benchmarking en klinisch onderzoek om de resultaten van patiënten te verbeteren. Dit netwerk maakt samenwerking en uitwisseling van onderzoeksmethoden en ideeën eenvoudig te realiseren.

Daarnaast zijn er ook drie punten waarop de project synergetisch zijn en er wordt **samengewerkt**.

- Ten eerste zullen we onderzoeken voor de IC's die deelnemen aan zowel NICE als CovidPredict, of het gebruik van diepere, meer gedetailleerde gegevens rond ICU-opname de **prestaties verbeteren** van onze modellen. Aangezien de modellen alle Nederlandse IC's moeten ondersteunen, zullen de modellen op basis van de continue NICE kwaliteitsregistratie ons belangrijkste resultaat zijn.
- Ten tweede is een **overlap van projectleden**, t.w., Nicolette de Keizer (Amsterdam UMC locatie AMC, penvoerder IRIS), Paul Elbers (Amsterdam UMC locatie VUmc, penvoerder CovidPredict) en Mihaela van

der Schaar (Cambridge University, projectadviseur). Deze overlap betekent inherente samenwerking en afstemming tussen de projecten.

- Ten derde wordt in beide projecten het belang onderschreven om met patienten, hun mantelzorgers en artsen te evalueren hoe ontwikkelde voorspelmodellen het beste ingezet kunnen worden in het proces van samenbeslissen tussen patient en arts. Deze evalutie wordt onder andere gedaan in samenwerking met de FCIC door het **opstellen van patiëntenpanels en organiseren van focusgroepen**. Bij de twee projecten zal hiervoor gezamenlijk opgetrokken worden, wat ten goede komt voor de beschikbaarheid van patiënten, mantelzorgers en artsen, en tevens de belasting voor hen vermindert.

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: RA (Rudy) Scholte (AMC), Institute: Amsterdam UMC ☐ 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: NICE registration ☐ Biological materials: Klik of tik om tekst in te voeren. ☐ Research software: Klik of tik om tekst in te voeren. ☐ 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 plan (including the protocols, methods, etc).	☒ In case of preregistration: Provide the link or registration code: To follow ☐ 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.

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: Klik of tik om tekst in te voeren. ☐ Collaboration with COVID-19 data collection(s) ☐ 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) The NICE registry is an OHDSI-EHDEN data partner. OHDSI is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics and making data FAIR. All OHDSI solutions are open-source. ☐ 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.