FULL APPLICATION FORM – COVID-19 VACCINE STUDIES

COVID-19 PROGRAM

Deadline for submission: January 4th, 2021 (10:00 h)

PLEASE READ ALL INSTRUCTIONS IN THE CALL TEXT AND APPENDICES (BIJLAGE - TOELICHTING INDIENING SUBSIDIEAANVRAAG) CAREFULLY!

Once you have completed the form, please:

1. **Convert to a pdf file and check in detail**
2. **Upload the completed form as attachment to your submission in Projectnet**
3. **Upload all appendices in Projectnet**

BASIC APPLICATION DETAILS

NAME OF MAIN APPLICANT:

5.1.2e 5.1.2e. 5.1.2e

ORGANISATION:

Amsterdam UMC, in collaboration with affiliated hospitals, UMC Groningen and Erasmus UMC

FULL PROJECT TITLE IN ENGLISH:

COBRA-KAI study: COVID-19 vaccination in patients with reduced **B**-cell and T-cell immunity: response **a**fter vaccination of a **ka**leidoscopic group hematological patients, what's the **i**mpact?

TITLE IN DUTCH (KORTE NEDERLANDSE TITEL VAN MAX. 12 WOORDEN):

COVID vaccinatie in patiënten met een hematologische aandoening

DUTCH LAY SUMMARY (MAX 1/2 A4 (KOMT OP WEBSITE):

ACHTERGROND

De pandemie veroorzaakt door het SARS-CoV-2 ('het' coronavirus) heeft wereldwijd inmiddels meer dan 100 miljoen mensen geïnfecteerd en ruim 2 miljoen slachtoffers geëist (https://coronavirus.jhu.edu/map.html). Patiënten met een onderliggende hematologische ziekte hebben een hoog risico op een ernstig beloop van COVID: patiënten die korter dan een 1 jaar bekend zijn met een hematologische maligniteit hebben een 3x hoger overlijdensrisico en patiënten met sikkelcelziekte hebben zelfs een 6x verhoogd risico op overlijden ten gevolge van COVID. Het is derhalve van groot belang patiënten met een hematologische ziekte te beschermen tegen COVID door middel van vaccinatie. Het is echter de vraag of vaccinatie voldoende bescherming biedt aan patiënten met een hematologische aandoening, want de activatie van T-cellen en het produceren van antistoffen kan verhinderd worden door enerzijds de ziekte en anderzijds behandelingen die het afweersysteem onderdrukken. Dit is de reden dat bij deze patiënten vaak van vaccinatie wordt afgezien. Het is zeer de vraag of dit terecht is, en zo lang we dat niet zeker weten lopen patiënten het risico ten onrechte niet gevaccineerd te worden. Daarom willen wij onderzoeken of patiënten met een hematologische aandoening, ondanks hun verminderde afweer, wel beschermd zullen zijn na vaccinatie.

ONDERZOEKSVRAGEN:

1. Kunnen patiënten met hematologische aandoeningen beschermd worden door COVID-19 vaccinatie?
2. Kunnen we specifieke patiënten groepen identificeren die ondanks COVID-19 vaccinatie onvoldoende beschermd zijn?

ONDERZOEKSOPZET:

In dit onderzoek zullen we bij 850 patiënten met hematologische ziekten die tegen COVID-19 gevaccineerd worden de reactie van het afweersysteem op de vaccinatie meten. Hiervoor worden bij patiënten zowel voorafgaand aan de vaccinatie als op vaste tijdspunten erna bloed afgenomen. In dit bloed zullen verschillende aspecten van de afweerreactie tegen SARS-CoV-2 gemeten worden, zoals antistoffen en de werking van cellen van het afweersysteem (B- en T-cellen). Ook zullen gegevens van patiënten verzameld

worden zoals de precieze hematologische diagnose, eerdere anti-kanker behandelingen, huidige behandeling en medicijngebruik.

TE VERWACHTEN RESULTATEN:
Na het onderzoek verwachten we in staat te zullen zijn om enerzijds patiëntengroepen te identificeren die tegen de verwachting in toch goed reageren op vaccinatie. Anderzijds kunnen we voor patiënten die onvoldoende beschermd zijn na vaccinatie extra bescherming genereren door huisgenoten te vaccineren (ringvaccinatie) of patiënten zelf een 'booster' vaccinatie te geven (waarvan we het effect in een vervolgstudie zullen onderzoeken). Deze kennis zal daarnaast ook toegepast kunnen worden bij jaarlijkse vaccinatiecampagnes tegen griep en andere ziekteverwekkers.

ENGLISH SUMMARY (MAX 2000 (NU 1992) CHARACTERS) (KOMT OP WEBSITE):

RESEARCH QUESTION
Can we identify patients with hematologic conditions that A) respond, B) partially respond or C) not respond to COVID-19 vaccination?

HYPOTHESIS
Most patients with hematologic conditions are considered immunocompromised, either due to the underlying condition, and/or because of the therapy they receive. Contrary to current dogma's we hypothesize that most patients with hematologic conditions will mount sufficiently protective immune responses against SARS-CoV-2 after vaccination. Identification of non-responders is important to be able to provide additional protective measures for these specific patient groups.

STUDY DESIGN
Observational cohort study

STUDY POPULATION
Patients with hematologic conditions who are considered immunocompromised, either because of the hematological disease or due to immunosuppressive treatment. Seventeen clinically relevant specific patient groups are identified, each with specific immunodeficiencies.

INTERVENTION
We will investigate COVID-19 vaccination responses in a cohort of 850 patients. In particular, clinical parameters (hematologic condition, therapy), pre-vaccination immune parameters such as B- and T-cell numbers, serologic evidence of prior SARS-CoV-2 infection, and post-vaccination antibody and T-cell responses will be measured. Post-vaccination immune responses will be followed longitudinally until one year after completion of the vaccination schedule.

OUTCOME MEASURES
- antibody and neutralizing antibody titers
- CD4 and CD8 T-cell responses
- durability of immune responses
- correlation between immune responses and pre-vaccination parameters including B- and T-cell numbers, immunoglobulin levels and clinical parameters.

SAMPLE SIZE/DATA-ANALYSIS
Based on disease- and therapy related immune deficiency, we identified 17 subgroups of patients (n=50 patients per group) to estimate the response rate with a precision between 7 and 29% for the Clopper-Pearson (exact) 95% confidence intervals.

ZonMw

Full application – COVID-19 VACCINE STUDIES

RESEARCH PROPOSAL (max 8 pages A4 – literature references included; title page not included) Font type Arial 10 pts.

1. PROBLEM DEFINITION, URGENCY AND OBJECTIVE(S):

BACKGROUND

Patients with hematologic conditions have a high mortality risk when infected with SARS-CoV-2.[1–3] Protection from infection in this specific patient cohort is therefore of vast importance. Although vaccination is the strategy of choice to obtain protection in the general population, it might yield suboptimal responses in hematologic patients, as many of these patients are immunocompromised, the extent of which varies considerably. Immunocompromised states can either be the result of the underlying disease or can be induced by therapy. Patients with (malignant) B-cell disorders such as B-cell lymphomas and leukemias, plasma cell dyscrasias, and patients with acquired functional asplenia, such as sickle cell disease, may have suboptimal humoral immune responses. It is generally assumed that patients receiving (immuno) chemotherapy and/or autologous or allogeneic hematopoietic stem cell transplantation (HCT), will respond poorly to vaccination. Furthermore, new upcoming treatments, such as small molecules inhibiting signaling pathways or B-cell depleting CD19 CAR-T therapy, not only affect cancer cells but also impair normal immune function. Robust detailed data on vaccination responses in these hematologic immunocompromised patients are currently lacking.

The paucity of data and the many uncertainties regarding immunocompetence in this patient group have led to conservative vaccination guidelines.[4] It is for example generally assumed that patients will be less responsive to vaccination in the first 6 months after B-cell targeting therapy (e.g. the monoclonal anti-CD20 antibody rituximab). This is based on the observation that B-cells are restored on average 6 to 9 months after last infusion. It is not known however, what minimum number of B-cells is necessary for an adequate response to vaccination. For autologous and allogeneic stem cell transplantation, it is advised to postpone vaccination to at least 3-6 months after transplant. In specific situations, such as severe hypogammagobulinaemia or severe graft versus host disease (GVHD), vaccination is considered not effective, although data are lacking or very scarce, similar as for patients with myeloid malignancies. Comparable conservative considerations are now contemplated in the context of COVID-19 vaccination.

PROBLEM DEFINITION

Assumptions regarding reduced COVID-19 vaccination efficacy have several consequences. First, clinicians may decide to interrupt or defer certain therapies (e.g. rituximab, lenalidomide, others) in anticipation of vaccination, which may have a negative impact on prognosis. Second, patients may be advised against COVID-19 vaccination, possibly wrongfully withholding them protection against COVID-19. Alternatively, patients may respond less well than anticipated, and consider themselves protected while in reality they are not. Therefore, data about vaccination efficacy in patients with various hematological diseases are urgently needed.

HYPOTHESIS

COVID-19 vaccine efficacy data suggest that minimal antibody responses may be protective.[5] This, together with anecdotal observations of sufficient antibody responses after COVID-19 infection in patients with low B-cell numbers led us to hypothesize that an important proportion of hematology patients will in fact acquire sufficient protection following COVID-19 vaccination, despite disease- and/or therapy-related immunodeficiencies. Sufficient protection is defined as seroconversion (≥ 4-fold increase of antibody levels compared to baseline).

OBJECTIVES

The aim of this study is to investigate COVID-19 vaccine responses in patients with hematologic diseases, in particular those patients who are considered immunocompromised, either due to the hematologic condition, or as a result of immunosuppressive therapy.

Primary Objective:

1. To identify subcategories of hematology patients with A) sufficient protection against COVID-19 +28 days after completion of the standard COVID-19 vaccination schedule (responders: seroconversion), B) insufficient protection, who may benefit from booster-vaccinations (low-responders; antibody

response but no seroconversion), and C) insufficient protection (non-responders: no seroconversion, no antibody response).

Secondary Objective(s):

1. To characterize the humoral responses (including kinetics and persistence of antibodies, role of previous exposure to SARS-CoV2 infection) after COVID-19 vaccination;
2. To characterize the cellular immune response (CD4 and CD8 T-cell responses including Th1 skewing of CD4 T-cells) after COVID-19 vaccination;
3. To identify immune parameters associated with responses to COVID-19 vaccination;
4. To identify clinical parameters (e.g. hematologic diagnosis, current and past therapies, date of last therapy) associated with responses to COVID-19 vaccination;
5. To monitor serious adverse events (SAE) < 7 days after each COVID-19 vaccination
6. To monitor SARS-CoV-2 infection and severity (including death) after COVID-19 vaccination.

Results of this study will have immediate consequences for hematologic patients. It will allow specification of international COVID-19 vaccination guidelines to a) categorize patient groups into responders, low-responders and non-responders, and b) develop tailored advice to these patient groups. Examples of such advice are measures to prevent infection, including vaccination of household members and care providers for non-responders, follow-up of antibody titer measurements in responders with significant antibody titer decline over time, and COVID-19 booster vaccination strategies for low-responders and responders with titer decay. Booster strategies will be designed and tested in a follow-up study, similar as we have designed for allogeneic HCT recipients with insufficient or with sufficient but decaying antibody titers following pneumococcal vaccination.[6]

2. STRATEGY:

DESIGN
Observational cohort study

STUDY POPULATION/DATA SOURCES
The following adult patient cohorts will be included:

- B-cell non Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative diseases (MPN), patients with hemoglobinopathies (sickle cell disease and thalassemia), patients who received cell therapy (autologous HCT, allogeneic HCT or CAR T cell therapy); AND
- Patients that either currently receive or have in the past 6 months received immuno-chemotherapy or targeted agents, or have received autologous or allogeneic stem cell transplantation no longer than 6 months ago or have received CAR-T therapy (see Figure 1).

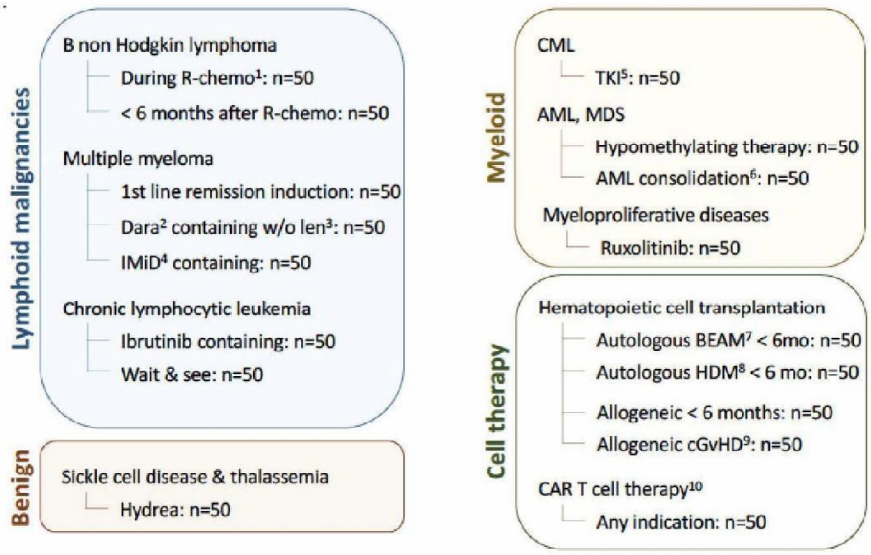

Figure 1: Study population. Specific patient groups are further specified. [1]rituximab containing immunochemotherapy (R-CHOP, R-CVP, R-bendamustine); [2]daratumumab; [3]without lenalidomide; [4]Immunomodulatory drugs; [5]tyrosine kinase inhibitor; [6]AML consolidation course with chemotherapy only (etoposide, mitoxantrone) or with busulphan and cyclophosphamide followed by autologous HCT; [7]BEAM: carmustine, etoposide, cytarabine, melphalan; [8]HDM: high dose melphalan; [9]cGvHD: chronic graft versus host disease; [10]CD19-directed CAR T cells.

The following patients will not be eligible for inclusion:

- Age < 18 years
- Unwilling or unable to consent
- Known allergy to one of the components of the vaccine
- Of note: although we will investigate serologic evidence of prior infection with SARS-CoV-2 in all participants, seropositivity is not an exclusion criterion. The main reasons for this are first that we expect seroprevalence to be well below 5%, because of the stringent isolation measures that are in place in this patient population; second, a test-first-strategy for seroprevalence would seriously hamper the speed of vaccination rollout, whereas vaccination of seropositive patients is indicated nonetheless, according to the national vaccination guidelines.

INTERVENTION

Patients will be invited to visit the outpatient clinic for blood sampling prior to the first vaccination and return for blood sampling at 2 and 4 weeks, 6 and 12 months after completion of the vaccination schedule. The following data and materials will be collected at each timepoint:

	Baseline	2 weeks[1]	4 weeks[1]	6 months[1]	12 months[1]
Informed consent	x				
Inclusion/exclusion criteria	x				
Demographic characteristics[2]	x				
WHO-PS	x	x	x	x	x
Hematologic diagnosis	x				
Lines of treatment[3,4]	x				
Current therapy	x	x	x	x	x
Supportive care[5]	x	x	x	x	x
Concomitant medication	x			x	x
Sars-CoV-2 exposure [6]	x	x	x	x	x
SAE[7]		x			
WBC[8]	x	x	x	x	x
Blood analysis[9]	x	x	x	x	x
SARS-CoV2 antibodies[10]	x	x	x	x	x
Biobanking	50 ml	50 ml	50 ml	50 ml	50 ml

Table 1: Time points and collection of data and materials. [1]after completion of the vaccination schedule; [2]Demographic characteristics (age, gender, ethnicity, comorbidities, vaccination history); [3]including date of last treatment; [4]In case of HCT: type (allogeneic, autologous), date, donor, conditioning regimen, past and current use of immunosuppressants, disease status, current or past acute/chronic GvHD, donor lymphocyte infusions y/n; [5]IVIG suppletion; [6]confirmed diagnosis of SARS-CoV-2 infection, hospitalization, treatment, outcome; [7]within 7 days after each vaccination; [8]white blood cell count; [9]IgG/IgG1-4/IgA/IgM, T-, B-, NK-lymphocyte subset quantification; [10] antibody titer and neutralizing antibody response

OUTCOME PARAMETERS

Primary Endpoint

1. Humoral response (IgG) against SARS-CoV-2 spike antigen +28 days after completion of the COVID-19 vaccination schedule.

Secondary Endpoints

2.1 SARS-CoV-2 S-protein specific antibody glycosylation, types and titers up to 12 months after completion of the COVID-19 vaccination schedule;
2.2 Proportion of Th1 and Th2 T-cells and proportion of SARS-CoV-2 S-protein specific CD4 and CD8 T-cells up to 12 months after completion of the COVID-19 vaccination schedule;
2.3 Pre-vaccination baseline leukocyte counts, humoral and cellular immune parameters (including T- and B-cell numbers and IgA, IgM, IgG and IgG1-4 levels), demographic parameters and medical history including comorbidities and concomitant medications;
2.4 SAE within 7 days after both vaccinations;
2.5 Incidence of COVID-19, COVID-19 related hospitalization and death following the first COVID-19 vaccination.

DATA-ANALYSIS

10.1 Data management and FAIR principles
Data management of the project will be supported by the research data management specialists of the Research Support at Amsterdam UMC, and of the Netherlands Comprehensive Cancer Organisation (iKNL). Data collection will contain clinical data and laboratory data. Clinical data are data in electronic patient records that can be made available through CRF and includes patient characteristics, standard laboratory tests and treatment details. These clinical data are provided by the local databases and electronic patient record systems. Laboratory data are provided by the specialized reference laboratories and includes blood cell counts, flow cytometry data, elispots and ELISA.

The study will be submitted to the local medical ethical committees shortly. All included patients will give informed consent prior to start of the study. The patient data will be coded and patient identifiers are stored by the responsible investigators, separate from the participating institutes. All patient consent and the potential withdrawal of the consent will be monitored according to Good Clinical Research Practice and data are acquired and stored according to General Data Protection Regulations. Data will be findable, accessible, interoperable and reusable according to the FAIR principles and in line with the VOICE study, to allow exchange and comparison of data between patient groups. Data will be made available to (inter)national COVID-19 vaccination databases of LAREB, RIVM, and the international ACCESS database (*https://vac4eu.org/covid-19-vaccine-monitoring/*).

10.2 Primary study parameter
The primary study parameter is the antibody based immune response to vaccination against COVID-19 on day 28 after completion to the COVID-19 vaccination schedule. Seroconversion is defined as a ≥ 4-fold increase of antibody levels compared to baseline. SARS-CoV-2 S-specific serum IgG antibody concentrations will be measured by bead-based multiplex immune assay (MIA) at the RIVM. Geometric mean concentrations (GMCs) and 95% confidence intervals (CIs) will be calculated for the SARS-CoV-2 S-protein-specific IgG antibodies at baseline and day 28 after vaccination for each cohort. Participants will be classified as responders (seroconversion), low-responders (antibody response below seroconversion threshold) or non-responders (no antibody response). If a serological correlate of protection for COVID-19 based on anti-S protein IgG antibody levels (in IU/mL) will be known before data analysis, the definition of a responder/low-responder/non-responder will be based on having a serum concentration of anti-S protein IgG antibodies above this cut-off, at day 28 after completion of the COVID-19 vaccination schedule. Percentage of responders will be calculated for each of the patient cohorts, with corresponding Clopper-Pearson (exact) 95% CIs.

10.3 Secondary study parameters
Secondary parameters will be described by frequency and percentage, mean ± standard deviation or median [(interquartile) range]. Levels of SARS-CoV-2 S-specific IgG antibodies at day 28 after completion of the vaccination schedule will be compared with baseline for that specific patient cohort, using Paired Samples T-test or Wilcoxon Sign tests, depending on the distribution of the data. Univariate (logistic regression) analysis will be used to assess the association between the humoral and cellular response to COVID-19 vaccination and pre-vaccination parameters, demographic parameters and medical history. Multivariable analysis of the most relevant above-mentioned factors associated with humoral and cellular responses to COVID vaccination will be performed with a stepwise selection procedure.

SAMPLE SIZE CALCULATION
In this project we aim to identify those patients that respond sufficiently to COVID-19 vaccination, with 'sufficient' defined as 'seroconversion' (responders), low-responders and non-responders. In this merely

descriptive study we consider n=50 per subgroup as appropriate to quantify antibody levels; this will allow us to estimate the seroconversion proportion with a precision between 7 (at 0 or 100% seroconversion) and 29% (at 50% seroconversion) for the Clopper-Pearson 95% CIs.

DIVERSITY
Patients included in this study will be representative for the population of patients with hematologic conditions. Some known differences in the prevalence of hematologic conditions will also be present in our cohort, with the ethnical background of sickle cell disease patients being the most notable. In addition, hematologic malignancies are slightly more prevalent in males (55% of patients, according to data of iKNL.nl). In our evaluations we will investigate possible sex-related differences in responses to vaccination, although thusfar no such differences have been noted. Overall, our study will not be powered to investigate correlations between socio-economic, ethnic or age-related differences and outcome.

3. FEASIBILITY OF THE PROJECT:

TIME SCHEDULE (please make clear when results can be expected)

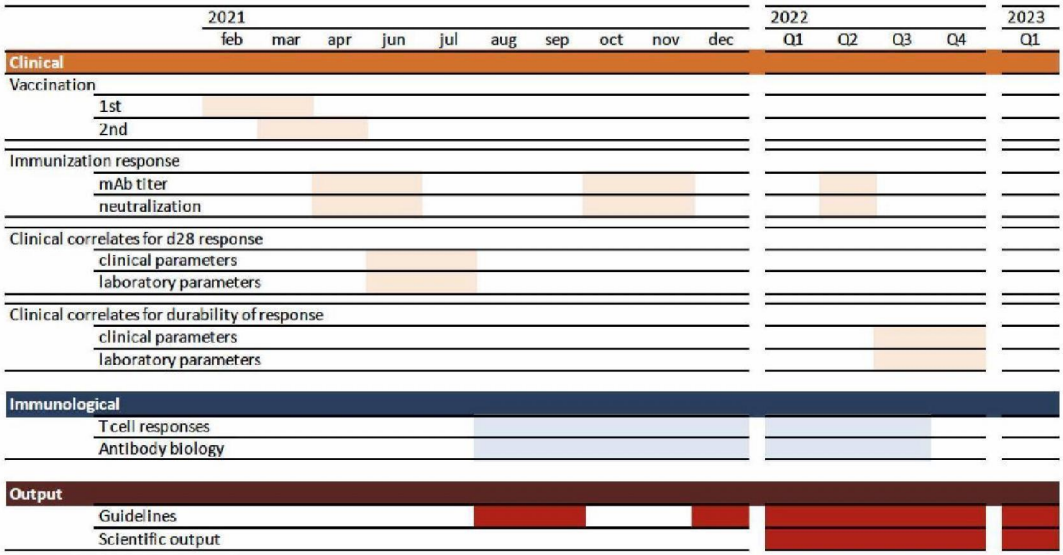

Figure 2: GANNT chart

Results can be expected as indicated in the GANNT chart (Figure 2). The most important threat to this project is the imminent shortage of laboratory plastics in The Netherlands. The organization of this project on such short notice is challenging but feasible (see below).

MOTIVATE FEASIBILITY
We have teamed up with the project group of the VOICE study, and the laboratories that they work with (including RIVM for antibody responses), and can make use of the same infrastructure. Our institute has ample experience with rapid organisation and execution of COVID-19 vaccination, as they have proven for the healthcare workers, family practitioners and nursing home residents. We will use the Amsterdam UMC COVID-19 vaccination facilities, that are set up to vaccinate large numbers of participants in limited time, and to take pre-vaccination blood samples. The other participating centers (UMCG, Erasmus UMC) have similar experience and facilities, and will vaccinate patients at their local sites. We are supported by iKNL for help with datamanagement, and through this structure, we will be able to share data between the VOICE and our cohorts. We will make use of the experience with blood sample processing and biobanking that we have at Amsterdam UMC and the infrastructure of Sanquin Research. The board of directors of our institute strongly supports this initiative and will facilitate the project. It should be noted that at the time of the writing of this project proposal, a number of details still needs to be worked out. This is related to the short notice of this call. Despite the short time-frame in which this project is organized we think its organization is feasible.

RECRUITINGSTRATEGY

IKNL will provide a list of all patients with a diagnosis of a malignant hematologic disease within the past 5 years of each participating center (i.e. Amsterdam UMC, UMCG, Erasmus MC). Patients eligible for this study are selected and addressed, using a pre-screening Participant Information Form (PIF) that will be sent to potential participants. After signing of the pre-screening PIF, baseline information will be collected by IKNL. As soon as vaccination can start, selected patients will be invited for the informed consent procedure, which will be done according to the ICH guidelines on Good Clinical Practice. Participating patients will be vaccinated according to national protocols.

4. RELEVANCE:

This project addresses a timely and relevant issue: the ability of patients with hematologic malignancies to generate robust, protective and also durable immune responses to COVID-19 vaccination. Many hematologic malignancies are associated with (severe) immunodeficiency, either due to depletion of immune cells, or due to functional deficit of non-malignant immune cells (for example: T-cell dysfunction in CLL patients). In addition, therapies that are aimed at eliminating malignant cells will per definition also damage the non-malignant cells of the same compartment (for example: rituximab and chemotherapy in R-chemo therapy for B-cell non-Hodgkin lymphoma's), further aggravating patients' immunodeficiencies. There are nevertheless very limited data on vaccination responses in patients with hematologic malignancies. Vaccination guidelines are mostly based on dogma's and often lack scientific grounds.

This has a number of consequences: i) with the current pandemic, physicians may adjust therapy regimens (for example: defer rituximab) to preserve immune functionality as much as possible (but negatively affecting prognosis of the underlying hematologic condition); ii) patients may wrongfully be advised not to take COVID-19 vaccination, based on the assumption that it will not be effective, which may deprive patients of potential protection against the virus; or, alternatively, iii) patients may assume they are protected against COVID-19 after vaccination while in reality they are not.

With this project, we will learn which groups of patients will, despite their immunodeficiency, mount protective immune responses after COVID-19 vaccination, and we will identify parameters that may help to identify those patients that will or will not respond to COVID-19 vaccination. The clinical consequences are clear:

- Patients with sufficient immune function as defined by parameters tested in this study ('responders') will no longer be wrongfully deprived of vaccination;
- Patients with antibody responses below the threshold of seroconversion (low-responders) may benefit from booster vaccinations, as we have shown for pneumococcal vaccination in allogeneic HCT recipients.[6] We will design a COVID-19 booster vaccination schedule for low-responders and investigate the efficacy in a follow-up study.
- Patients with severe immunodeficiency as defined by parameters tested in this study ('non-responders') will not be subjected to unneccesary / uneffective vaccinations. For these patients, "ring vaccination" of household contacts and behavioral advice such as social distancing and the use of face masks will be actively propagated.

Importantly, results of this study will be shared with relevant parties (health care providers, patient organizations, government institutions such as RIVM, (inter)national COVID-19 vaccination databases) and with the general population as soon as possible, and will be implemented in (inter)national guidelines on vaccination of immunocompromised patients via the members of the project group that are all involved in vaccination guideline committees.

5. PATIENT PARTICIPATION:

The Dutch patient organizations and their members are part of, and take an important role in, determining the policies and guidelines of hematologic diseases through umbrella organizations such as HOVON. Every scientific working group within HOVON has 2 patient representatives. The study proposal is aligned within these working groups. The board of the patient advocacy groups Hematon (for patients with hematological malignancies), and 5.1.2e (for patients with sickle cell disease and thalassemia) were consulted and indicated to support the project. They wrote letters of support (appendix 1). Patients will be involved in the further development of the study in case of ZONMw approval in writing of the patient information. They will receive regular updates on the course of the study and help disseminate the results of the study among the groups they represent. Potential costs for their participation are included in the budget.

6. PROJECTGROUP AND STAKEHOLDERS:

PROJECTGROUP
Our project group consists of clinical hematologists, immunologists, an MD in infectious diseases specialized in vaccination of immunocompromised individuals, a biostatistician and a pharmacologist of Amsterdam UMC. Some have additional jobs that are relevant, for example at Sanquin Research, or as members of national committees such as HOVON and LNAZ. In addition we have involved representatives of RIVM and iKNL, and two additional hematology centers (UMCG and Erasmus UMC). See for details appendix 2.

STAKEHOLDERS
Stakeholders in this project are the Hemato-Oncology Foundation for Adults in the Netherlands (HOVON), the Dutch Society of Hematology (NVVH) and the Netherlands Comprehensive Cancer Organisation (iKNL), who are all committed to this project. These organizations strongly endorse the study.

7. COMMUNICATION AND IMPLEMENTATION ACTIVITIES:

Deliverables and implementation

1. *Guidelines:* Results of this study will be directly implemented in (inter)national guidelines on vaccination of immunocompromised individuals. Almost all members of the project group are involved in (inter)national networks and vaccination guidelines committees;
2. *Diagnostics:* Included in the guidelines will be the advice to monitor antibody responses in low- and non-responder subgroups and in responder subgroups with loss of response over time;
3. *Booster-vaccination:* Low-responders (antibody response below seroconversions threshold) may benefit from booster-vaccination strategies. In parallel to the present study we will set up a follow-up study on the effect of booster vaccination strategies in patients that did not acquire sufficient immunity after vaccination.

Dissemination activities
Results of the study will be shared through open access publications and be presented at meetings of the national and international hematology, infectious diseases and immunology communities. The patient community will be involved via Hematon, 5.1.2e, AYA and other networks.

8. LITERATURE REFERENCES:

1. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. 2020;136(25):2881–2892.
2. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430–436.
3. States U, May M, Panepinto JA, et al. Coronavirus Disease among Persons with Sickle Cell Disease. *J. Emerg. Dis.* 2020;26(10):2473-2476
4. Cordonnier C, Einarsdottir S, Cesaro S, et al. Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect. Dis.* 2019;19(6):e200–e212.
5. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N. Engl. J. Med.* 2020;383(27):2603–2615.
6. Langedijk AC, van Aalst M, Meek B, et al. Long-term pneumococcal vaccine immunogenicity following allogeneic hematopoietic stem cell transplantation. *Vaccine*. 2019;37(3):510–515.