Het studieprotocol

Ten behoeve van de koppeling van sociaaleconomische status data van het CBS met data van IC-patiënten uit de NICE database

Aanleiding

Sociaal Economische Status (SES) is een belangrijke determinant voor gebruik van gezondheidszorg en uitkomsten in verscheidene ziektebeelden. Of SES daadwerkelijk een effect heeft op (korte- en lange termijn) uitkomsten na IC-opname is onduidelijk, want in Nederland is hier nog geen onderzoek naar gedaan en de resultaten uit andere landen zijn meerduidig. In Nederland is de SES niet gelijkmatig verdeeld en bestaat het vermoeden dat de SES een verklaring kan zijn van de verhoogde mortaliteit onder IC-patiënten in bepaalde regio's.

Om hier meer inzicht in te krijgen is vanuit het Maastricht UMC+ (MUMC) een extractieverzoek ingediend om de zogeheten "Limburgfactor" verder te onderzoeken. Met dit onderzoek wordt beoogd om de verschillen in SES tussen regio's en verschillende patiëntgroepen te identificeren en de associatie tussen de SES en verschillende IC-uitkomsten te ontrafelen. Indien blijkt dat SES geassocieerd is met mortaliteit na IC-opname, is het ook interessant om te onderzoeken of het APACHE IV model dat gebruikt wordt voor case-mix correctie verbeterd kan worden door de SES hierin op te nemen. Vanuit het Amsterdam UMC is in samenwerking met MUMC een extractieverzoek ingediend om hier verder onderzoek naar te doen.

In de NICE registratie zijn geen gegevens opgenomen met betrekking tot de SES op patiëntniveau. Om dit onderzoek uit te kunnen voeren is het noodzakelijk om een koppeling met de CBS-data tot stand te brengen waarbij uiteraard rekening wordt gehouden met alle privacy- en dataveiligheidsreglementen.

In de volgende slides worden de onderzoeksvragen en de benodigde data behorende bij de data extractieverzoeken *'2022.01 Socioeconomic state and outcome of critically ill patients in The Netherlands: a nationwide cohort study'* (onderzoeksvraag 1t/m4) en *'2022.11 Unravelling the potential drivers of increased intensive care unit mortality rates in Limburg through patient clustering: a retrospective study'* (onderzoeksvraag 5&6) verder uitgewerkt en een overzicht gegeven van het proces voor datakoppeling. De extractieverzoeken zijn ook vermeld op onze website**:** Extractie verzoeken (stichting-nice.nl)

Vraag 1: Hoe varieert de SES op patiënt niveau in de Nederlandse IC-populatie?

Benodigde data en onderbouwing:

Om de (demografische) spreiding van de SES in Nederland inzichtelijk te maken, zijn de volgende NICE variabelen nodig:

- Type ziekenhuis (academisch/STZ/perifeer)
- Regio ziekenhuis
- Opnamejaar

Om de spreiding van de SES in Nederland onder verschillende klinische groepen inzichtelijk te maken, zijn de volgende NICE variabelen nodig:

- Opnametype (medisch/electief chirurgisch/spoed chirurgisch)
- Leeftijd (gegroepeerd in 5-jaars categorieën) (18-24) t/m (90+)
- Geslacht (M/F)
- BMI (gegroepeerd)
- Mechanisch geventileerd in de eerste 24 uur van opname (1/0)
- Glasgow Coma Scale (per component)
- Chronische diagnosen (chronische nierinsufficiëntie, chronische dialyse, metastatisch neoplasma, hematologische maligniteit, cirrose, chronische cardiovasculaire insufficiëntie, respiratoire insufficiëntie, immunologische insufficiëntie, COPD, diabetes)
- APACHE III APS score
- APACHE IV opnamecategorie (sepsis, OHCA, CAP, trauma, cardiochirurgie)
- APACHE IV sterfterisico (laag/midden/hoog)
- IC behandelduur (in dagen)

N.B. deze informatie wordt ook gebruikt om te achterhalen welke confounders in de vervolgonderzoeken meegenomen moeten worden

Vraag 2: Is een lagere SES op patiënt- en wijkniveau in de Nederlandse IC-populatie geassocieerd met een hogere ziekenhuis- en lange termijn mortaliteit?

Benodigde data en onderbouwing:

De associatie wordt zowel univariaat als multivariaat (gecorrigeerd voor belangrijke klinische gegevens) getoetst. Om goed te corrigeren voor de confounders, hebben we ook afhankelijk van de resultaten van vraag 1 de volgende NICE variabelen nodig:

- Type ziekenhuis (academisch/STZ/perifeer)
- Regio ziekenhuis
- Opnamejaar

Klinische variabelen:

- Opnametype (medisch/electief chirurgisch/spoed chirurgisch)
- Leeftijd (gegroepeerd in 5-jaars categorieën) (18-24) t/m (90+)
- Geslacht (M/F)
- BMI (gegroepeerd)
- Mechanisch geventileerd in de eerste 24 uur van opname (1/0)
- Glasgow Coma Scale (per component)
- Chronische diagnosen (chronische nierinsufficiëntie, chronische dialyse, metastatisch neoplasma, hematologische maligniteit, cirrose, chronische cardiovasculaire insufficiëntie, respiratoire insufficiëntie, immunologische insufficiëntie, COPD, diabetes)
- APACHE III APS score
- APACHE IV opnamecategorie (sepsis, OHCA, CAP, trauma, cardiochirurgie)
- APACHE IV sterfterisico (laag/midden/hoog)
- IC behandelduur (in dagen)

De volgende uitkomsten worden geanalyseerd:

- Ziekenhuismortaliteit
- Sterfte 3 en 6 maanden na IC-opname

Vraag 3: Is de voorspellende kracht van het APACHE IV case-mix model voor de gehele IC-populatie of voor bepaalde subgroepen te verbeteren door het toevoegen van SES op patiënt en/of wijkniveau?

Benodigde data en onderbouwing:

Om het APACHE IV model te kunnen valideren en de verschillende performancematen te kunnen berekenen, hebben we de volgende NICE variabelen nodig:

- APACHE IV verwachte sterftekans
- Ziekenhuissterfte
- Sterfte 3 en 6 maanden na IC-opname

We hebben dezelfde klinische variabelen nodig:

- Opnametype (medisch/electief chirurgisch/spoed chirurgisch)
- Leeftijd (gegroepeerd in 5-jaars categorieën) (18-24) t/m (90+)
- Geslacht (M/F)
- BMI (gegroepeerd)
- Mechanisch geventileerd in de eerste 24 uur van opname (1/0)
- Glasgow Coma Scale (per component)
- Chronische diagnosen (chronische nierinsufficiëntie, chronische dialyse, metastatisch neoplasma, hematologische maligniteit, cirrose, chronische cardiovasculaire insufficiëntie, respiratoire insufficiëntie, immunologische insufficiëntie, COPD, diabetes)
- APACHE III APS score
- APACHE IV opnamecategorie (sepsis, OHCA, CAP, trauma, cardiochirurgie)
- APACHE IV sterfterisico (laag/midden/hoog)
- IC behandelduur (in dagen)

Om het APACHE IV model te recallibreren hebben we de volgende aanvullende variabelen nodig:

- Zwaarste APACHE IV opnamereden
- Herkomst (1-17)
- Aantal ziekenhuisdagen voor IC-opname
- Trombolytische therapie (1/0)
- P/f ratio
- Aantal grafts

Vraag 4: Leidt het uitbreiden van het APACHE IV-model met een SES-score op patiënt- en/of wijkniveau tot verschillen in de SMR's van ziekenhuizen?

Benodigde data en onderbouwing:

Om het APACHE IV model te kunnen verrijken met SES en de SMR per ziekenhuis te kunnen vergelijken op basis van originele APACHE IV model en het aangepaste model, hebben we de volgende NICE variabelen nodig:

- Clusternummer per ziekenhuis
- Type ziekenhuis (academisch/STZ/perifeer)
- Regio ziekenhuis
- Opnamejaar

We hebben dezelfde klinische variabelen nodig:

- Opnametype (medisch/electief chirurgisch/spoed chirurgisch)
- Leeftijd (gegroepeerd in 5-jaars categorieën) (18-24) t/m (90+)
- Geslacht (M/F)
- BMI (gegroepeerd)
- Mechanisch geventileerd in de eerste 24 uur van opname (1/0)
- Glasgow Coma Scale (per component)
- Chronische diagnosen (chronische nierinsufficiëntie, chronische dialyse, metastatisch neoplasma, hematologische maligniteit, cirrose, chronische cardiovasculaire insufficiëntie, respiratoire insufficiëntie, immunologische insufficiëntie, COPD, diabetes)
- APACHE III APS score
- APACHE IV opnamecategorie (sepsis, OHCA, CAP, trauma, cardiochirurgie)
- IC behandelduur (in dagen)

En de volgende uitkomstmaten:

- Ziekenhuissterfte
- Sterfte 3 en 6 maanden na IC-opname
- APACHE IV verwachte sterftekans

Om het APACHE IV model te recallibreren hebben we de volgende aanvullende variabelen nodig:

- Zwaarste APACHE IV opnamereden
- Herkomst (1-17)
- Aantal ziekenhuisdagen voor IC-opname
- Trombolytische therapie (1/0)
- P/f ratio
- Aantal grafts

Vraag 5: Kunnen we patiëntenclusters identificeren?
Vraag 6:Wat zijn de cluster fenotypes, komen ze overeen tussen provincies, verschilt SMR en mortaliteit tussen clusters, en heeft Limburg een andere cluster verdeling als andere provincies?

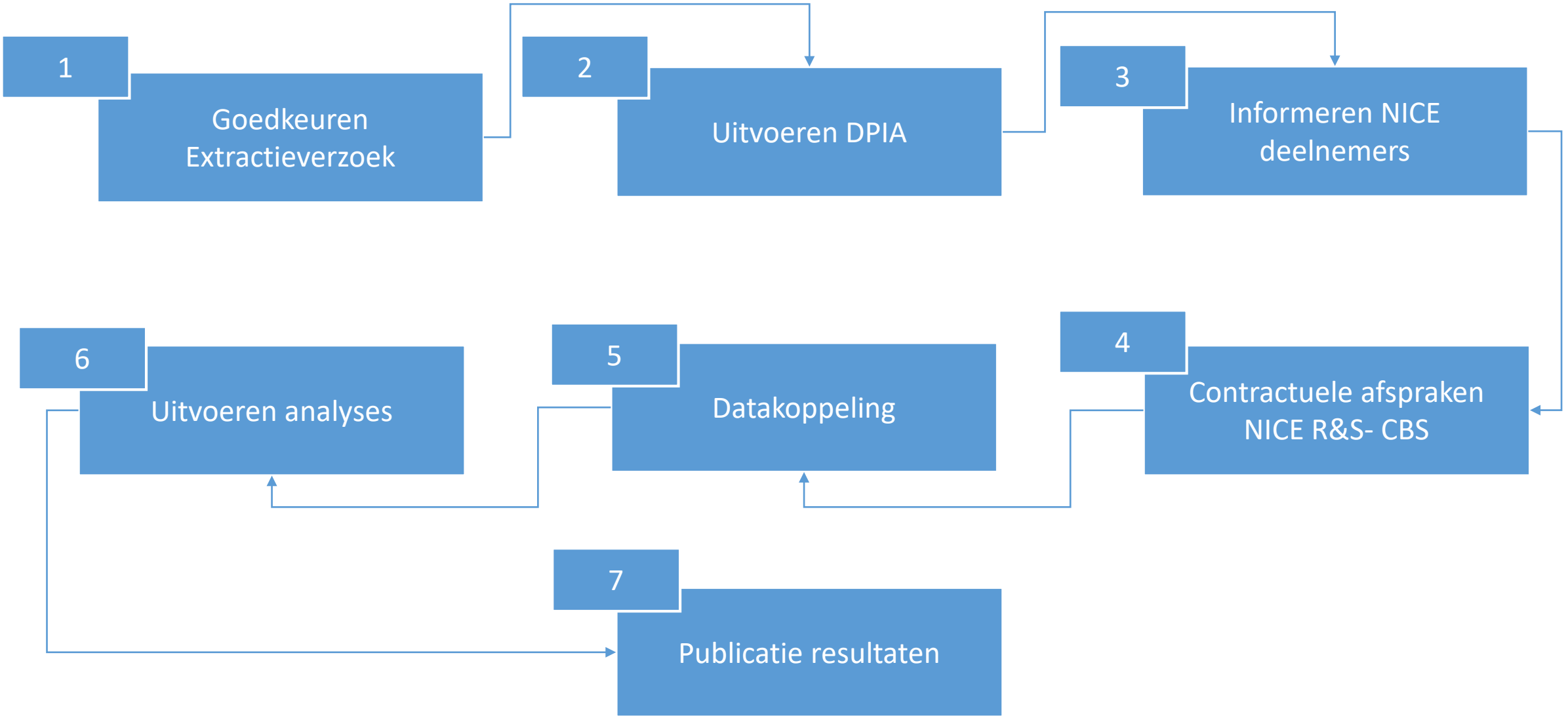
Benodigde data en onderbouwing:

Bij deze twee vragen maken we gebruik van geavanceerde machine learning technieken. Ten behoeve van het stratificeren van patiënten, om verschillen tussen groepen, en het effect van het verschil in patiëntpopulaties in kaart te brengen, hebben we ten opzichte van de vorige vraag nog de volgende aanvullende NICE variabelen nodig:

- Overgeplaatst van ander ziekenhuis of niet (1/0)
- IC ontslag bestemming (1-10)
- BMI
- Vasoactieve medicatie in de eerste 24 uur van opname
- Hoogste en laagste laboratorium waarde in de eerste 24 uur van opname
- Hoogste en laagste fysieke parameters in de eerste 24 uur van opname

N.B. Voor het clusteren van patiënten hebben we alle fysiologische en laboratorium variabelen nodig. Deze zijn namelijk indicatief voor de gezondheidsstaat van een patiënt, vooral wanneer andere gegevens zoals diagnose niet toereikend zijn. Voor het cluster model zijn lab waardes dus ook de belangrijkste variabelen voor het identificeren van patiënt groepen, zoals is gedemonstreerd door Castella Forte et al. (2021)

Proces


1
Goedkeuren Extractieverzoek
2
Uitvoeren DPIA
3
Informeren NICE deelnemers
4
Contractuele afspraken NICE R&S- CBS
5
Datakoppeling
6
Uitvoeren analyses
7
Publicatie resultaten

Proces

1: De wetenschapescommissie van Stichting NICE heeft het onderzoek goedgekeurd en de opdracht gegeven om de koppeling met de CBS data tot stand te brengen.

2: Er is een gegevensbeschermingseffectbeoordeling (DPIA) uitgevoerd om onder andere de privacyrisico's m.b.t. NICE data te beoordelen en maatregelen te nemen.

3: Het bestuur van Stichting NICE informeert de NICE deelnemers over het onderzoek en geeft ze de gelegenheid om vragen te stellen over dit onderzoek en eventueel bezwaar te maken tegen het verrijken van de data van hun ziekenhuis in de CBS omgeving tot 1 februari 2023.

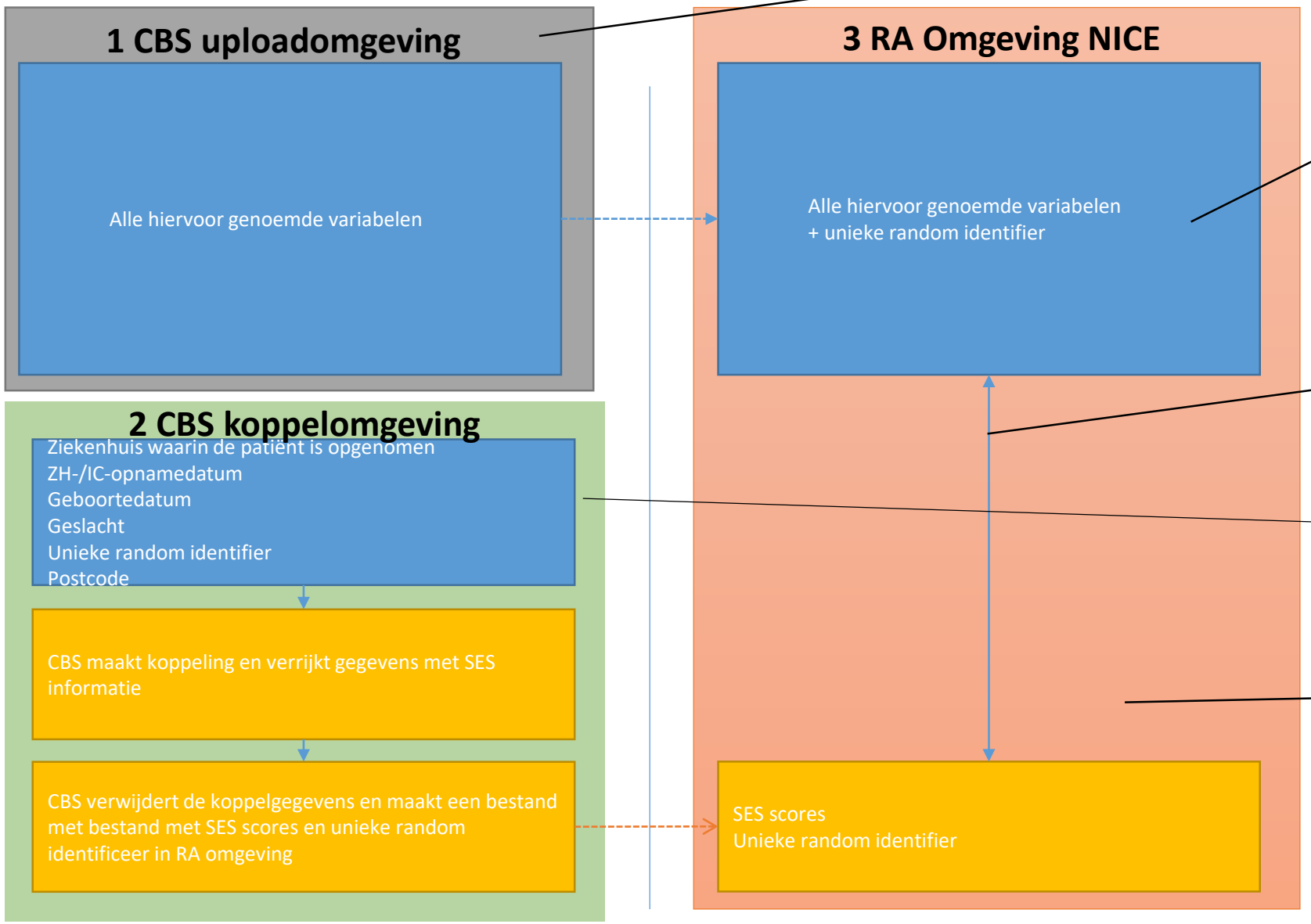
4: Op basis van de DPIA en eventuele opmerkingen vanuit de NICE deelnemers worden contractuele afspraken gemaakt m.b.t. koppelingsproces, toegang en bewaartermijn van de data.

5: De koppeling wordt in afgeschermde RA-omgeving van CBS tot stand gebracht. Een uitgebreide procesomschrijving is opgenomen op de volgende dia.

6: De onderzoekers van NICE R&S voeren de analyses uit zoals beschreven in de data-extractieverzoeken en volgens wetenschappelijke standaarden.

7: De resultaten worden middels nieuwsbrieven, de NICE discussiebijeenkomst en wetenschappelijke publicaties teruggekoppeld aan de deelnemers.

Het proces van datakoppeling



CBS medewerkers krijgen geen toegang tot de geüploade dataset van NICE.

CBS medewerkers krijgen geen toegang tot RA omgeving NICE.

Koppeling gebeurt door NICE medewerker.

Medewerkers van het CBS krijgen eenmalig toegang om de patiënten een rinpersoonsnummer te geven en te verrijken met SES data. NICE heeft geen toegang tot deze omgeving.

NICE-gegevens in RA omgeving worden na afronden onderzoek verwijderd. NICE bewaart een kopie van data (blauw) binnen AMC. CBS bewaart een kopie eigen data (geel).

Toelichting datakoppeling

1 CBS uploadomgeving:

- De beveiligde uploadomgeving van CBS is volgens AVG richtlijnen ingericht. NICE data kunnen op een veilige manier geüpload worden.

2 CBS koppelomgeving:

- De koppeling vindt plaats op basis van opname- en persoonsgegevens die NICE heeft ontvangen van deelnemende IC's. De koppeling wordt gedaan door een CBS medewerker. Als de gegevens voldoende overeenkomen zodat een koppeling tot stand kan komen, wordt er een SES-score toegevoegd aan de patiënt. Dit wordt gedaan op basis van het microdatabestand SESWOA van het CBS.
- Nadat de koppeling is voltooid, worden de gebruikte variabelen direct weer verwijderd, zodat alleen de SES data en de unieke random identifier gegevens over blijven.
- NICE onderzoekers ontvangen het koppelingsrapport met de benodigde informatie.

3 CBS RA Omgeving NICE:

- De RA-omgeving is een beveiligde online-omgeving waar alleen NICE-medewerkers toegang tot krijgen middels een persoonlijke token. Deze omgeving voldoet aan alle huidige veiligheids- en privacy-eisen.
- Alleen de aangewezen onderzoekers van NICE ontvangen persoonlijk inloggegevens en een token voor de RA-omgeving.
- De koppeling tussen SES en de IC-gegevens vindt plaats in de RA-omgeving door een NICE medewerker.

Output en bewaartermijn:

- Na de analyses met de gekoppelde data toetst het CBS of de output voldoet aan alle richtlijnen (d.w.z. geen herleidbare gegevens worden getoond, onthullingsrisico, et cetera), voordat NICE het mag exporteren en gebruiken voor publicaties.
- Nadat de analyses zijn afgerond, worden alle gegevens verwijderd bij het CBS. De gegevens (exclusief SES-score) staan enkel nog voor controle van het onderzoek ter beschikking van NICE medewerkers in hun beveiligde omgeving in het Amsterdam UMC locatie AMC waar NICE Research en Support is gevestigd op de afdeling Klinische Informatiekunde.

Application form for NICE data extraction and analysis for a scientific publication

Please complete this form fully and submit it to extractieverzoek@stichting-nice.nl.

1.1 What is the project title? We suggest to use the provisional title of the proposed scientific publication.

Socioeconomic state and outcome of critically ill patients in The Netherlands: a nationwide cohort study

1.2 Give at least five keywords which describe the project.

Socioeconomic state, intensive care, mortality, APACHE IV, regional differences

2.1 Who is the researcher conducting the study? This person can be a junior researcher (e.g. PhD student). Will he/she act as contact person for this project with NICE? Is (s)he contact person for NICE in his/her ICU*

Name	Daniëlle J.M. Koornneef
Academic title	Master of Science
Position and organization	Datamanager and PhD student NICE R&S (Medical informatics, Amsterdam UMC)
Telephone number	
E-mail address	
NICE contactperson for an ICU (yes/no)	no
Contactperson for this researchproject (yes/no)	yes

2.2 Who is the project leader /supervisor? Will he/she act as contactperson for this project with NICE? Is (s)he contactperson for NICE in his/her ICU*

Name	Dr. Bas C.T. van Bussel
Position and organization	Intensivist and epidemiologist at Maastricht UMC+
Telephone number	
E-mail address	
NICE contactperson for an ICU (yes/no)	no
Contactperson for this researchproject (yes/no)	yes

2.3 Who else is involved in the project group? Please provide all information on all members and indicate if this person is NICE contact person. *

Application form for NICE data extraction and analysis for a scientific publication

Name	Prof. Dr. Nicolette F. de Keizer
Position and organization	Chair of department and professor of medical informatics
E-mail address	
NICE contact person for an ICU (yes/no)	no
Name	Dr. Sylvia Brinkman
Position and organization	Researcher NICE R&S (Medical informatics, Amsterdam UMC)
E-mail address	
NICE contact person for an ICU (yes/no)	no
Name	Dr. Fabian Termorshuizen
Position and organization	Researcher and methodologist NICE R&S (Medical informatics, Amsterdam UMC)
E-mail address	
NICE contact person for an ICU (yes/no)	no
Name	Jip de Kok, MSc
Position and organization	PhD student Maastricht UMC+
E-mail address	
NICE contact person for an ICU (yes/no)	no
Name	Prof. Dr. Iwan C.C. van der Horst
Position and organization	Intensivist at Maastricht UMC+ and chair NVIC
E-mail address	
NICE contact person for an ICU (yes/no)	no

All Medical Informatics Amsterdam UMC employees will follow the integrity rules and other regulations of Amsterdam UMC. The Maastricht UMC employees will follow their regulations. Everyone with access to the data has signed a confidentiality agreement and a certificate of conduct.

2.4 Which hospital(s), participating in NICE, is/are supporting this application?

Maastricht UMC+, Maastricht, the Netherlands

2.5 What are the responsibilities of the project team? Describe how this proposal fits into the project leader's and members' research lines and expertise. Please specify which member of the project team will be primarily responsible for writing the manuscript and/or supervising the writing process.

Daniëlle Koornneef is a PhD student at NICE R&S and is responsible for the analysis and writing process of this project. She has a master in Health Economics and is experienced with conducting research/data analysis with the socioeconomic state (SES). In addition, as a data manager, she knows how NICE monitors clinical data.

Daniëlle Koornneef will be supervised by a research team consisting of:

- Fabian Termorshuizen is a methodologist, and he is involved in all the research projects on NICE data and performs analyses. With his excellent skills and expertise in statistical methods, he supervises researchers by assisting and/or performing analyses. In addition, he has experience using CBS data and their remote facilities.
- Sylvia Brinkman obtained a PhD on prognostic models used in intensive care to correct for case-mix. As a senior researcher at NICE, she has much experience with the database, developing and validating prognostic models and other statistical analyses. She will be in control of the daily supervision of Daniëlle.
- Nicolette de Keizer is a professor of Medical Informatics, and her research focuses on quality of care and health information systems. As one of the founding mothers of the NICE registry, she has an excellent knowledge of the meaning, possibilities and limitations of the available data. In addition, she supervised more than 30 PhD students.

This research team will be in close collaboration with the research team in Maastricht as they initiate this project. Furthermore, this project will be strengthened by the project: "Unravelling the potential drivers of increased intensive care unit mortality rates in Limburg through patient clustering" as this combines a common interest and goal. This team consists of the following:

- Bas van Bussel is the initiator of this project and is motivated to find reasons that can explain the "Limburgfactor" of which SES may be one. He is an experienced intensivist and epidemiologist at Maastricht UMC and a member of the NICE board. His clinical and epidemiological knowledge will be helpful during the research process. In addition, he is supervising Jip de Kok in his research on subgroups in Limburg.
- Jip de Kok is Unravelling the potential drivers of increased intensive care unit mortality rates in Limburg through patient clustering. He has experience with many Machine Learning (ML) concepts and has already applied clustering techniques to ICU data from MUMC+. He can contribute to the analysis with his data analysis and ML knowledge. The projects have common interests, so he can also support writing and comparing results.
- Iwan van der Horst is chair of the department of Intensive Care in Maastricht, intensivist and chair at the NVIC. With his outstanding experience in research as a professor of intensive care

medicine, he will be involved in the study design. Moreover, he will improve the written manuscripts with his clinical and scientific knowledge.

Nicolette de Keizer, Fabian Termorshuizen, Sylvia Brinkman, and Daniëlle Koornneef are responsible for this project. Bas van Bussel, Jip de Kok, and Iwan van der Horst are responsible for the project "Unravelling the potential drivers of increased intensive care unit mortality rates in Limburg through patient clustering: a retrospective study". We can help each other with the projects but operate the studies ourselves. There will be meetings where we give updates and ask for help when needed.

2.6 Is the project part of a larger project? If the answer is 'yes', please give details of how this project fits into the larger project. If this project is part of someone's PhD project, explicitly state that you are aware of the art 8 of '*Voorwaarden voor NICE extractieverzoeken*'.

This research is not part of a larger project as it is a separate project. We collaborate with the subgroups Limburg project and have common goals. However, this research on the SES and outcomes of critically ill patients is not defined as a subproject as it is a complete PhD project of Daniëlle Koornneef. We know the art 8 of 'Voorwaarden voor NICE extractieverzoeken'.

2.7 Given the duration and complexity of the projects, no projects will be awarded that are carried out by internship students or which are part of internships. Please explicitly state that this project is not part of an internship.

This project is not part of an internship.

3.1 What is the scientific background to the project? Include references to appropriate recent literature and information on the additional value and implications of the project. It should consist of 500 to 1,000 words. This section and the section on the research question (3.2) should, together, be equivalent to the introduction section in a scientific publication.

Various reports have shown the (hospital) mortality rate is higher in (southern) Limburg compared to various other Dutch regions even when adjusted for case-mix (i.e. differences in disease severity, comorbidities, and age) between hospitals ("Limburgfactor") (1, 2). Raising the question of what other possible explanations exist for the association with higher mortality in Limburg (1). For example, socioeconomic state (SES), lifestyle, environmental factors, and quality of care may play a role in this association (1). This research will focus on the effect of SES as a composited measure on outcomes of the Intensive Care Units (ICUs) in The Netherlands for several reasons.

Firstly, SES, defined as a relative position in society based on occupation, income, and education, is an essential determinant for health outcomes (3-6). Generally, a lower SES is associated with differences in incidence, course of illness, more healthcare use, and adverse healthcare outcome (3-10). For example, in patients with stroke, cardiovascular diseases, and chronic obstructive pulmonary

disease (COPD) (8-10). These worse outcomes for disadvantaged patients are also known as the social gradient, a phenomenon seen as the main challenge for public health in many western countries (3-6). Although multiple studies have found an association between lower SES and worse health, a universal conclusion about determinants and their impact is missing, as well as the identification of an effect of SES for every specific disease in every country (1, 3-10).

Secondly, the ICU will generally admit the most seriously ill patients. Therefore, the mortality rate of a hospital partially depends on the outcome in the ICU department. Therefore, it is common to correct for SES in the hospital mortality rate, while in the Acute Physiology And Chronic Health Evaluation (APACHE) IV model, used for the hospital mortality rate of critically ill patients, SES is omitted (2, 11). Although comparability and benchmarking of mortality rates are encouraged, separate measures still use a different case-mix correction. If an association between SES and mortality is found, this is another crucial reason to add SES to prognostic models. Therefore, we will investigate if extending the APACHE IV model with a SES score is beneficial. Then, calculating individual mortality risk and the case-mix correction may become more accurate (less residual confounding) (12).

Thirdly, some research has investigated the effect of SES and ICU outcome in different countries (13-16). In these studies, different patient characteristics have been identified, and for instance, higher SES groups have more often elective surgery, are older and have fewer comorbidities (14, 15). According to the systematic review by Jones et al. 2019, SES is already associated with adverse ICU outcomes in terms of hospital and long-term mortality (13). Nevertheless, after analyzing the individual studies and recently published research, the results regarding SES and mortality after critical illness are more ambiguous (15). This ambiguity can be due to differences in cohorts, healthcare organization, operationalization of SES scores, and study designs (3, 13, 15).

Moreover, a study of the association of SES with mortality after a critical illness has never occurred in the Dutch ICU population. Nowadays, we suppose the social gradient in terms of a worse outcome after critical illness for patients with a lower SES is present in the Dutch population. However, we do not have proof for this yet, and we do not know whether the mixed results of other studies are generalizable to the Dutch population (3, 6, 13, 15). The generalizability of the outcomes is restricted through, for example, the definition and operationalization of SES as relative score, the healthcare organization, and access to healthcare (3, 6, 13, 15). Besides this, it is questionable if SES plays a role when a patient is so ill that they must be admitted to the ICU. One assumption is that after discharge, the patients with a lower SES have less availability to essential resources during recovery, for instance, financially (6). Another assumption is that patients with a lower SES have a worse condition at admission and the case-mix correction is insufficiently effective in correcting this (1, 2, 12).

Additionally, we want to investigate the effect of SES in The Netherlands specifically because regions in the Netherlands have deviant mortality and SES scores (1, 2). For example, in Limburg, SES is, on average lower while mortality is higher (1, 2). It is hypothesized that the higher mortality in

Limburg might be partially driven by a lower SES (1). With this study, we will be able to address this.

A final reason to investigate the effect of SES on outcome in critically ill patients is that we will have access to a database with SES scores at the household level from Statistical Netherlands (CBS). Many other studies have used geographical SES scores, for example, with a postal code (13). However, these postal codes do not always represent an individual patient (13, 15). Therefore, with a score at a household level, we can conduct a more accurate investigation of the association of SES with mortality after critical illness. Moreover, we will also have accessibility to SES scores at the postal code level to identify differences between the two measures and their association.

Finally, this study will investigate if we can improve the case-mix correction in Dutch ICU patients with a SES score. For benchmarking (i.e. monitoring room for improvement in quality of intensive care), the standardized mortality ratio (SMR) is commonly used to standardize the mortality rate by dividing the observed mortality by the predicted mortality. The predicted mortality is often estimated based on the APACHE IV model. However, it is known that the APACHE IV model performs differently for ICU subgroups, which may not be distributed uniformly (12). Furthermore, it is known that SMRs vary among regions in The Netherlands, which may partially explain (regional) SMR differences. (1, 2). Therefore, updating the APACHE IV with SES may clarify that the (regional) differences found in the SMR may (partially) be explained by the variance in SES and distribution of subgroups instead of the differences in the quality of care now assumed. If the extension of the APACHE IV model improves the prediction of the individual mortality risk, we will examine whether this results in different SMRs and benchmark results for Dutch ICUs.

3.2 **What is the research question?** This section is equivalent to the last paragraph in the introduction section in a scientific publication and should include the aims and objectives of the project.

We will investigate the following research questions:

1) Does SES vary among the Dutch ICUs and/or regions?
2) Is a lower SES associated with higher hospital and long-term mortality in the Dutch ICU population?
3) What are the (practical) differences between using postcode-based SES scores and using household-based SES scores in the association with hospital mortality?
4) Does extending the APACHE IV model with SES scores improve the prediction of the individual mortality risk in the Dutch ICU population?

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a) Does the extended APACHE IV model with SES result in differences in benchmark results (SMR) of the Dutch ICUs?

b) Does the extended APACHE IV model used for SMR calculation affect regional SMR differences, and does this explain pre-existing regional differences in SMR?

The aim is to describe the variation of SES across critically ill patients admitted to Dutch ICUs and to investigate the association between SES and ICU outcomes. Furthermore, to examine whether SES affects individual mortality risks and benchmarking of ICUs by expanding the prognostic Acute Physiology And Chronic Health Evaluation (APACHE) IV model with SES.

Firstly, we want to examine differences in patient characteristics and regions of the admitted Dutch ICU patients based on SES. Additionally, we want to investigate the association between SES and (hospital/long-term) mortality. This is in order to explain different mortality among SES groups in ICUs and regions. Furthermore, we want to determine whether the benchmarking of Dutch ICUs can be improved with a more accurate prediction of individual mortality risk by extending the APACHE IV model with a SES score.

c) **Which data are required?** Please provide a complete, but concise description including inclusion and exclusion criteria and time period. Use the NICE datadictionary on https://stichting-nice.nl/dd/#start to describe the required data. A minimum amount of variables will be used to ensure data protection and privacy. Describe how variables will be categorized, if appropriate. Non-standard definitions should be supported by references to the literature. This section should, together with the sections on outcomes and statistical methods, be equivalent to the methods section in a scientific publication. Contact Stichting NICE for questions regarding available variables and definitions.

In order to obtain access to the CBS database and to meet the privacy rules, we will use the data as aggregated and minimalized as possible. We will only have access to pseudonymized data. We will request the security measures of CBS and assess them with our internal expert. Besides that, we will establish security measures in the contract regarding processing agreements with CBS. The department of Medical Informatics Amsterdam UMC “klinische informatiekunde” (processor of NICE) is responsible for the linkage with CBS. Moreover, the department of Medical Informatics will ensure that information security rules are contractually determined and followed by the relevant employees. From the NICE database, we need the following variables:

1. For the linking with CBS data:
    - Hospital admission date
    - ICU admission date
    - Date of birth
    - Gender

- Unique random identifier
- ABG hospital number
- Postal code

2. For insight into the demographical distribution of SES in The Netherlands:
    - Age (groups of 5 years)
    - Gender (male/female)

3. For insight into clinical groups:
    - Admission type (medical/elective surgery/emergency surgery)
    - Mechanical ventilation in the first 24 hours of ICU admission (yes/no)
    - Chronic diagnosis (yes/no) (renal, liver, immunologic, respiratory, cardio, oncologic, diabetes, COPD)
    - APACHE IV reason for admission (sepsis, OHCA, CAP, trauma, cardio)
    - APACHE IV mortality risk (low/middle/high)
    - APACHE III APS score
    - APACHE IV reason for admission (grouped based on coefficients)

4. The following outcome variables will be explored:
    - Hospital mortality (yes/no)
    - Date of death (if existing)
    - APACHE IV mortality probability

5. For insight into the distribution of SES in The Netherlands:
    - NICE anonymized hospital identification number
    - Type of hospital
    - Region hospital (depends on the chosen regions)

6. For insight into the predictive performance of models:
    - SMR per year per hospital
    - Calibration
    - The area under the curve score
    - Brier score

7. Any additional variables:
    - SESWOA from statline (SES score on a neighbourhood level)
    - Admission year (2014, 2015, 2016, 2017, 2018, 2019)
    - nice_ap4_excluded (yes/no) to determine the APACHE IV subgroup
    - COVID (yes/no), if CBS has updated the database with data from 2020 and 2021.

From CBS, we will obtain a connection to the following variables:

- An anonymized number to connect the patient
- AGB hospital number
- SESWOA, SES score on household level
- An anonymized postal code to make a connection with statline SESWOA variables

- Date of death for the deceased patients

The cohort will be formed by all NICE registered patients in The Netherlands admitted to a Dutch ICU between 01-01-2014 and 31-12-2019. Around 300.000-400.000 patients will be included. Possibly the inclusion time can be extended to 31-12-2021 when CBS has updated the SESWOA database with data for 2020 and 2021.

4.2 What are the outcomes used in the project? Please define the primary outcome and any secondary outcomes clearly and fully, including references to the literature where necessary.

For the first question, SES will be the outcome measure to investigate the variance of the ICU population and regions.

In the second question, we will explore the association of SES scores with hospital mortality (yes/no). Moreover, we will investigate 1-year mortality based on the date of death and possibly 3-year mortality. This question will be examined using an unadjusted and adjusted mixed effects logistic regression model and a cox proportional hazard model.

In the third question, the outcome variables of question two will be used again because we want to observe possible differences between postal code SES scores and household SES scores.
In the fourth question, we want to observe whether the APACHE IV model is improved by adding SES. The outcome of the APACHE IV model is the individual predicted mortality probability. This probability will be compared with the observed mortality. Therefore, hospital mortality is the outcome variable. If improvement is approved, we want to assess benchmark and regional results using the SMR as an outcome variable.

4.3 What statistical methods will be used in the project? Please be as precise as possible. Contact Stichting NICE regarding advise on available statistical methods. For complex questions it is recommended to plan a meeting to discuss methodology.

Firstly, we will follow CBS procedure to obtain access to the relevant data: fill in certain forms, have a consultation, and establish the final decisions. After signing the agreement, the CBS will encrypt and connect the SES data to our NICE linkage variables, after which we can link the CBS dataset with the clinical variables from the NICE registry. When we have access to the data, we will examine and

validate the data. We will need to clean the data before starting the analysis. Moreover, we will look into the randomness of the missing data and judge if it is beneficial to impute the data.

We will analyze the variance in SES for regions and patient characteristics for the first question. For example, assessing differences in SES scores for hospital type, groups of diagnosis (OHCA, CAP, sepsis, and trauma), disease severity, demographic characteristics, et cetera. We will investigate whether household SES scores are associated with these various patient characteristics. For this purpose, we will use different tests, but mostly the t-test and Chi-squared test. Also, frequencies, percentages, means, standard deviations, medians, and interquartile ranges will be described. Finally, we will use a multivariable ordinal logistic regression model to examine the SES scores of the variables combined.

The second question is whether the SES of the Dutch ICU population is associated with mortality. Firstly, we will investigate if SES is associated with hospital mortality using a univariate logistic regression model. After that, we will use mixed effects multivariate logistic regression models to estimate odds ratios of mortality associated with the total SES score and to correct for confounders (i.e. see variables above). Furthermore, to correct for clustering within hospitals, the hospital of admission will be added as random effect. Moreover, we will use proportional cox hazard models to conduct a survival analysis for ICU patients and investigate 1-year and 3-year mortality after ICU admission. With this model, we can add different covariates and observe the possible association of SES with long-term mortality.

In the third research question, we will explore the association of SES scores with mortality. We will compare two measures of SES scores in a mixed effects multivariate logistic regression model. First, we will create one model using a SES score at the neighbourhood level based on the patients' domestic address postal code. Additionally, we will create the same model, but this time with SES score at the household level. After that, we will compare both models using performance statistics. This will give insight into whether it is sufficient to correct for SES based on postal code, which is often more feasible as SES based on postal codes (e.g. four numbers) are open data.

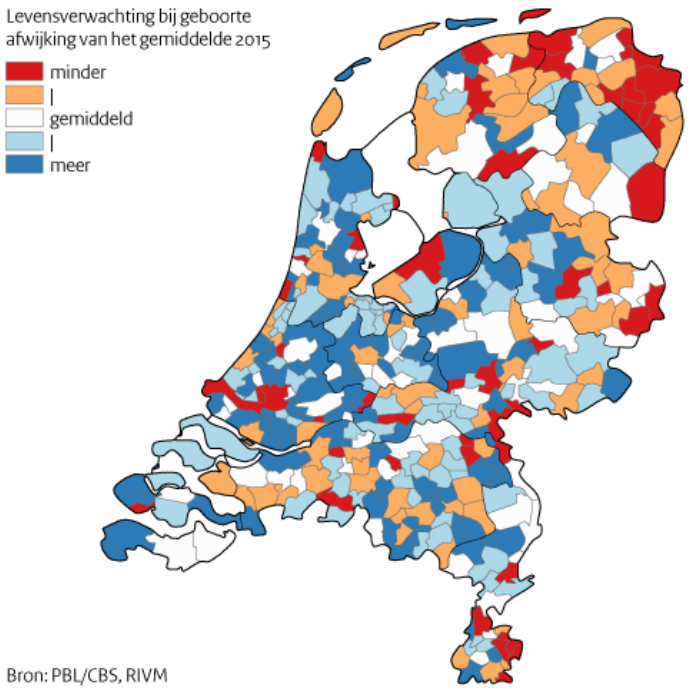
The fourth question is whether the performance of the existing disease severity APACHE IV model may be improved by including the SES scores. For this question, a tenfold cross-validation is used to split the cohort into two groups randomly. One for developing the adapted APACHE IV model (training set) and another for validating this new model (test set). We will again evaluate the difference between using the SES score on a household or neighbourhood level by comparing the prognostic performance of both models to the current APACHE IV model. Assessing the prognostic performance will be done using the AUC, brier score, and calibration. Furthermore, we will look into the differences between the models and their practical implications. One can wonder whether it would be feasible to use household SES scores to assess the mortality risk, as this is often

unavailable. If the prognostic performance of the updated APACHE IV model improves, subquestions a and b will be investigated. Firstly, the SMRs need to be estimated for every hospital and year using the original APACHE IV model and the updated version. To examine whether the benchmark results of the Dutch ICUs have changed, we will compare the updated SMR with the original SMR (possibly per year). This approach will be redone, but we will combine the SMRs of ICUs based on region to observe changes across regions. To compare SMRs, different approaches can be used, for example, a leave center out analysis (LCOA). Nevertheless, we will wait for the results of the other questions before deciding on the methods of the analysis of SMRs. Moreover, the output has to be approved by the CBS and, therefore, will depend on the regulations of the CBS. Possibly we are not allowed to show the SMRs per ICU due to traceability.

4.4 **Which tables or figures do you want to include in your scientific publication?** Please provide empty tables and 'fake' figures (or copies from other sources), with as much information on the data you require.

These are all example figures and will be adapted to the appropriate form as the research question describes.

Question 1:



Application form for NICE data extraction and analysis for a scientific publication

Table 1 Case mix, activity, and outcome for 78 631 adult admissions to 138 critical care units from April 30, 2000, to April 29, 2002, by quintile of IMD

		Quintiles of IMD				
		1 (least deprived)	2	3	4	5 (most deprived)
No. of admissions		10 751 (13.7)	14 641 (18.6)	15 781 (20.1)	16 792 (21.4)	20 666 (26.3)
Age (y), mean (SD)		62.2 (18.5)	62.3 (18.6)	61.0 (19.2)	59.4 (19.7)	56.3 (20.0)
Sex, n (%)	Male	6398 (59.5)	8489 (58.0)	9001 (57.0)	9577 (57.0)	11 847 (57.3)
	Female	4353 (40.5)	6152 (42.0)	6780 (43.0)	7215 (43.0)	8819 (42.7)
Type of admission, n (%)	Nonsurgical	5858 (54.5)	8107 (55.4)	8895 (56.4)	9882 (58.9)	13 253 (64.2)
	Elective surgical	2653 (24.7)	3543 (24.2)	3763 (23.9)	3661 (21.8)	3540 (17.1)
	Emergency surgical	2231 (20.8)	2986 (20.4)	3115 (19.8)	3240 (19.3)	3866 (18.7)
Source of admission, n (%)	Accident and emergency same hospital or other hospital	2218 (20.7)	2964 (20.3)	3430 (21.8)	4008 (23.9)	5848 (28.3)
	Clinic or home	26 (0.2)	46 (0.3)	42 (0.3)	45 (0.3)	56 (0.3)
	ICU/high dependency unit	912 (8.5)	1174 (8.0)	1299 (8.2)	1506 (9.0)	2067 (10.0)
	Theater	4884 (45.5)	6529 (44.6)	6878 (43.6)	6901 (41.1)	7406 (35.9)
	Ward or other intermediate care area	2700 (25.1)	3920 (26.8)	4119 (26.1)	4316 (25.7)	5271 (25.5)
Medical history, n (%[a])	Liver	171 (1.6)	230 (1.6)	265 (1.7)	292 (1.8)	504 (2.5)
	Respiratory	251 (2.4)	377 (2.6)	510 (3.3)	535 (3.2)	744 (3.7)
	Renal	134 (1.3)	173 (1.2)	183 (1.2)	222 (1.3)	298 (1.5)
	Immunosuppressed	890 (8.4)	1099 (7.6)	1058 (6.8)	1023 (6.2)	1105 (5.4)
Mechanical ventilation received on admission to the unit or at any time during the first 24 h of admission to the unit, n (%)		6719 (62.8)	8849 (60.7)	9867 (62.8)	10 762 (64.5)	14 005 (68.2)
Severe sepsis in the first 24 h of admission to the unit, n (%)		2184 (20.3)	2883 (19.7)	3110 (19.7)	3338 (19.9)	4202 (20.3)
AKI, n (%)	None	6764 (62.9)	9415 (64.2)	10 175 (64.5)	10 777 (64.2)	13 441 (65.0)
	Risk	1397 (13.0)	1914 (13.1)	1984 (12.6)	2140 (12.8)	2492 (12.1)
	Injury	1274 (11.9)	1606 (11.0)	1792 (11.4)	1888 (11.3)	2351 (11.4)
	Failure	1181 (11.0)	1543 (10.5)	1649 (10.5)	1765 (10.5)	2087 (10.1)
	End stage	135 (1.3)	173 (1.2)	181 (1.2)	222 (1.3)	295 (1.4)
ICNARC physiology score, mean (SD)		18.2 (10.2),	18.0 (10.2)	18.1 (10.2)	18.5 (10.3)	18.9 (10.2)
ICNARC predicted hospital mortality, median (IQR)		22.8 (6.9-54.0)	22.6 (7.1-53.3)	21.6 (6.7-53.6)	22.3 (6.8-53.1)	22.3 (6.7-52.6)
Acute hospital length of stay before admission to the critical care unit (d)[b], median (IQR)		1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
Unit length of stay (d), median (IQR)	Unit survivors	1.9 (0.9-4.7)	1.9 (0.9-4.7)	1.8 (0.9-4.6)	1.9 (0.9-4.8)	1.9 (0.9-5.1)
	Unit nonsurvivors	1.9 (0.6-5.7)	2.0 (0.6-6.1)	2.0 (0.6-5.8)	1.9 (0.6-5.8)	2.0 (0.7-6.2)
	All	1.9 (0.9-4.9)	1.9 (0.9-4.9)	1.8 (0.9-4.8)	1.9 (0.9-4.9)	1.9 (0.9-5.4)
Hospital length of stay (d)[b], median (IQR)	Hospital survivors	17 (10-34)	17 (10-34)	17 (10-33)	18 (10-35)	18 (9-36)
	Hospital nonsurvivors	9 (3-23)	9 (3-21)	8 (3-21)	8 (2-21)	8 (2-21)
	All	15 (8-30)	15 (8-30)	15 (7-30)	15 (7-31)	15 (6-32)
Readmissions within the same acute hospital stay, n (%)		590 (5.5)	810 (5.5)	793 (5.0)	872 (5.2)	1102 (5.3)
Mortality, n (%)	Unit	2182 (20.3)	3062 (20.9)	3326 (21.1)	3678 (21.9)	4745 (23.0)
	Hospital[b]	3137 (31.5)	4345 (32.1)	4681 (32.0)	5186 (33.3)	6440 (33.8)

[a] Percentage of those with evidence to assess medical history.
[b] Excluding readmissions within the same hospital stay.

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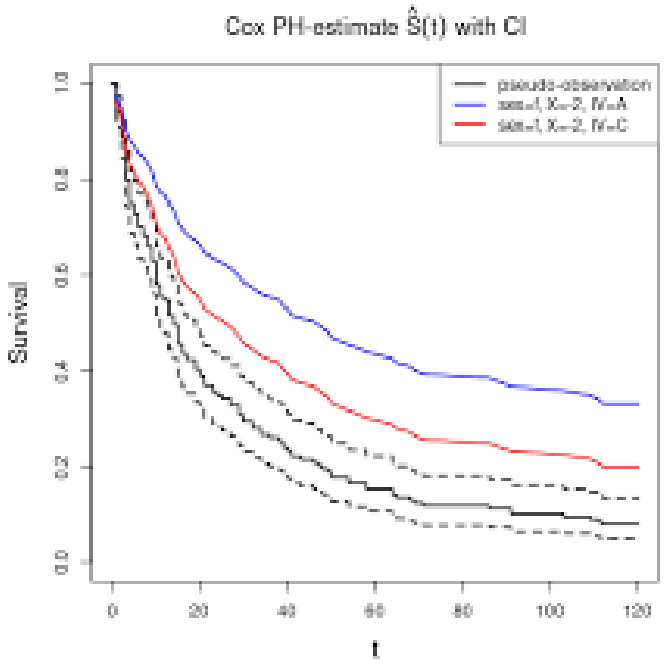
Questions 2 and 3:

Table 2 Odds ratios for ultimate hospital mortality by quintile of IMD, overall, and by type of admission

Analysis		Quintiles of IMD					*P*	*P* test for interaction
		1 (least deprived)	2	3	4	5 (most deprived)		
Unadjusted		Reference	1.03 (0.97-1.09)	1.02 (0.97-1.08)	1.09 (1.03–1.15)	1.11(1.06-1.17)	<.001	
Adjusted for case mix and unit [a]		Reference	1.08 (1.00-1.16)	1.11 (1.03-1.19)	1.16 (1.08-1.25)	1.19 (1.10-1.28)	<.001	
Type of admission, n (%)	Nonsurgical	Reference	1.09 (0.99-1.19)	1.08 (0.99-1.19)	1.14 (1.04-1.25)	1.16 (1.06-1.27)	.019	.452
	Elective surgical	Reference	0.98 (0.81-1.18)	1.19 (1.00-1.43)	1.24 (1.04-1.49)	1.19 (.99-1.43)	.003	
	Emergency surgical	Reference	1.11 (0.96-1.29)	1.12 (0.97-1.30)	1.15 (0.99-1.33)	1.26 (1.10-1.47)	.009	

Values are odds ratio (95% confidence interval).

[a] Adjusted for age, sex, medical history ICNARC physiology score, diagnostic category, source of admission to the unit, unit-level mean IMD quintile, and unit-level random effect.



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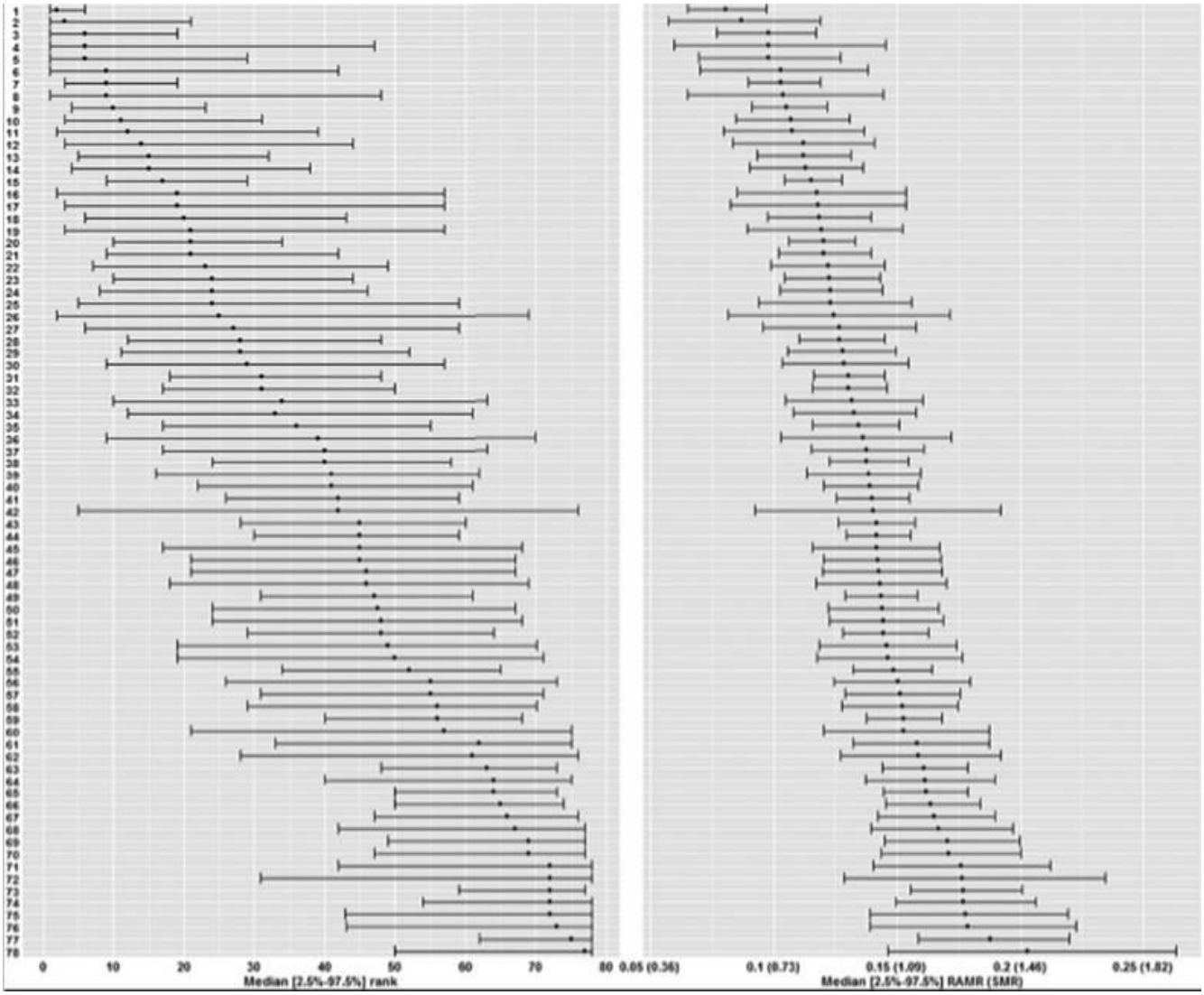
Question 4:

Table 3. Performance of the original and customized APACHE IV model

Model	AUC (CI)[a]	Ĉ-statistic (CI)	Brier score (CI)	R^2	SMR (CI)
APACHE IV original non-CABG	0.87 (0.86-0.87)	822.67 (693.31-955.75)	0.10 (0.10-0.10)	0.29	0.87 (0.86-0.88)
Admission type					
Medical	0.85 (0.84-0.86)	795.62 (601.79-1002.49)	0.13 (0.13-0.14)	0.28	0.87 (0.85-0.90)
Urgent surgery	0.83 (0.81-0.84)	156.22 (93.32-232.98)	0.12 (0.12-0.13)	0.23	0.87 (0.83-0.91)
Elective surgery	0.82 (0.81-0.84)	75.95 (40.07-120.65)	0.05 (0.04-0.05)	0.14	0.85 (0.78-0.91)
Subgroups[b]					
Bacterial pneumonia	0.73 (0.70-0.76)	190.69 (106.34-294.89)	0.18 (0.17-0.19)	0.09	0.82 (0.75-0.89)
Cardiac arrest	0.71 (0.69-0.74)	682.37 (476.19-914.48)	0.25 (0.23-0.27)	0.00	0.78 (0.75-0.82)
Colon/rectal cancer	0.80 (0.75-0.83)	69.42 (36.11-1121.09)	0.09 (0.08-0.10)	0.10	0.71 (0.60-0.81)
Abdominal aortic aneurysm	0.77 (0.68-0.84)	30.87 (11.14-72.77)	0.04 (0.03-0.05)	0.08	0.83 (0.62-1.06)
Thoracotomy for lung cancer	0.74 (0.61-0.85)	41.40 (23.83-62.18)	0.03 (0.02-0.04)	0.03	0.48 (0.30-0.68)



4.5 In case you will be using Vektis data for long-term outcomes, provide full details for invoicing for the contribution of 2000,- euros.

We might be able to use the date of death in the CBS workspace, which is more accurate than Vektis data and makes it possible to do a survival analysis. If we obtain this data, data from Vektis will not be used. Additionally, this question depends on the collaboration in the CBS workspace between NICE and Maastricht UMC+. See also extractieverzoek “Unravelling the potential drivers of increased intensive care unit mortality rates in Limburg through patient clustering: a retrospective study”.

5.1 Are additional permissions from ICUs or patients required for this project? If the answer is 'yes', give details of the permissions required, including the person responsible for obtaining them and the expected timescale.

No, permissions are not required. However, hospitals will be informed by the newsletter of NICE and get the chance to ask questions and to object. Hence, they do not need to permit this project explicitly. However, Daniëlle Koornneef will ensure she answers the questions and registers the objects. Moreover, a METC waiver will be submitted.

5.2 Are any additional (non-NICE) data required to carry out this project? If the answer is 'yes', give details of the data required, including the person responsible for obtaining the data and the expected timescale.

Yes, CBS data will be used to gain insight into the SES scores of ICU patients. The data is already collected, cleaned, and, if necessary, imputed by the CBS. We will get access by a linkage with an encrypted anonymized patient number. The variables of interest are already mentioned in the variable set. We will obtain both household-level SES scores and postal code-level SES scores. With this, we can compare the results of both measures and give practical implications for applying these measures in analysis. Furthermore, we will possibly obtain the date of death of deceased patients to conduct a survival analysis.

Extra information in Dutch:

- StatLine-cijfers en toelichting: CBS Statline
- Korte onderzoeksbeschrijving: SES-WOA scores per wijk en buurt (cbs.nl)
- Documentatierapport: Seswoa: Sociaaleconomische statusscores huishoudens (cbs.nl)
- Artikel: Statusscore per wijk en buurt o.b.v. welvaart, opleidingsniveau en arbeid (cbs.nl)
- Corporate artikel: CBS brengt sociaaleconomische statusscores van wijken en buurten in kaart
- Rapportage: Berekenwijze SES score per wijk/buurt (cbs.nl)

The CBS is responsible for obtaining the SES data from the Dutch population commissioned by the Dutch ministry of health. The department of Medical Informatics (Amsterdam UMC) is responsible for the linkage of CBS data and data of the NICE registry. Hospitals will be informed and have time to object against the linkage with CBS. Furthermore, we will consider the applicable privacy rules, contracts, and regulations to protect the data and patients.

The VEKTIS data will only be used if the date of death is unavailable in the CBS workspace. Then we will use long-term mortality data to analyze the association of SES with mortality.

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6. **Do you consider carrying out the analyzes yourself at the department of Medical Information at the AMC with the supervision of the NICE researchers?** *It should be noted the this is subjected to strict conditions and we cannot guarantee that there is always room for it.*

Yes, but not different as stated in my PhD agreement. NICE researchers are my supervisors and, therefore, will automatically supervise the analyzes at the department. Furthermore, I have my own place to work out this research; hence the following subquestions are not applicable.

6.1. If yes, are you a PhD candidate who wants to include more than two publications in your PhD theses based on NICE data ?

6.2. If yes, can you prove by means of diplomas / certificates that you are qualified to carry out the analyzes?

6.3. If yes, provide names for certified persons who will provide you with epidemiological and statistical guidance during the research project.

6.4. If yes, provide information which days during which time period you can visit the department.

6.5. If yes, provide full details for invoicing for the contribution of 1000,- euros. We can start the procedure after receiving this amount.

7. **How will this project be funded**? *Preferably, the costs for the analyses are included in the fundraising. If the application is not part of a funded project, an alternative can be considered in consultation with the KIK.*

NICE research and support (located at Medical Informatics (Amsterdam UMC)) is processor of the association NICE. NICE R&S obtains funding from the NICE foundation to process and analyze data and perform innovations such as better case-mix correction in this case. This is PhD project is part of this funding.

8. **Please include an estimate of the time needed for data extraction, analysis and interpretation and state your means of funding for this part of the project.**

During the time of the PhD project, approximately 4.5 years left.

9. **Do you wish to work with a particular member of the board of directors of NICE?** If the answer is 'yes', please name this person.

Yes, Nicolette de Keizer, Bas van Bussel as stated in question 2.5. In addition, Sylvia Brinkman is officially not a board member, but she is present during their meetings to represent NICE R&S.

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10. Dutch language summary. Please describe your research in approximately 100 words in Dutch. This summary will be published on the NICE website.

Binnen dit project wordt de variatie van sociaaleconomische status (SES) van de patiënten opgenomen op een Nederlandse IC beschreven en daarnaast onderzocht wat de associatie is tussen SES en ziekenhuismortaliteit en andere IC-uitkomsten. SES is een belangrijke determinant in andere ziektebeelden en er in Nederland nog geen onderzoek uitgevoerd naar de associatie tussen SES en mortaliteit op de IC. Bovendien kunnen we op basis van de uitkomsten van deze studie analyseren of SES toegevoegd moet worden aan APACHE IV model. Door benchmarken is gebleken dat in bepaalde regio's een verhoogde SMR is, die mogelijk gedeeltelijk te verklaren is door een ontoereikende case-mix correctie (voor bepaalde subgroepen) en/of door een lagere SES score. De SES scores zullen door het Centraal Bureau voor Statistiek gekoppeld worden aan NICE data.

11. What are the intended journals? Please provide three options.

- British Medical Journal
- Critical Care Medicine
- Journal of Crit Care

By submitting this form, I agree to be bound by the "Voorwaarden verbonden aan een data-extractieverzoek bij NICE" attached to this document.

Name: Daniëlle Koornneef

Date: 25-10-2022

Signature:

Name: Bas van Bussel

Data: 21-10-2022

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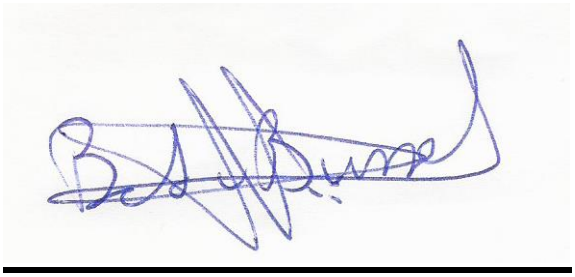
Signature: 

**: These data are stored for administrative and communication purposes and are subject to the Privacy Policy as described on the website of the NICE Foundation.*

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