

Algemene gegevens / General Information

Programma / Programme : **COVID-19 Programma**
 Subsidiëronde / Subsidy round : **Bottom-up ronde COVID-19 aandachtsgebied 3**
 Projecttitel / Project title : **Dynamical indicators for retrospective and prospective evaluations of the effect of control measures on the spread of COVID-19**
 Projecttaal / Project language : **Engels / English**
 Geplande startdatum / Planned start date : **27-07-2020**
 Geplande duur / Planned duration : **18 maanden / months**
 Datum indienen / Date of application : **25-05-2020**
 Projecttype / Project type : **Toegepast onderzoek / Applied research**
 Vervolg eerder ZonMw-project / Continuation previously funded project : **Nee / No**
 ZonMw

Projectleden / Project members**Prof. dr. E.R. Van den Heuvel (Main applicant)**

Functie / Position: (10)(2e) | Opleiding / Education: WO
 Studierichting / Subject: (10)(2e)
 T: (10)(2e) | F: | E: (10)(2e) @tue.nl

Eindhoven University of Technology
 Department of Mathematics and Computer Science
 Postbus 513
 5600 MB EINDHOVEN

Prof. dr. E.R. Van den Heuvel (Projectleader and secretary)

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

COVID19 - Lijn 3 of WiP / COVID19 - Lijn 3 or WiP

Dossier nummer / Dossier number: 50-56300-98-893

DEFINITIEF

Rijksinstituut voor Volksgezondheid en Milieu
Centre for Infectious Disease Control (CIb)

Antonie van Leeuwenhoeklaan 9
3721 MA BILTHOVEN

(10)(2e)

Functie / Position: (10)(2e) | Opleiding / Education: WO

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

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Postbus 513
5600 MB EINDHOVEN

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

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3721 MA BILTHOVEN

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

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Department of Mathematics and Computer Science
Postbus 513
5600 MB EINDHOVEN

Projectgegevens / Project information**Samenvatting / Summary**

BACKGROUND: Detecting change in the spread of COVID-19 and quantifying effects of implementing and eliminating governmental measures for (sub)populations within and across countries requires solid data analysis of the number of infections, hospitalizations, and deaths (accompanied with other publicly available data). Literature has described many approaches in the field of epidemic disease modeling and infectious disease surveillance, that would be potentially appropriate, but there are many serious limitations.

CHALLENGES: The collected data is subjected to selection bias, since individuals are being collected by purposive sampling, prohibiting an analysis with a single method. Surveillance models typically do not take the dynamics and heterogeneities in disease spread into account. Epidemic disease models are sensitive to unknown assumptions of virus characteristics (incubation and recovery times), which are not well-known during a pandemic.

SOLUTION: We propose to further develop our novel and recently initiated data-oriented approach, where we use multiple data analyses methods jointly to capture and understand the information present in the data and to validate patterns across countries. Our approach uses statistical quantities at a national level based on epidemic disease models and growth curve analysis, but they require additional research to be able to signal and explore possible spatial-temporal changes in the spread of the virus within subpopulations (sex, age-group) more regionally to enhance our understanding of implementing and eliminating control measures.

GOALS: We will further develop, study, and validate novel statistical quantities, create a dashboard able to retrospectively and prospectively identify and quantify the effects of implementing/eliminating governmental measures on virus spread in (sub)populations locally and nationally (in European countries), and implement our approaches at RIVM to help maintain control over the pandemic.

Trefwoorden / Keywords

disease modeling, real-time surveillance, data science

COVID19 - Lijn 3 of WiP / COVID19 - Lijn 3 or WiP

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DEFINITIEF

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

Ja / Yes

Organisaties

Rijksinstituut voor Volksgezondheid en Milieu
Centre for Infectious Disease Control (CIb)
Antonie van Leeuwenhoeklaan 9
3721 MA BILTHOVEN

Financiële gegevens / Financial data**ZonMw budget**

Kostenpost	Jaar / Year								Totaal / Total
	1	2	3	4	5	6	7	8	
Personeel	249.621	100.038	0	0	0	0	0	0	349.659
Materieel	5.000	0	0	0	0	0	0	0	5.000
Implementatie	11.822	5.911	0	0	0	0	0	0	17.733
Apparatuur	0	0	0	0	0	0	0	0	0
Overig	11.822	5.911	0	0	0	0	0	0	17.733
Totaal / Total	278.265	111.860	0	0	0	0	0	0	390.125

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status
Rijksinstituut voor Volksgezondheid en Milieu	146.862	Wordt aangevraagd

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			
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

not applicable

Dynamical indicators for retrospective and prospective evaluations of the effect of control measures on the spread of COVID-19

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

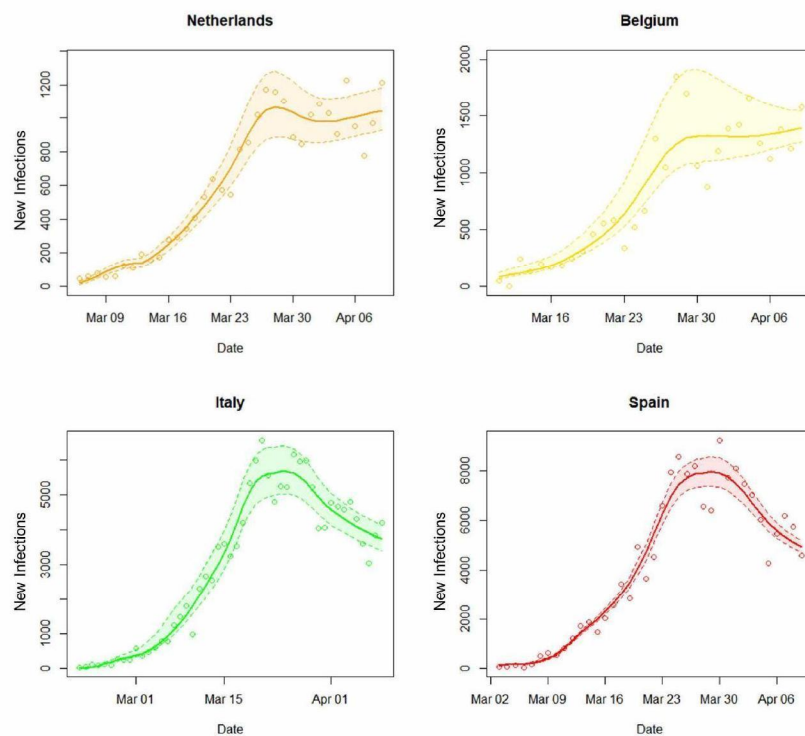
Edwin van den Heuvel

ORGANISATIE:

Eindhoven University of Technology

PROJECTTITEL:

Dynamical indicators for retrospective and prospective evaluations of the effect of control measures on the spread of COVID-19



DATASTEWARD:

Ik betrek een datasteward bij mijn project:

Naam: Sjeff Öllers

Instituut: Eindhoven University of Technology

E-mail: s.ollers@tue.nl

Was aanwezig bij de webinar: Ja Nee

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

1.1. Background: Infectious disease surveillance methods [1] and epidemic disease models [2] can detect, monitor and describe the spread of a virus among a population. Surveillance methods can be broadly divided into test-based and model-based methods. They have been employed both by various European institutes for infectious disease control. Epidemic disease models describe how inhabitants transit between stages, starting from being susceptible to an infection of the virus to being exposed or infectious, and then transition to different outcomes (hospitalized, died, or recovered). Surveillance and disease models describe (changes in) virus spread at an aggregated or population level and are essential to our understanding of public health, since they can be used to quantify the effect of governmental control measures (on e.g. COVID-19 [3]).

1.2. Limitations: The outbreak of COVID-19 has revealed some critical limitations for these two approaches. Firstly, daily data on confirmed number of infections, hospitalizations, and deaths are subjected to selection bias, since individuals are being collected by purposive sampling. Subpopulations at risk (e.g., health-care personnel) are being oversampled, contacts of known cases are being traced and tested, and governments constantly change their testing policies during the pandemic. A second limitation is the lack-of-knowledge on virus characteristics. Incubation periods, patient recovery times, immunity after infection are being determined with little precision and agreement. They affect calculations of monitoring statistics (like R_t) and complicate the choice of the most appropriate analysis techniques. Thirdly, surveillance methods are not fully equipped to address the current unknown dynamics of COVID-19. Test-based algorithms presume a static disease process and ignore spatial and endemic heterogeneities across and within countries. Model-based algorithms have the potential of addressing these limitations, but have considered only generic statistical models (e.g., generalized linear mixed models), instead of epidemic disease models or growth curve models. Furthermore, model-based detection algorithms are sensitive to the unknown assumptions on virus characteristics. Finally, monitoring statistics (like R_t) are useful for controlling the spread of the virus, but they are less suitable for monitoring changes when control measures are being relaxed. Thus there is an urgent need to address all these limitations to be able to better evaluate consequences of control measures on the pandemic.

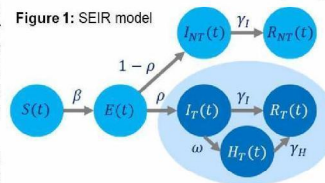
1.3. Solution: A common scientific approach is to consider an existing single infectious disease method and start improving it to accommodate limitations. This leads to more complex epidemic disease methods, which are most likely more sensitive to (virus characteristic) assumptions. Therefore, we rather propose to further develop our data-oriented approach, where multiple data analyses methods are used jointly to capture and understand information and patterns present in the data, to explore differences across and within countries, and to signal spatial-temporal changes in the spread of the virus due to implementation and elimination of control measures. We will implement our methods on real-time daily numbers of infections, hospitalizations, and deaths from different countries, areas and sub-populations, and complement it with other (publicly) available data to retrospectively evaluate effects of previously implemented control measures. Additionally, our data-oriented approach will be used as dashboard (in line with goals of the Dutch government [4]) to prospectively identify when, where, and what change in virus spread will occur due to elimination of control measures. A dashboard will make our knowledge accessible and usable to other (non-)researchers, freely and worldwide, and it can be reused when the coronavirus spreads again or in case of another virus outbreak.

1.4. Goals: Our goal is to (further) develop and validate dynamical indicators of change (DIOCs) that can detect and quantify spatial-temporal changes in virus spread in (sub)populations both retrospectively and prospectively that are directly related to implementation and elimination of governmental control measures. A DIOC is a statistical quantity, like R_t , calculated from real-time infectious disease data. It is dynamic since it is updated daily and adapted to other information available during the crisis. We will focus on DIOCs for (changes in) growth rates and effective contact rates, since control measures of governments are typically targeted to social distancing. Our quantities extend and complement current quantities used at European institutes and will help RIVM quickly track changes and maintain control of the spread of the virus.

2. PLAN VAN AANPAK:

Our approach is composed of two parts. The first part will study the behavior of various novel DIOCs, which are derived from epidemic disease models and sigmoidal growth curve analysis, using several simulation scenarios. Setting criteria for our DIOCs to signal changes of COVID-19 after the summer, will be based on ideas from disease detection and surveillance [1]. The second part studies the behavior of all DIOCs jointly, to understand their coherence, to sharpen criteria, and to build a dashboard with [R] software. Both parts will evaluate/validate our DIOCs retrospectively and prospectively to detect and quantify changes in virus spread related to (the implementation and elimination of) governmental control measures. Our approaches will take into account changes in test policies, to be able to isolate changes due to variations in virus transmission.

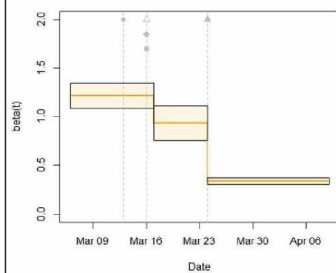
PART 1.1. DIOCs for epidemic disease modeling: Recently, we have developed a data-oriented approach, based on the SEIR



(Susceptible-Exposed-Infected-Removed) model (Figure 1) to estimate non-increasing daily contact rates β from being susceptible to exposed (Figure 2). Our SEIR model contains and addresses latent stages of infected (untested $I_{NT}(t)$) and removed (untested $R_{NT}(t)$) individuals at day t and addresses that susceptible ($S(t)$) and exposed ($E(t)$) individuals at day t aren't observed either. Exposed individuals are in a transition phase, where they have been in contact with the virus but they are not yet contagious. Incubation time distributions in SEIR models are typically assumed exponential, but literature on COVID-19 suggests a Weibull distribution [5], which we have implemented. Individuals are contagious in the infected stage, but we assumed that they are not contagious in hospitalized ($H_T(t)$) and removed stages ($R_{NT}(t)$ and $R_T(t)$).

Available information for estimation of our SEIR model, including estimation of tested individuals (ρ), comes from observed stages on infected and hospitalized individuals, that were tested positively ($I_T(t)$, $H_T(t)$). Since we deal with a non-standard SEIR model, we developed an iterative Poisson regression analysis and estimated a piece-wise constant daily effective-contact rate β , which drops in value when the observed data suggests this. Figure 2 shows the estimated profile (colored horizontal lines) for the Netherlands with 95% confidence bands (horizontal black lines). Vertical gray lines indicate moments of governmental interventions (\blacktriangle = lockdown; \triangle = work from home; \blacksquare = closing schools; \bullet = banning events; \blacklozenge = closing restaurants). The

Figure 2: Daily growth-rate profile of the Netherlands



moments of interventions nicely overlap with the change points in daily contact rates, indicating our method is capable of retrospectively detecting change. Reproduction number R_t is less suitable here (too imprecise), since it is a complicated function of transition rates β , ω , and γ 's (Figure 1).

We will use our daily effective-contact rate estimate as a DIOC to prospectively detect changes in virus spread by inverting the monotonicity restriction and looking for increases that warn us about losing control over the pandemic when measures are eliminated. This will be cross-checked with (e.g. mobility data) behavioral changes in the individuals. When more and more information becomes available (e.g., more precise incubation and recovery times) we will incorporate this information in our SEIR model and obtain a more accurate DIOC. Our daily effective-contact rate has not yet been studied properly to be used as DIOC. We will study in more detail influences of our

assumptions (on distributions and contagious stages), sensitivity to changes, and delays in signaling changes. Furthermore, we will further study this method on data from other countries and smaller areas (provinces), and how we can include subpopulation characteristics (e.g. gender, age-group).

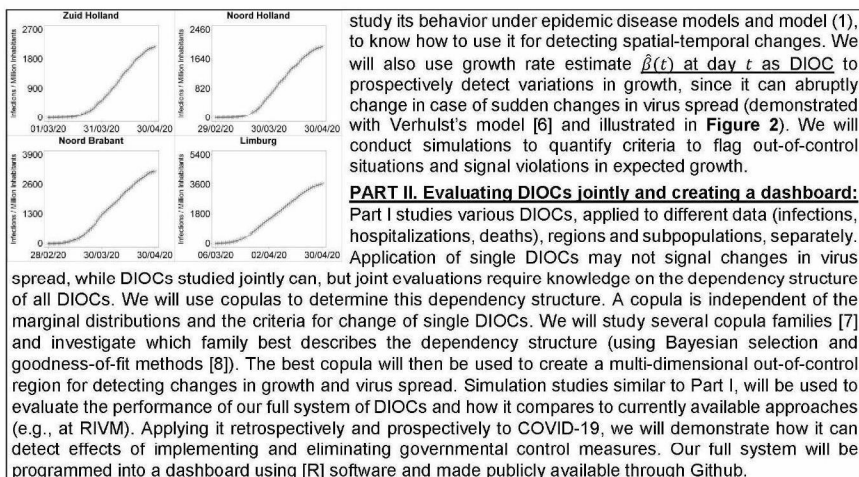
PART I.2. DIOCs for sigmoidal growth curves: Population dynamics and biological growth have been studied with many different sigmoidal curves [6], with Verhulst's logistic growth curve being the earliest and simplest contribution. Some sigmoidal curves connect directly to epidemic disease models (e.g., Verhulst's model describes a Susceptible-Infected model), but they focus on one aspect of virus spread. They describe changes over time for a particular outcome $Y(t)$ (infections, hospitalizations, or deaths), without making any further assumptions on transitions between stages. A large family of sigmoidal growth curves is described by its growth rate (i.e. the derivative of growth at day t) having the following form:

$$(1) \quad \frac{d}{dt} Y(t) = \beta [Y(t)]^\alpha \left[1 - \left(\frac{Y(t)}{M} \right)^\eta \right]^\gamma,$$

with β an unknown parameter for the contact rate, α , γ , η unknown growth parameters, and M the unknown maximum outcome. Verhulst's model is a special case with $\alpha = \gamma = \eta = 1$. We have estimated model (1) on the number of infections for different countries (Table 1), with $\gamma = \eta = 1$ and data until April 30, 2020. Large differences across countries in growth rate β are clearly visible, showing that studying virus spread is necessary for understanding differences in governmental measures retrospectively. Figure 3 shows an excellent fit of this model to four Dutch provinces, illustrating the model fits well also at local level, and it may be used also for prospective evaluations.

The goal is to formulate DIOCs for model (1), to determine spatial-temporal growth changes in the number of infections, hospitalizations, and deaths prospectively and retrospectively. This research fits with test-based algorithms from disease surveillance, but DIOCs for model (1) are novel. We have used $Y(t)/\hat{M}(t)$ as DIOC on COVID-19's number of infections to determine the turning point of the virus spread (we reported March 31 for the Netherlands), with $\hat{M}(t)$ the estimated maximum at day t . At the end of the virus spread $Y(t)/\hat{M}(t)$ gets close to one, thus if it starts deviating from one, we have a signal for an increase in virus spread. We will

Table 1	α	$\log(\beta)$	M
Belgium	0.736 [0.726; 0.747]	0.479 [0.384; 0.574]	55306 [54889; 55724]
Canada	0.715 [0.705; 0.725]	0.546 [0.459; 0.634]	79491 [77758; 81224]
Denmark	0.579 [0.550; 0.608]	1.017 [0.805; 1.229]	12045 [11580; 12510]
France	0.782 [0.776; 0.788]	0.349 [0.289; 0.409]	135858 [135574; 136142]
Germany	0.720 [0.715; 0.724]	1.101 [1.052; 1.150]	170303 [170020; 170586]
Iran	0.676 [0.668; 0.685]	1.038 [0.953; 1.123]	107896 [107283; 108509]
Italy	0.651 [0.647; 0.656]	1.632 [1.582; 1.682]	228775 [228093; 229456]
Netherlands	0.715 [0.702; 0.727]	0.586 [0.475; 0.696]	44519 [44154; 44884]
South Korea	0.609 [0.597; 0.622]	1.363 [1.259; 1.467]	10794 [10783; 10804]
Sweden	0.684 [0.664; 0.704]	0.286 [0.128; 0.444]	41860 [38636; 45084]
USA	0.664 [0.662; 0.666]	2.133 [2.107; 2.158]	1491805 [1486473; 1497138]
UK	0.746 [0.741; 0.752]	0.635 [0.576; 0.693]	225039 [223178; 226900]



3. HAALBAARHEID VAN HET PROJECT:

3.1. Time schedule: We request funding for 18 months. Part I is urgent and will be conducted in the first 6 months with 2 fte post-docs and 0.5 fte (0.3 UD + 0.2 HGL) supervision (to compensate teaching obligations in Q1, 2020-2021) at TU/e to be able to use our DIOCs real-time on data of COVID-19 and help RIVM detect possible changes after the summer. Part 2 will take 1 year using 1 fte post-doc and 0.2 fte supervision (0.1 UD + 0.1 HGL) at TU/e for research, development of [R] software package, and retrospective/prospective validation on COVID-19. RIVM will contribute 0.6 fte in-kind (0.5 researcher + 0.1 supervision) for the full project for research, discussions, meetings, development software and implementation.

3.2. Motivation feasibility: Researchers of TU/e & RIVM have broad experience in process monitoring and surveillance and in biological growth modeling. Dr. Van den Heuvel has been working in the field of statistics for epidemiological research and has a large group of statisticians working on the topics proposed in this proposal. Dr. Wallinga is a renowned researcher in epidemic disease modeling and has support of a large group of researchers at RIVM. Collaboration was initiated by RIVM to join forces during the corona crisis.

TU/e and RIVM have both experience in creating [R] codes for web-based applications. At TU/e we are building a web-based statistical software package for pharmaceutical microbiologists. RIVM has built several packages for disease modeling (e.g. phylbreak) and made it available through Github.

4. RELEVANTIE VOOR DE PRAKTIJK:

Our proposal is an immediate solution for theme I "Onderzoek naar de effectiviteit en impact van maatregelen/strategieën in respons op de coronacrisis" of focus area "Maatschappelijke dynamiek". It extends our recently conducted research on COVID-19 on developing quantities that can properly describe and compare changes in virus spread as consequences of implementing/eliminating governmental measures in different countries. Part I is urgent and cannot be executed later since it will be used prospectively during the pandemic.

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

Researchers from TU/e and RIVM (in-kind contribution of 0.6 fte/year over 18 months) will jointly execute the proposal. RIVM will share their data with TU/e to enable the execution of the research.

6. LITERATUURREFERENTIES (optioneel):

[1] Unkel *et al.*, Statistical methods for the prospective detection of infectious disease outbreaks: a review, *Journal of the Royal Statistical Society A*, 2012, 175(1):49-82. [2] Held *et al.*, Handbook of infectious disease data analysis. Boca Raton, FL: CRC Press, 2020. [3] Pan *et al.*, Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China. *JAMA* 2020; 323: 1915–23. [4] <https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/kamerstukken/2020/05/20/kamerbrief-stand-van-zaken-covid-19/Kamerbrief+update+stand+van+zaken+Covid+19.pdf> [5] Backer *et al.*, The incubation period of 2019-nCoV infections among travellers from Wuhan, China. *Eurosurveillance* 2020; 25: 2000062. [6] Tsoularis *et al.*, Analysis of logistic growth models, *Mathematical Biosciences*, 2002, 179: 21-55. [7] Nelsen RB, *An introduction to copula's*, Springer, New York, 2006. [8] Genest *et al.*, Goodness-of-fit for copulas: A review and a power study, *Insurance Mathematics and Economics*, 2009, 44(2): 199-213.

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 / FTE	Monthly Gross salary (for Other)	% fee (for the project)	Salary costs	Gross salary, 40% increment (for Other ruling only)	Overhead % (for Other ruling only)	Total
1	PD - TUE	VSNU	Sr wet. Medewerker	8	€ 35.455		100%	€ 35.455,00	€ -	-	€ 35.455,00
2	PD - TUE	VSNU	Sr wet. Medewerker	8	€ 35.455		100%	€ 35.455,00	€ -	-	€ 35.455,00
3	PD - TUE	VSNU	Sr wet. Medewerker	12	€ 78.818		100%	€ 78.818,00	€ -	-	€ 78.818,00
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	HGL - TUE	Supervision at TUE	€ 113,00	301	€ 34.013
2	UD - TUE	Supervision at TUE	€ 56,00	378	€ 21.058
3	RVM	In-kind contribution at RVM (research, discussions, meetings, and implement)	€ 115,73	1269	€ 146.961
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		€ -	-	€ -
16	to be specified		€ -	-	€ -

