NWA 1292.19.272

Dutch Research Council (NWO)

Consortium AGREEMENT

NWA PROJECT

"Virtual Human Platform for Safety Assessment"

Academic Partners:

1. **University Utrecht**, having its registered office in Heidelberglaan 8, 3584 CS at Utrecht, the Netherlands, more specifically the Faculty of Veterinary Medicines, Faculty of Sciences and Faculty of Geosciences hereinafter referred to as "**UU**", legally represented by prof. dr. A. Pijpers, president of the executive board of UU**;**
2. **Foundation University of Applies Sciences Utrecht**, having its registered office in Padualaan 99, 3584 CS at Utrecht, the Netherlands, more specifically the Faculty of Sustainable Healthy Living hereinafter referred to as "**HU**", legally represented by dr. J. Boogerd, president of the executive board of HU;
3. **Maastricht University**, for specifically its Faculty of Health, Medicine and Life Sciences (FHML)/ School of Nutrition and Translational Research in Metabolism (NUTRIM)/ Department of Bioinformatics BIGCAT and School for Oncology and Developmental Biology/ Department of Toxicogenomics, having its registered office in Minderbroedersberg 4-6, 6211 LK at Maastricht, the Netherlands, hereinafter referred to as "**UM**", on behalf of the Executive Board legally represented by 5.1.2e 5.1.2e
4. **Wageningen University, department Agrotechnology and Food Sciences,** having its registered office at Stippeneng 2, 6708 WE at Wageningen, the Netherlands, hereinafter referred to as "**WU**", legally represented by its 5.1.2e 5.1.2e
5. **Vrije Universiteit Amsterdam**, having its registered office in De Boelelaan 1105, 1081 HV at Amsterdam, the Netherlands, more specifically the Faculty of beta sciences hereinafter referred to as "**VU**", legally represented by 5.1.2e 5.1.2e;
6. **Leiden University**, having its registered office in Rapenburg 70, 2311 EZ at Leiden, the Netherlands, more specifically the Faculty of Sciences hereinafter referred to as "**LU**", legally represented by Drs. M. Ridderbos RC, Vice-president College van Bestuur;
7. **University Medical Center Utrecht** , having its registered office in Heidelberglaan 100, 3584 CX at Utrecht, the Netherlands, more specifically Division of Internal Medicine and Dermatology hereinafter referred to as "**UMCU**", legally represented by 5.1.2e 5.1.2e and 5.1.2e ;
8. **Erasmus Medical Centre**, having its registered office in Dr. Molewaterplein 40, 3015 GD at Rotterdam, the Netherlands, more specifically the Faculty of Medicines hereinafter referred to as "**Erasmus MC**", legally represented by vice –president of Executive Board prof. J.P.T.M. van Leeuwen;

9. **Stichting VUmc**, having its registered office in De Boelelaan 1117, 1081 HV at Amsterdam, the Netherlands, more specifically the Faculty of Medicines hereinafter referred to as "**VUMC**", legally represented by 5.1.2e 5.1.2e and 5.1.2e
10. The **State of the Netherlands**, represented by his Minister of Health, Welfare and Sport, on behalf of the Minister represented by Prof. Dr. Ing. J. Brug, acting Director-General of the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu) (**RIVM**), having his home office at Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, the Netherlands, hereinafter referred to as "**RIVM**";
11. **TNO Innovation for Life,** having its registered office in Utrechtseweg 48, 3704 HE at Zeist, the Netherlands, hereinafter referred to as "**TNO**", legally represented by 5.1.2e 5.1.2e

Non-Academic Partners:

12. **ORTEC Logicare BV,** having its principal office in Houtsingel 5, 2719 EA at Zoetermeer, The Netherlands, hereinafter referred to as "**ORTEC**", legally represented by 5.1.2e 5.1.2e
13. **Unilever Global IP Limited,** having its principal office at Port Sunlight, Wirral, Merseyside CH62 4ZD, United Kingdom, hereinafter referred to as "**Unilever**", legally represented by 5.1.2e
14. **Cosmetics Europe The personal care Association,** having its principal office in Avenue Herrmann Debroux 40, B-1106 at Brussels, Belgium, hereinafter referred to as "**Cosmetics Europe**", legally represented by 5.1.2e
15. **Bayer SAS,** having its principal office in 16 rue jean-Marie Leclair, 69009 Lyon, France, hereinafter referred to as "**Bayer**", legally represented by 5.1.2e
16. **Shell International BV,** having its principal office in Carel van Bylandtlaan 30, 2596 HR at Den Haag, The Netherlands, hereinafter referred to as "**Shell**", legally represented by 5.1.2e
17. **Ministry of Agriculture, Nature and Food Quality,** having its principal office in Bezuidenhoutseweg 73, 2594 AC at Den Haag, The Netherlands, hereinafter referred to as "**LNV**", legally represented by 5.1.2e
18. **Nederlandse Brandwonden Stichting,** having its principal office in Zeestraat 29, 1941 AJ at Beverwijk, The Netherlands, hereinafter referred to as "**Brandwondenstichting**", legally represented by 5.1.2e
19. **NEFARMA, Dutch Association Innovative Medicines,** having its principal office in Prinses Beatrixlaan 548-550, 2595 BM at Den Haag, The Netherlands, hereinafter referred to as "**VIG**", legally represented by 5.1.2e
20. **Charles River Laboratories Den Bosch BV,** having its principal office in Hambakenwetering 7, 5231 DD at, Den Bosch, The Netherlands, hereinafter referred to as "**Charles River**", legally represented by 5.1.2e
21. **Certara UK Lmt,** having its principal office in One London Wall, 6th floor, London, EC2Y 5EB, United Kingdom, hereinafter referred to as "**Certara**", legally represented by 5.1.2e 5.1.2e
22. **KWR Water BV,** having its principal office in Groningerhaven 7, 3433 PE at Nieuwegein, The Netherlands, hereinafter referred to as "**KWR**", legally represented by 5.1.2e 5.1.2e
23. **Galapagos NV,** having its principal office in Generaal De Wittelaan L11 A3, 2800 at Mechelen, Belgium, hereinafter referred to as "**Galapagos**", legally represented by 5.1.2e 5.1.2e
24. **Stichting Proefdiervrij,** having its principal office in Groot hertoginnenlaan 201, 2517 ES at Den Haag, The Netherlands, hereinafter referred to as "**St Proefdiervrij**", legally represented by 5.1.2e

25. **Dutch Kidney Foundation,** having its principal office in Groot Hertoginnenlaan 34, 1405 EE at Bussum, The Netherlands, hereinafter referred to as "**Nierstichting**", legally represented by 5.1.2e

Together referred to as "**Parties**" and individually as "**Party**".

Parties no. **1-11** together will be referred to as "**Academic Partners**" and Parties no. **12-25** together will be referred to as "**Non-Academic Partners**" also referred to as co-funder in the research proposal.

WHEREAS:

- NWO is the Dutch Research Council and its mission is to advance world-class scientific research that has scientific and societal impact. NWO facilitates and funds excellent, curiosity-driven disciplinary, interdisciplinary and multidisciplinary research with a focus on all scientific disciplines and on the entire knowledge chain with an emphasis on scientific research;

- The overarching ambition of the Dutch Research Agenda (Dutch acronym: NWA) programme is to provide a positive and structural contribution to the global knowledge society of tomorrow, in which new knowledge flows freely from researcher to user and where new questions from practice and society quickly and automatically find their way into new research. This can only be achieved by building bridges today in order to address the scientific and societal challenges together;

- The Academic Partners, having considerable experience in the field concerned, have submitted a research proposal for the project to NWO as part of the Dutch Research Agenda (NWA), Call **"NWA-ORC 2019"**

- The Executive Board of NWO has decided to award funding to this research proposal entitled **"Virtual Human Platform for Safety Assessment"**; file number NWA.1292.19.272

- The Non-Academic Partners have committed to support the Project as indicated in the Research Proposal and/or their respective support letters and as specified in this Agreement;

- The Parties wish to collaborate under the terms and conditions as set forth in this Agreement.

NOW, THEREFORE, IT IS HEREBY AGREED AS FOLLOWS

Article 1
Definitions

This Agreement means this agreement, including the recitals and the Annexes.

Affiliate means a legal entity that controls a Party or that is under the control of a Party, or under the same control as the Party. Controlling meaning controlling in any of the following forms:
a) the direct, or indirect through (but not together with) other entities, holding of more than 50% of the voting rights of the shareholders or associates of that entity; or
b) the power to determine the policy of the legal entity concerned in a decisive way.

Annexes means the annexes to this Agreement, which include:
Annex 1: Intellectual Property Rights, Confidentiality and Publication Procedure;
Annex 2: Research Proposal, including the support letters and budget;
Annex 3: Grant Award Decision NWO.
Annex 4: Access Form
Annex 5: Innovation Disclosure form
Annex 6: List of members Steering Committee, Cooperation Partners and International Scientific Advisory Group.

Background Information has the meaning as defined in Annex 1

Call for Proposals "NWA-ORC 2019"

Confidential Information has the meaning as defined in Annex 1

Consortium means the consortium of Parties to this Agreement.

Cooperation Partner means a member in the Stakeholder Group or International Scientific Advisory Group without being a Non-Academic Partner in the project. The Cooperation Partners are considered a third Party.

Coordination Team means the Coordination Team as mentioned in article 8.1.1.3, which shall consist of the Project Leader, Project Manager, Vice Project Leader Impact, Vice Project Leader Science

Effective Date means the signing date of the last Party to sign this Agreement.

Grant Award Decision means the decision by NWO, as included in Annex 3 to this Agreement.

International Scientific Advisory Group means the International Scientific Advisory Group mentioned in article 8, which shall consist of world-renowned experts in the field. The International Scientific Advisory Group shall be chaired by

	the Vice Project Leader Science. They are considered a third Party or third Parties.
Materials	means any chemical, biological materials and other materials, (for example analytical equipment or computers) provided or collected for the purpose of, or generated during, the Project.
NWO Grant Rules	means the NWO Grant Rules 2017 ("*NWO Subsidieregeling 2017*"),as published in the Dutch Government Gazette ("*Staatscourant*") on 9 May 2017 (Stcrt. 2017, 25491) and lastly amended on 30 January 2019 (Stcrt. 2019, 6555)[1])
Publication	means the disclosure of Results, in any manner or by any method whatsoever, excluding any disclosure resulting from an application for a patent on the Results (article 5.1 NWO Grant Rules).
Project	means the research project entitled **"Virtual Human Platform for Safety Testing" (file NWA.1292.19.272)** as further specified in the Research Proposal.
Research Proposal	means the Research Proposal submitted to and granted by NWO, included in Annex 3 to this Agreement;
Results	means all inventions, results, materials, methods, processes, programs, software, findings or discoveries that are generated within the Project (article 5.1 NWO Grant Rules).
Steering Committee	means the Steering Committee as mentioned in article 8, which members shall consist of one representative of each Party both Academic and Non-Academic Partners. The Steering Committee shall be chaired by the Project Leader, who shall be a representative of Utrecht University.
Stakeholder Group	means the Stakeholder Group mentioned in article 8, which shall consist of one representative of each Non-Academic Partner (Co-funder) and one representative of each Cooperation Partner. The Stakeholder Group shall be chaired by the Vice Project Leader Impact.
Whole Project Consortium	shall consist of the Steering Committee, the Stakeholder Group and the International Scientific Advisory Group (this includes third Parties).

Article 2
Conduct of the Project

1. The Project will take place [redacted] 5.1.2e the Project Leader. The Parties shall conduct the Project in accordance with the Research Proposal, the Grant Award Decision and the applicable NWO Grant Rules 2017 and taking into account the criteria and standards applicable to scientific and/or technological research.

[1] The most recent consolidated version is available at: https://wetten.overheid.nl/BWBR0039531/2019-02-07.

2. The Project Leader is responsible for the scientific quality, coordination, Project management and progress of the Project and to this extent arranges for:
   a. the organization of a kick-off meeting to be organized at the start of the Project to which all Parties shall be invited;
   b. the organization of meetings for the Whole Project Consortium, that will take place at least once per year. During the meetings, the progress of the Project towards both science and knowledge utilisation shall be discussed and evaluated;
   c. the preparing of a progress report before the meetings of the International Scientific Advisory Group and reporting on these meetings;
   d. managing the process of obtaining societal, economic and/or scientific value out of the Results;

3. The Project Leader may appoint a Project Manager in or outside UU and delegate his/her Project management tasks such as the organization and conduct of project meetings. For any avoidance of doubt, the Project Leader remains responsible for the delegated tasks.

4. The Parties shall inform each other in the event that new information emerges which is relevant to the Project or the utilization of the Results. If any patentable invention is created in the Project, the respective Party that created it shall inform the Project Leader. The Project Leader shall inform the other Parties thereof by sending a completed invention disclosure form in Annex 5, to Parties.

5. In the event that the Project cannot be conducted in accordance with this Agreement, the Project Description and/or the NWO Grant Rules 2017, the Project Leader notifies NWO immediately. All possible solutions shall be discussed, upon which a possible decision on the continuation of the Project shall be taken by NWO.

6. All Parties shall be privileged to obtain first-hand information on the progress of the Project and on the Project in general. All parties are given the opportunity to express interest, before any third Parties, in specific generated Results for which (commercial) usage rights can be negotiated in accordance with Annex 1.

7. A Party that enters into a subcontract or otherwise involves third parties in the Project, i.e. International Advisory Group and Cooperation partners, remains solely responsible for carrying out its relevant part of the Project and shall ensure that any agreements entered into between the Party and such third party (including any subcontractor), contain terms and conditions no less stringent than the terms and conditions set out in this Agreement (e.g. on confidentiality). The Party has to ensure that the involvement of third parties does not affect the rights and obligations of the other Parties under this Agreement.

Article 3

Contribution and Invoicing

1. Academic Partner(s) shall receive funding from NWO for execution of the Project in accordance with the Grant Award Decision. The Project Leader shall remit payments to an Academic Partner after receipt from NWO pro rata the budget every year. Any payment payable by the Project Leader under this Agreement will be made to the bank account provided by the respective Academic Partner.

2. Non-Academic Partner(s) that contribute to this Consortium in cash have made separate arrangements with NWO regarding payment of their cash contribution(s), which shall be invoiced by NWO in accordance with such arrangements.

3. Non-Academic Partner(s) that contribute to this Consortium with in kind contribution shall deliver the in-kind contribution(s) in accordance with their respective support letter(s).

4. In the event Non-Academic Partners' employees, as part of the in-kind contribution, are performing activities for the benefit of the Project, that Non-Academic Partner will submit to the Project Leader annually - before the end of March of the subsequent year - a registration of hours worked on the Research by the concerning employee and any kind of estimated value of materials and know how brought into the project.

5. In the event the Project is terminated prematurely, the Parties shall discuss in good faith the reimbursement possibilities of remaining instalments of Non-Academic Partners' contributions.

Article 4

Intellectual Property Rights, Confidentiality and Publication

Parties decide to follow the standard NWO policy on Intellectual Property Rights, Confidentiality and Publication with alterations made and agreed between Parties as specified in Annex 1.

Article 5

No Guarantee

Each Party shall carry out the tasks assigned to it in this Project and this Agreement with care and diligence. Nevertheless, no guarantee is given that any expected results will be achieved, or that the Results are fit for any particular purpose, or that the results generated in the Project do not infringe rights of third parties, or that patent applications result in granted patents. No Party shall create or develop any technology for the Project that knowingly infringes any third party intellectual property rights. For the avoidance of doubt, neither Parties' obligations in this respect comprise conducting of patent searches.

Article 6

Miscellaneous

1. No Party shall assign this Agreement or any part thereof without the prior written consent of the other Parties. However, a Party may assign this Agreement in its entirety without such consent but by notifying the other Parties to an Affiliate or in connection with the sale or merger of its business assets relating to this Agreement.

2. The aggregate liability by each Party towards the other Parties for direct damages is limited to the Project budget of the liable Party as laid down in the Grant Award Decision, this with a maximum of 500.000,00 € per Party. No Party shall be liable towards another Party for any indirect damages arising out of or in connection with this Agreement. For the sake of this Agreement: indirect damages meaning: loss of profit, loss of revenue and loss of business opportunities.

3. In case the Project Leader receives a claim by a third party or a Party to this Agreement, the Project Leader shall be indemnified by the Party which act or omission has caused the damage and none of the limitations of 6.2 above are applicable.

4. In case the Project Leader receives a request from NWO to reimburse any amount granted, the Project Leader shall be indemnified by the Academic Party which act or omission has caused the reimbursement decision.

5. In case of 6.2, when the damages of 6.2 exceed the limited amount, the remaining amount will be carried by the Academic Parties proportionally based on the Project budget per Academic Party as laid down in the Grant award (Annex 3)
In case of 6.2 when no Party whose act or omission has caused the damages can be established, the damages will be carried by the Academic Parties proportionally based on the Project budget per Academic Party as laid down in the Grant award (Annex 3).

6. In case of 6.4, when no Party whose act or omission has caused the reimbursement can be established, the remaining amount will be carried by the Academic Parties proportionally based on the Project budget per Academic Party as laid down in the Grant award (Annex 3).

7. In respect of any information or materials (incl. Results and Background Information) supplied by one Party to another under the Project or related to the Project, no warranty or representation of any kind is made, given or implied as to the sufficiency or fitness for purpose.

8. The decision whether to use the Background Information and/or Results is the sole decision and responsibility of each Party solely, and each Party shall assume sole responsibility for any claims or liabilities that may arise as a result of its use of the Background Information and/or Results.

9. Nothing in this Agreement limits or excludes either Party's liability which, by law, cannot be limited or excluded.

10. No Party will be liable towards the other Parties for any delays and cancellations resulting from governmental measures regarding any pandemic (including but not limited to COVID 19).

11. This Agreement may not be amended, modified or terminated orally; no provision of this Agreement may be waived orally; and no amendment, modification, or waiver of any of the provisions hereof shall be binding unless in writing and signed by all Parties.

    a. The addition of new Parties in the Consortium is possible in conformity with article 8

    b. After receiving the signed access form in Annex 4 and shall have effect from the date identified in the access form.

    c. All Results developed in the Project before the accession of a new party to the Consortium shall be deemed to be Background Information with regard to such new party.

12. If any covenant, obligation or term hereunder or the application of any part of this Agreement to any person, party or circumstance shall, to any extent, be illegal, invalid or unenforceable, the remainder of this Agreement or the application of such covenants, agreements or obligations other than those which are held to be invalid or unenforceable shall not be affected thereby; and each covenant, obligation and agreement contained herein shall be separately valid and enforceable to the full extent permitted by law. The Parties shall make a good faith effort to replace any invalid or

unenforceable provision with a valid and enforceable one such that the objectives contemplated by the Parties when entering into this Agreement may be realized.

Article 7

Term and Termination

1. This Agreement shall come into force on the Effective Date 1 June 2021 and shall thereafter remain in force until three months after the date of termination or the date of conclusion of the Project through a Grant Amount Decision as defined in article 5.1 of the NWO Grant Rules 2017.

2. With regard to a Party:

   i. that withdraws or has become a defaulting Party as described in article 8.1, without prejudice to the right of the other Parties to claim the direct losses they have suffered as a results of the default subject to provision of article 6(2);
   ii. in respect of which a suspension of payment is granted, bankruptcy is declared, an administrative order is filed, a receiver is appointed in respect of its assets or a general assignment for the benefit of creditors is made; or
   iii. that goes into liquidation or that permanently discontinues its business.

3. the Steering Committee may terminate this Agreement vis-à-vis such Party with immediate effect, without judicial intervention or any further summons being required, by giving written notice by registered mail.

4. Granting of rights by the defaulting Party -The above (under 7.2) mentioned defaulting Party or withdrawing Party, for which the Agreement has been terminated, shall continue to grant the other Parties rights to use its Background Information and Results, as if that Party was still a Party to this Agreement and such Party shall provide all input and documents for the remaining duration of the project and/or exploitation of Results to the extent described in this Agreement.

   Access Rights of a defaulting Party - Access Rights granted to a Defaulting Party and such Party's right to request Access Rights shall cease immediately upon receipt by the Defaulting Party of the formal notice of the decision of the General Assembly to terminate its participation in the consortium.

   Access Rights of a non-defaulting Party - A non-defaulting Party leaving voluntarily and with the other Parties' consent shall have the Access Rights to the Results developed until the date of the termination of its participation. It may request Access Rights until the end of the Project, but Parties are not obliged to grant the Access Rights.

5. The following articles shall survive termination of this Agreement:
   a. article 4 (confidentiality for the term mentioned in Annex 1);
   b. article 6 and any other articles that by their nature should survive.

6. The Steering Committee is entitled to terminate this Agreement towards a Non-Academic Partner upon liquidation or suspension of payment of such Non-Academic Partner.

Article 8.

Governance Structure of the Consortium

1. General structure, tasks & decisions

The organisational structure of the Consortium shall comprise of: Steering Committee, Stakeholder Group, International Scientific Advisory Group and the Coordination Team.

1.1. Steering Committee

The Steering Committee shall be free to act on its own initiative to formulate proposals and take decisions in accordance with the procedures set out herein. In addition, all proposals made by the Whole Project Consortium shall also be considered and decided upon by the Steering Committee.

The Steering Committee shall take decisions on the following subjects:

- content, finances and intellectual property rights;
- approval of the Research Plans, Budget Plans (Annex 2) and Total Budget (Annex 3), as well as modifications to these documents;
- entry of a new party to the Consortium and approval of the settlement on the conditions of the accession of such a new party;
- withdrawal of a Party (on its own request) from the Consortium and the approval of the settlement on the conditions of the withdrawal;
- declaration that a Party is to be a defaulting Party;
- remedies to be performed by a defaulting Party;
- termination of a defaulting Party's participation in the Consortium and measures relating thereto;
- all other decisions as laid down in this Agreement, both implicit as well as explicit.

In the event the Steering Committee identifies a breach by a Party of its obligations under this Agreement, the Steering Committee shall give written notice to such Party requiring that such breach be remedied within 30 calendar days. If such breach is substantial and is not remedied within that period or is not capable of remedy, the Steering Committee may decide to declare the Party to be a defaulting Party and to decide on the consequences thereof which may include termination of its participation in accordance with article 7.2 above. This provision does not refer to, nor does it exclude article 6:265 BW of Dutch law on 'ontbinding'.

In the event of withdrawal of a Party, the Steering Committee shall decide on rearrangements of tasks and on what conditions Parties should continue the Agreement in accordance with the NWO Grant Rules. Such rearrangement shall take into consideration the legitimate commitments taken prior to the decisions, which cannot be cancelled.

Written notice means communications between the Parties such as e-mail with acknowledgement of receipt, which fulfills the conditions of written form from a particular Party.

1.2. Whole Project Consortium

The Whole Project Consortium has the right to give advice to the Steering Committee on all matters mentioned in article 8.1.1, second paragraph (the bullets).

The Project Leader shall chair all meetings of the Whole Project Consortium, unless decided otherwise by the Coordination Team in a meeting of the Whole Project Consortium.

1.3. Project Leader

The Project Leader shall be responsible for:

- The proper execution of all the Subprojects and the Budget (Annex 2 and Annex 3);
- Adequate and timely distribution, among the Parties and towards NWO, of all relevant information regarding the Project;
- Monitoring compliance by the Parties with their obligations;
- Collecting, reviewing of, verifying consistency and submitting reports and other deliverables to the Steering Committee;
- Preparing the decisions and agenda of meetings of the Steering Committee;
- Administering the financial contribution of the Parties and fulfilling the financial tasks;
- Implementing the decisions of the Steering Committee;
- Executing all other specific tasks which are laid down in the various articles of this Agreement.

1.4. Coordination Team

The Coordination Team (hereinafter called "CT") shall consist of the Project Leader, Project Manager, [redacted 5.1.2e] Vice Project Leader Impact [redacted 5.1.2e], Vice Project Leader Science [redacted 5.1.2e]. CT meetings will be held at least once a month. The Consortium will be informed in writing when members of the CT change.

2. Meetings and agenda

2.1 The Steering Committee meets at least once a year or at any time upon written request of any member of the Steering Committee.

2.2 The Whole Project Consortium meets at least once a year or at any time upon written request of the Steering Committee. The Whole Project Consortium meeting shall be chaired by the Project Leader. This event will incorporate parallel meetings, Research Line and Work Package Leader Group as described in the Project description (chaired by the Vice Project Leader Science), Stakeholder Group (chaired by the Vice Project Leader Impact), International Scientific Advisory Group (chaired by the Vice Project Leader Science).

2.3 Any member of the Steering Committee may add an item to the original agenda by written notification to all of the other members of the Steering Committee and to all of the members of the Whole project consortium.

2.4 Meetings of the Steering Committee may also be held by teleconference or other telecommunication means.

2.5 Decisions will only be binding once these, by means of the relevant part of the minutes, have been accepted according to article 8.5.

3. Voting rules and quorum

3.1 The Steering Committee shall not deliberate and decide validly unless two-thirds (2/3) of its members are present or represented (quorum).

3.2 Each member of the Steering Committee shall have 1 (one) vote.

3.3 Defaulting Parties are not allowed to vote nor does their presence count for the quorum.

3.4 Decisions shall be taken by two-thirds of the votes, unless otherwise agreed in this Agreement. The Chairperson of the Steering Committee does not have the right to clear an even voting scenario by a tie-breaking vote. In case of an even voting a new voting shall take place in order to achieve consensus.

3.5 A change in the Budget and/or the total Contribution or request for accession of a new Party or a request for withdrawal of a Party from one of the Parties, requires the consent from all those affected.

3.6 Each Party may give a power of attorney in writing and signed for one vote to another Party. A Party can hold at maximum one such power of attorney of another Party.

4. Veto rights

4.1 A Party which can show that its own work, time for performance, costs, liabilities, intellectual property rights or other legitimate interests would be severely affected by a decision of the Steering Committee, may exercise a veto with respect to the corresponding decision or relevant part of the decision.

4.2 A Partner which is not a member of the Steering Committee, which can show that its own work, time for performance, costs, liabilities, intellectual property rights or other legitimate interests would be severely affected by a proposed decision placed as an agenda point of a meeting by the Steering Committee, may submit an adequately motivated observation in writing to the chairperson, of the Steering Committee wherein that decision is planned to be taken, not later than two (2) working days before the meeting. The chairperson shall distribute these observations to all members of the Steering Committee, prior to the meeting. The Steering Committee shall take the observations into consideration, but is not required to alter the proposed decision but is required to motivate its decision

4.3 A Party may not veto decisions relating to its identification as a defaulting Party. The defaulting Party is not allowed veto decisions relating to its participation and termination in the Consortium or the consequences thereof.

4.4 A Party requesting to withdrawal from the Consortium is not allowed to veto decisions relating thereto.

5. Minutes of meetings

5.1 The Chairperson of the Steering Committee shall produce written minutes of each meeting which shall be the formal record of all decisions taken. He/She shall make the

minutes available to all members, and to all members of the Whole Project Consortium, within ten (10) calendar days of the meeting.

5.2 The minutes shall be considered accepted if, within fifteen (15) calendar days from sending, no member has objected in writing to the Chairperson with respect to the accuracy of the draft of the minutes.

5.3 The Chairperson shall send the accepted minutes to all the members of the Steering Committee, the Whole Project Consortium and the Project Leader. The Project Leader shall safeguard the minutes. If requested the Project Leader shall provide copies to Parties.

5.4 In case a Party objects to the minutes the Chairperson of the Steering Committee shall discuss with the objecting Party and other involved Parties and attempt to find a solution to the general satisfaction of all Parties.

5.5 The objected decision shall not come into force until the Steering Committee has come to a new decision. This decision can be made in an extraordinary meeting or outside a meeting by email or other telecommunications means. If this decision is made outside the meeting, all members of the Steering Committee must decide with 2/3 of the votes. To this new decision no further appeal is open (8.2.5 and 8.5.2. are not applicable here), except in accordance with article 9 on dispute resolution.

Article 9

Applicable law and disputes

This Agreement is exclusively governed by and construed under the Laws of the Netherlands, without regard for the conflicts of law provisions thereof. Any dispute arising from or in connection with this Agreement shall be submitted to the competent court of Midden-Nederland (Utrecht), the Netherlands. Parties shall however endeavour first to settle amicably any and all disputes arising from or in connection with this Agreement.

DRAWN UP IN [25] FOLD AND SIGNED:

University Utrecht

Utrecht, The Netherlands

Prof.dr. A. Pijpers

President of the Executive Board

Date:

Foundation University of Applied Sciences Utrecht

Utrecht, The Netherlands

Dr J. Boogerd

President of Executive Board HU

Date:

Maastricht University

Maastricht, The Netherlands

[redacted]

Date:

Wageningen University

Department Agrotechnology and Food Science

Wageningen, The Netherlands

5.1.2e

Date:

VU

Faculty of beta sciences

Amsterdam, The Netherlands

[redacted]

Date:

NWA.1292.19.272

Leiden University

Leiden, The Netherlands

Drs. M. Ridderbos RC
Vice-president CvB

[redacted]

Date: 17 June 2021

University Medical Center Utrecht

Utrecht, The Netherlands

5.1.2e

Date:

Erasmus Medical Centre

Rotterdam, The Netherlands

Prof. J.P.T.M. van Leeuwen

Vice-president of Executive Board

Date:

NWA.1292.19.272

Stichting VUmc

Utrecht, The Netherlands

[redacted] 5.1.2e

Date:

RIVM

Bilthoven, The Netherlands

Prof.Dr.Ing. J. Brug

Director-General

Date:

NWA.1292.19.272

TNO Innovation for Life

Zeist, The Netherlands

[redacted]

Date:

ORTEC Logicare BV

Zoetermeer, The Netherlands

5.1.2e

Date:

Unilever Global IP Limited

Port Sunlight, United Kingdom

5.1.2e

Date:

Cosmetics Europe

The personal care Association

Brussels, Belgium

5.1.2e

Date:

Bayer SAS

Valbonne, France

5.1.2e

Date:

Shell International BV

Den Haag, The Netherlands

5.1.2e

Date:

LNV

Den Haag, The Netherlands

5.1.2e

Date:

Nederlandse Brandwonden Stichting

Beverwijk, The Netherlands

5.1.2e

Date:

VIG

Den Haag, The Netherlands

5.1.2e

Date:

Charles River Laboratories

Den Bosch, The Netherlands

[redacted]

Date:

Certara UK Lmt

London, United Kingdom

5.1.2e

Date:

KWR Water BV

Nieuwegein, The Netherlands

5.1.2e

Date:

Galapagos NV

Mechelen, Belgium

5.1.2e

NWA.1292.19.272

Stichting Proefdiervrij

Den Haag, The Netherlands

5.1.2e

Date:

Nierstichting

Bussum, The Netherlands

5.1.2e

Date

Annex 1 Intellectual Property Rights, Confidentiality and Publication Procedure

A.1 Additional Definitions

Background Information means all information, techniques, know-how, software and materials (regardless of the form or medium in which they are disclosed or stored), as well as any Intellectual Property Rights pertaining thereto which is in the possession of a Party or any of its Affiliates prior to commencement of the Project, or is generated by a Party or any of its Affiliates before or outside the Project and which is necessary to carry out the Research.

Confidential Information means all non-public or proprietary information, including Background Information and material and Results of whatever nature or in whatever form which is disclosed by one of the Parties or any of their Affiliates on behalf of that Party ("the Disclosing Party") to one of the other Parties or any of their Affiliates ("the Receiving Party") in connection with the Project after the Effective Date and which

(i) if disclosed in tangible form, was marked as Confidential at the time of such disclosure; or

(ii) if disclosed orally, was stated to be confidential at the time of such disclosure and confirmed as confidential in writing within 30 days after disclosure; or

(iii) should reasonably be understood to be confidential.

EU Framework means the Framework for State Aid for Research and Development and Innovation, as published in the Official Journal of the European Union, 2014/C 198/01.

Field of Use means the field of use of a Non-Academic Party to be specified, in which the Non-Academic Party concerned can use the Option to apply for a licence on Results on a commercial basis.

IPR means Intellectual Property Rights, including industrial property rights, database rights, and any similar forms of statutory protection, arising or available wherever in the world.

Non-commercial research means use for academic research purposes or other not-for-profit or scholarly, which means purposes not involving the performance of services for a fee or the production or manufacture of products for sale to third parties.

Option means the right of the Non-Academic Party(ies) to acquire an exclusive right to use the Results generated by the Academic Party(ies) in a Field of Use or acquire ownership of those Results.

A.2 Results and Background Information

1. This Agreement does not affect the ownership of any Background Information.
2. When a Party (the "Provider") sends Material to another Party (the "Recipient") in respect of the Project, a bilateral material transfer agreement may be concluded between such Parties to specify the conditions applying to such transfer of material. The Material shall only be used for

the purpose of the Project and only for as long as is necessary for that purpose. The Recipient will be entirely responsible for the use of the Material and the Provider shall have no obligation or liability for the Material, except for Provider's own gross negligence or willful misconduct. Material provided in the performance of the Project shall remain the property of the Provider. The Recipient shall not be entitled to transfer the Material to any third party (including another Party hereto) without the Provider's prior written consent.

3. Results are owned by the Party that generates it. In case Results are jointly generated by one or more Parties, then such Results shall be jointly owned by such Parties
4. The Parties hereby grant, at their own discretion, rights to use their Background Information and/or their Results free of charge on a non-exclusive, non-transferable, and non-sublicensable basis to the Party and their Affiliates needing the Background Information and/or the Results for the purpose of executing the Project and solely for the duration of this Agreement. The licence granted under this article A.2 does and shall not entail any obligation on the licensor to disclose or transfer any of its Background Information to the licensee(s). This licence shall survive withdrawal of any of the Parties from the Consortium. Such possible license to Background Information and/or Results from the Party who withdraws from the Consortium shall remain in force as if that Party has not withdrawn from the Consortium.
5. Access rights to Results if needed for exploitation of a Party's own Results shall be granted on fair and reasonable conditions.
6. Each Party has the right to seek patent on their own generated Results that they own, nevertheless subject to the provisions of article A.3. If Results of other Parties are essential for the patent application, the patent application shall be shared with all of the Parties who have jointly generated Results. The costs of the patent application shall be shared with all Parties who are seeking patent rights on their jointly owned Results.
7. Each of the joint owners shall be entitled to use their jointly owned Results for non-commercial research activities on a royalty-free basis, and without requiring the prior consent of the other joint owner(s), and each of the joint owners shall be entitled to otherwise Exploit the jointly owned Results and to grant non-exclusive licenses to third parties (without any right to sub-license), if the other joint owners are given:
   (a) at least 45 calendar days advance notice; and
   (b) (b) Fair and Reasonable compensation to be negotiated.
8. Parties can also choose not to seek patent on their own or jointly generated results but can choose for ' the option' as described below and expressed in writing with signature. In case of joint ownership all owners need to consent.
9. All Academic Partners shall retain the right at all times to use Results for further non-commercial research activities and education on a royalty-free basis.
10. All Non-Academic Partners shall retain the right at all times to use Results for further non-commercial research activities on fair and reasonable conditions to be negotiated.

A.3 The Option

1. The Party(s) owning results pursuant to article A.2 ("Owning Party(s)") hereby grant to the other Parties and their Affiliates a non-transferable and non-exclusive licence to use the Results for the purpose of conducting the Project, without the right to sublicense to third parties.
2. The Owning Party(s) hereby grants to the other Parties an Option to acquire an exclusive or non-exclusive right to own or exploit the Results in the respective Party's Field of Use.
3. Each Party may exercise the Option ("Exercising Party") for any specific part of the Results by written notification to the Owning Party(s) within three (3) months of being informed of the Results. In case two or more Parties intend to exercise the Option, the concerned Parties shall discuss in good faith on the best way forward, enabling the interests of all Parties concerned.

4. Upon exercising the Option, the Parties concerned shall promptly enter into negotiations in good faith to reach agreement on fair and reasonable conditions within six (6) months of the written exercise of the Option. The licence or transfer agreement between the Owning Party(s) and the Exercising Party relating to the specific part of the Results shall include at least the following provisions:
5. The respective Non-Academic Partner obtains the right to use and exploit the Results in its Field of Use;
6. The respective Non-Academic Partner pays to the Academic Partner(s) that own the Results a fair and reasonable market price. Non-Academic Partners have to contribute a reasonable market price in exchange for a non-exclusive licence in the Field of Use of the respective Non-Academic Partner. The fair and reasonable market price shall be determined in line with the provisions of EU Framework;
7. The respective Non-Academic Partner shall make best reasonable endeavours to exploit the Results in its Field of Use and report to the Academic Partner(s) on the progress of the exploitation frequently;
8. All Academic Partners shall retain the right at all times to use Results for further non-commercial research activities and education on a royalty-free basis;
9. All Non-Academic Partners shall retain the right at all times to use Results for further non-commercial research activities on fair and reasonable conditions. Activities of such Non-Academic Partners relating to assessment of safety and toxicity of chemical compounds and compositions containing such chemical compounds shall be considered to be non-commercial research activities.
10. The Party(ies) shall not be held liable for any loss or damage incurred arising out of the use or exploitation of the Results by another Party. The Party obtaining the license shall indemnify the previous (joint) owners of the Results against claims from third parties arising out of the use or exploitation of the Results by or through the indemnifying Party.
11. Any licence or transfer agreement pursuant to this Agreement shall take into account the Ten Principles for Socially Responsible Licensing as laid down in the NFU Report: NFU report on 'Ten Principles for Socially Responsible Licensing' https://www.nfu.nl/sites/default/files/2020-10/Tien_Principes_MVL.pdf
12. In the event that a Non-Academic Partner has failed to exercise the Option within the set timeframe the Option for the Results concerned shall lapse and the respective Academic Partner(s) shall be free to offer the Results concerned to a third party.

A.4 Publication, Confidentiality and Personal Data

1. Paragraph A.1 of the NWO Grant Rules is implemented and applicable here.
2. Before a Publication can be released, each Party intending to publish shall submit a draft of the Publication 30 days before its anticipated submission to a third party to the other Parties.
3. Any of the Parties may object to the publication within 30 days after receipt of a copy of the intended Publication on any of the following grounds:
    i. That they consider the protection of Results and/or the protection of objecting Party's Background Information would be adversely affected by the proposed Publication;
    ii. That the intended Publication includes Confidential Information of the objecting Party;

The objecting Party may request adaptation of the Publication in such a way that the objections are resolved, however, the scientific Integrity may not be affected. The Publication may be delayed by the Project Leader for a maximum period of 4 months of the submitting date mentioned in article (2) of this article on the grounds mentioned under A.4 (3) i and ii above. Parties may extend this period by mutual consent up to 6 months.
If the publishing Party has not received a written notice from the other Party or Parties within 30 days of the date of the Publication Notice, it will be free to publish the publication.

Nothing in this Agreement shall be construed as conferring rights to use in advertising, publicity or otherwise the name of the Parties or any of their logos or trademarks without their prior written approval.

The Parties undertake to cooperate to allow the timely submission, examination, publication and defense of any dissertation or thesis for a degree that includes the Results subject to the confidentiality an publication provisions agreed in this Agreement.

For the duration of this Agreement and for 5 years thereafter, the Parties shall be obliged to observe secrecy in respect of all Confidential Information.

This duty to observe confidentiality shall not be applicable to:

i. Information of which a Party can prove was in the possession of a Party or any of its Affiliates at the moment that this Party was informed of the Confidential Information;
ii. Information which is generally known on the day on which a Party is informed thereof by the other Party;
iii. Information of which a Party can prove it has been legitimately obtained by a Party or any of its Affiliates from third parties, without restriction of disclosure;
iv. Information which has become generally known after the date on which a Party has been informed thereof, other than through the illegitimate action or negligence of this Party or any of its Affiliates;
v. Information of which a Party or any of its Affiliates can prove is developed by or for a Party independent of the information disclosed by the Disclosing Party
vi. Information that is required to be disclosed by an order of any court of competent jurisdiction or governmental authority, provided that the Receiving Party, if legally and reasonably possible, (i) notifies the Disclosing Party; and (ii) complies with the Disclosing Party's reasonable instructions to protect the confidentiality of the Confidential Information at Disclosing Party's expense.

5. Parties shall process personal data in accordance with applicable data protection legislation (e.g. GDPR). In the event exchange of personal data between Parties is required for the execution of the Agreement, the Parties shall separately make appropriate additional arrangements in line with applicable data protection legislation.

Annex 2
Research Proposal, incl. support letters

pag 43-84

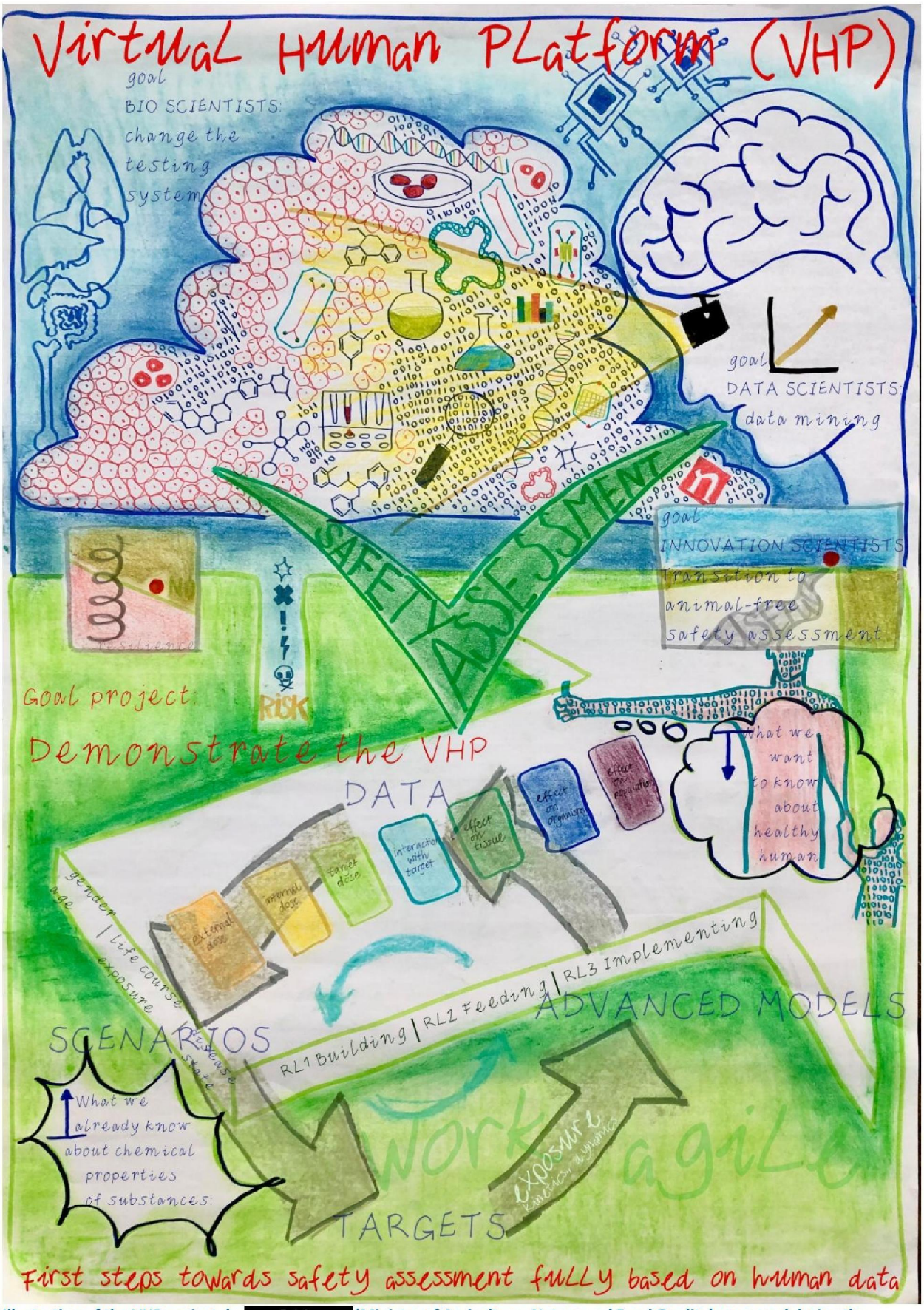

Illustration of the VHP project, by 5.1.2e (Ministry of Agriculture, Nature and Food Quality), prepared during the consortium meeting 29 October 2019, Utrecht.

1 APPLICATION DETAILS

Title of the proposal*	The Virtual Human Platform for Safety Assessment
Main Applicant **	5.1.2e
E-mail	5.1.2e @uu.nl
Correspondence preference	☐ Dutch ☒ English
1 NWA route applicable to the research proposal**	Creating value through responsible access to and use of big data
2 NWA route applicable to the research proposal**	Regenerative medicine: game changer moving to broad areas of application
Registration number of your initiative	HCR.1942
Keywords (max. five)***	Human biology, big data, animal free testing, new paradigm, risk assessment
Budget range requested budget	☐ ☐ 5.1.2b,5.1.2f ☒

1.1 LIST OF ABBREVIATIONS

ABBREVIATION	MEANS
ADME	Absorption, distribution, metabolism, and excretion
AI	Artificial Intelligence
AKI	Acute Kidney Injury
AI	Artificial Intelligence
(q)AOP	(quantitative) Adverse Outcome Pathway
FAIR	Findable, Accessible, Interoperable and Reusable
iPSC	Induced Pluripotent Stem Cells
ICT	Information and Communication Technology
MLP	Multi-Level Perspective
PBK modelling	Physiologically Based Kinetic modelling
PCM	Proteochemometric modelling
QIVIVE	Quantitative *in vitro* to *in vivo* extrapolation
QSAR	Quantitative Structure Activity Relations
RL	Research Line
SNP	Single Nucleotide Polymorphism
TA	Technology Assessment
TPI	Dutch Transition Programme for Innovations without animal testing
VHP	Virtual Human Platform
WGCNA	Weighted Correlation Network Analysis

1.2 TABLE OF CONTENTS

2 RESEARCH PROPOSAL

2.1 PROJECT DESCRIPTION

2.1.1 VISION

Imagine a world in which we perform precision safety testing of chemicals and pharmaceuticals without using laboratory animals. Imagine that the safety of chemicals and pharmaceuticals can be assessed for vulnerable groups such as infants, the elderly or the diseased. Imagine that we know how these substances interact with human biology and physiology and how they can be used safely at home, school or at work during the course of our lives. This is our **vision** for the future, the vision that underlies the development of the Virtual Human Platform for safety assessment (VHP). The VHP is an innovative approach to determine the safety of chemicals and pharmaceuticals based on human data rather than data from laboratory animals. We envision that as a result of co-creation between all relevant stakeholders in society, this project will contribute to trust and acceptance in the output of VHP for use in chemical and pharmaceutical safety assessment. The driving force of this project is an interdisciplinary and multi-stakeholder collaboration that will spearhead the transition from animal-based testing to innovative animal-free safety assessment.

2.1.2 PROBLEM DEFINITION

Current legal and regulatory frameworks for the assessment of the safety of chemicals and pharmaceuticals for human health rely predominantly on data from *in vivo* animal studies. However, the accuracy of animal studies to predict toxicity in humans is limited [1,2]. In addition, current animal testing regimes do not reflect human-relevant scenarios, such as differences in susceptibility due to age, gender, timing of exposure, or disease state. In a national and international arena urgently calling for the reduction of animal testing, the current approach to gradually refine, reduce and replace animal testing has not led to the necessary and desired pace of innovation in animal-free safety assessment. Furthermore, the opportunities offered by state-of-the-art technologies in human health and data science have hardly been yet explored in the realm of safety assessment.

2.1.3 GAME CHANGER

In this project, we propose the Virtual Human Platform (VHP) as a breakthrough in safety assessment of chemicals and pharmaceuticals, and a game changer in the fields of big data and regenerative medicine (see also 2.1.8). It is our **mission** to improve the prediction of the potential harmful effects of chemicals and pharmaceuticals based on a holistic, interdisciplinary definition of human health by developing the VHP and accelerating the transition from animal-based testing to innovative safety assessment. We will integrate data on human physiology, chemical characteristics and perturbations of biological pathways, for the first time in an inclusive and integrated manner that incorporates: 1) human-relevant scenarios to discriminate vulnerable groups (such as disease state, life course exposure, gender and age); 2) chemicals from different sectors (pharma, consumer products and chemical industry); and, 3) different regulatory and stakeholder needs. This project addresses the emerging societal challenge of the transition to animal-free safety assessment, by integrating various scientific disciplines and working with all stakeholders towards implementation and societal acceptance of an approach to chemical safety assessment that is based on human data rather than animal data.

2.1.4 GENERAL INTRODUCTION TO THE VHP

By taking full advantage of emerging state-of-the art developments in computational and data science, toxicology, human disease modelling, and transition management, we will develop the VHP for safety assessment as the new reference in safety assessment based on human data rather than animal testing. The concept of the Virtual Human Platform for safety assessment is outlined in *figure 1,* next page. The basis for **building** the VHP is the **output** that is urgently needed by the stakeholders participating in this project (scientists, industry, regulators, policy makers, clinicians and patients). The output will focus on three scenarios that cannot be addressed yet, or are insufficiently addressed, within current safety assessment approaches. For each scenario, concrete biological, toxicological and exposure data from human (models) will be collected and/or generated and integrated with existing human physiological information to form the **input** that will **feed** into the VHP (*figure 1*). These scenarios, described in more detail below, will provide a first proof-of-concept for the VHP and will demonstrate its technical feasibility and challenges. At the same time, we will investigate what is needed to **implement** the VHP, to ensure trust in the outcomes of the VHP, understand uncertainty, and to transition to animal-free safety assessment. We envision the development of the Virtual Human Platform as a responsible, secure, transparent and iterative process that results in an expanding platform, able to incorporate results from other (inter)national projects, and which allows continuous feedback between each new data entry (input) and the scenario analysed (output).

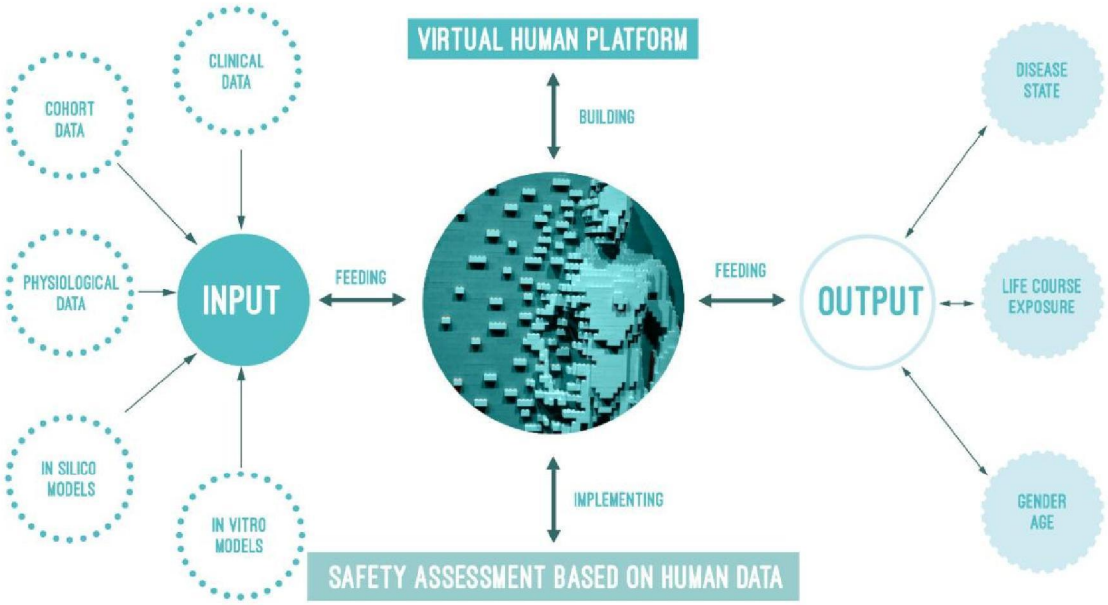

***Figure* 1: Conceptual overview of the Virtual Human Platform for safety assessment**

Based on the outcomes of five expert workshops held with multiple stakeholders during preparation of the preproposal and full proposal, from February to November 2019, we identified three human-relevant scenarios to address in the VHP. These scenarios - disease state, life course exposure, gender and age - are insufficiently addressed in current safety assessment based on animal testing, and specifically capture the potential variation in human physiology and sensitivity that can play a significant role in the safety of compounds. During the stakeholder workshops, we also identified specific case studies corresponding to each scenario in order to bring focus to the project.

The case studies were selected based on the following criteria:

1. realistic issues identified by stakeholders, in particular our co-funders;
2. the expertise of our consortium and the availability of human (clinical) data;
3. the importance of covering both pharmaceutical and industrial chemical regulations.

The following three scenarios and corresponding case studies were selected:

1. **Disease state:** Kidney disease and pharmacovigilance. Understanding how the safety of pharmaceuticals can be assessed based on vital organs of patients suffering from kidney disease.
2. **Life course exposure:** Neurodegenerative disease (Parkinson) and exposure to chemicals. Understanding safety of chemicals throughout the entire life course taking into account various exposure scenarios for different demographics (such as children, occupational and rural populations).
3. **Age and sex:** Thyroid mediated developmental neurotoxicity. Understanding age and sex dependent differences in thyroid homeostasis due to chemical exposure and consequent effects on development of the brain.

2.1.5 OVERALL OBJECTIVES OF VHP

The overall aim of this project is to develop the Virtual Human Platform as a holistic, interdisciplinary approach to determine the safety of chemicals and pharmaceuticals for human health without animal testing, solely based on human physiology and biology.

To ensure that the output of VHP is reliable, sustainable, acceptable and has translational value to human health, we have united all relevant stakeholders (including representatives from academia, industry, government and society) in a single consortium. In a collaborative effort of co-creation, each stakeholder will provide vital pieces of the VHP puzzle,

sharing knowledge and becoming a champion of the VHP version 1.0, that is developed within this project. In addition, this project sets the framework for beyond (VHP version 2.0, 3.0).

The project focusses on three major objectives that are reflected in the three research lines (RL) and related work packages (WP): **building**, **feeding** and **implementing** the VHP. Specifically, the objectives are:

- To build the VHP by integrating and analysing high quality data of human biology (RL1; WPs1.1-1.3)
  We will develop a platform to identify, collect, integrate and analyse relevant human data, using state-of-the-art technology for data integration to ensure the transparency and security of the process. We will use Adverse Outcome Pathways (AOPs) to define and model the mechanisms underlying perturbations to human biological pathways, as well as employ artificial intelligence (machine learning) to link these AOPs to chemical structures and the output of results from RL2 to make safety estimates based on exposure. Importantly, we will perform case studies to ensure a high predictive ability of components used to build the VHP. *In silico* modelling towards quantitative AOPs will aid in making safety predictions in the VHP for the case studies in RL2.
- To feed the VHP with human relevant data for application in safety and risk assessment (RL2; WPs 2.1-2.4)
  Based on the scenarios and case studies outlined above, we will collect existing human relevant data and generate new human data for defined sets of chemicals and pharmaceuticals, to feed into the VHP. Chemicals are case study specific and include pharmaceuticals (WP2.2) and chemical substances such as pesticides (WP2.3, 2.4). This will include data on exposure, toxicokinetics and toxicological effects, generated with advanced *in vitro* human models
- To implement the VHP and accelerate the transition towards animal-free safety assessment (RL3; WP3.1-3.3)
  We will investigate what is needed to gain confidence and trust in this new framework, in order to ensure a sustainable transition towards animal free safety testing, while striving for improved reproducibility and predictability in science. To this end we engage stakeholders from the start to determine the needs and requirements for the VHP and to identify incentives to change. Ample attention will be paid to training and educating (prospective) professionals. Ultimately it is our goal to embed the governance, sustainable development and implementation of the VHP in the safety assessment regime.

2.1.6 THE SOCIETAL CHALLENGE

In the Netherlands more than 530,000 animals are used annually for research, education and safety testing purposes [3]. Modern society is convinced that it is ethically, scientifically and economically unacceptable to continue on this trajectory [4, 5]. Accordingly, the Dutch government has released bold plans for the Netherlands to take on a world-leading role in the transition to animal-free innovations (TPI) [6]. On an international level, regulatory agencies such as the United States Environment Protection Agency have recently declared that they will eliminate all rodent testing from 2035 on [7]. The conviction is growing that it must be possible to determine the safety of chemicals and pharmaceuticals without using experimental animals. The major **societal challenge** that we are facing is: how can we change our animal-centric chemical assessment paradigm while ensuring safety and acceptance by all stakeholders in society?

2.1.7 SCIENTIFIC CHALLENGE

In the past decades, substantial attention has been paid to the replacement, reduction and refinement of animal experiments (3Rs) for safety assessment of chemicals and pharmaceuticals. However, this is a very slow and tedious process in which single *in vitro* models proceed from the research and development phase towards a lengthy validation and implementation process into regulatory frameworks [8]. In recent years, a transition has started in safety and efficacy assessment of compounds, moving away from animal data as the 'gold standard' towards a mechanism-based approach using human biological systems as a starting point for safety assessment. AOPs are at the basis of a mechanism-based toxicity approach by providing information on biological and physiological pathways, that may be perturbed by compound exposure leading to an adverse health effect [9]. AOPs are increasingly described in an integrative and quantitative manner using input from advanced *in vitro* models with a better predictivity due to their physiological resemblance to human tissues [10,11].

The **scientific challenge** ahead is to harvest the promise of recent technological developments in data science and human disease modelling, together with the innovative approach of quantitative AOPs (to predict chemical or pharmaceutical exposure responses to the AOP) in the field of safety assessment [12]. At the same time, we are faced with the scientific challenge of taking the needs, interests and values of all relevant stakeholders in society into account, using innovative and participatory approaches of technology assessment and co-creation.

As each of the research lines is focussed on harvesting these newest innovations, **the VHP project will take the field of safety assessment beyond the state of the art**. RL 1 will focus on innovations in data science, which include new approaches to combine large databases and analyse them in a transparent and secure way, as well as artificial intelligence (AI), machine learning to develop new algorithms to better understand the complexity of human biology and physiology. These *in silico* approaches can be used to link individual chemical structures to the described AOPs to

connect an expected phenotype to a known chemotype. RL2 will focus on innovations in human disease modelling, including human tissue culture (organoids), stem cell technology and organs-on-chip, to study the kinetics and effects of compounds and gain quantitative insight into the mode-of-action. Integrating existing human data (e.g. genetic and phenotypic data, exposure data), data from advanced *in vitro* models and clinical and human studies (e.g. biomonitoring), will lead to new mechanistic knowledge and improved algorithms to predict safety. In RL3, approaches from innovation studies and transition management aid in developing actionable knowledge on how these scientific and technological advancements can be aligned with the needs, interests and values of stakeholders and how connections can be made to existing initiatives to ensure broad acceptance and sustainability of the VHP.

2.1.8 CONNECTION WITH AND CONTRIBUTION TO THE NWA ROUTES

The VHP specifically addresses Q101: Can we design models of the human body and use smart technology for health, nutritional and toxicity research and thereby drastically reduce the use of laboratory animals?
The primary routes to which the VHP contributes are:

- Route 25 Creating value through responsible access to and use of big data.
- Route 19 Regenerative Medicine: game changer moving to broad areas of application.

This project is a **game changer** in **creating value through responsible access to and use of big data**. We aim to implement data-driven research to create value for human-based toxicology and safety assessment. We will build an ICT infrastructure to integrate various data sources in human biology, toxicology and chemistry and use innovative approaches, analysis methods and technologies (FAIR principles, smart algorithms, artificial intelligence, pattern recognition) to eventually make safety predictions for humans. We will co-create the VHP with stakeholders throughout the entire safety assessment knowledge chain to investigate how we can build a secure, transparent, open source, iterative VHP in a responsible way. In this process, we involve expert organisations, such as applied research organisations, SURFSara and the Dutch Techcentre for Life Sciences (DTL) to educate and train the involved stakeholders as well as next generation of professionals to effectively apply big data to improve safety assessment and human health. For sustainability of the VHP we will connect to (inter)national initiatives such as Health-RI and ELIXIR.

This project is also a **game changer** in **regenerative medicine: moving to broad areas of application** and integrates interdisciplinary research on stem cell technology and organoids. A collaboration partner of our project in this respect is the Institute for human Organ and Disease Model Technologies (hDMT), a Dutch expert network on human disease modelling and some of their partners (VUMC, WU). This project offers the translation of the technologies that are developed in **regenerative medicine** to practical application in toxicology and human-based safety assessment of chemicals and pharmaceuticals.

In addition to the NWA routes, this proposal also contributes to the missions formulated in the National 'kennis en innovatie agenda (KIA) 2020-2023 Gezondheid & Zorg' and addresses the KIA 'Sleuteltechnologieen'(including MJPs Artificial Intelligence and Biomedical Engineering for Health).

2.1.9 CONNECTION WITH EXISTING INITIATIVES

Table 1: Connections of VHP consortium with relevant initiatives

INITIATIVE, REPRESENTATIVE	TYPE OF PROJECT	AIM OF PROJECT/INITIATIVE	CONTRIBUTION TO VHP
[redacted]			

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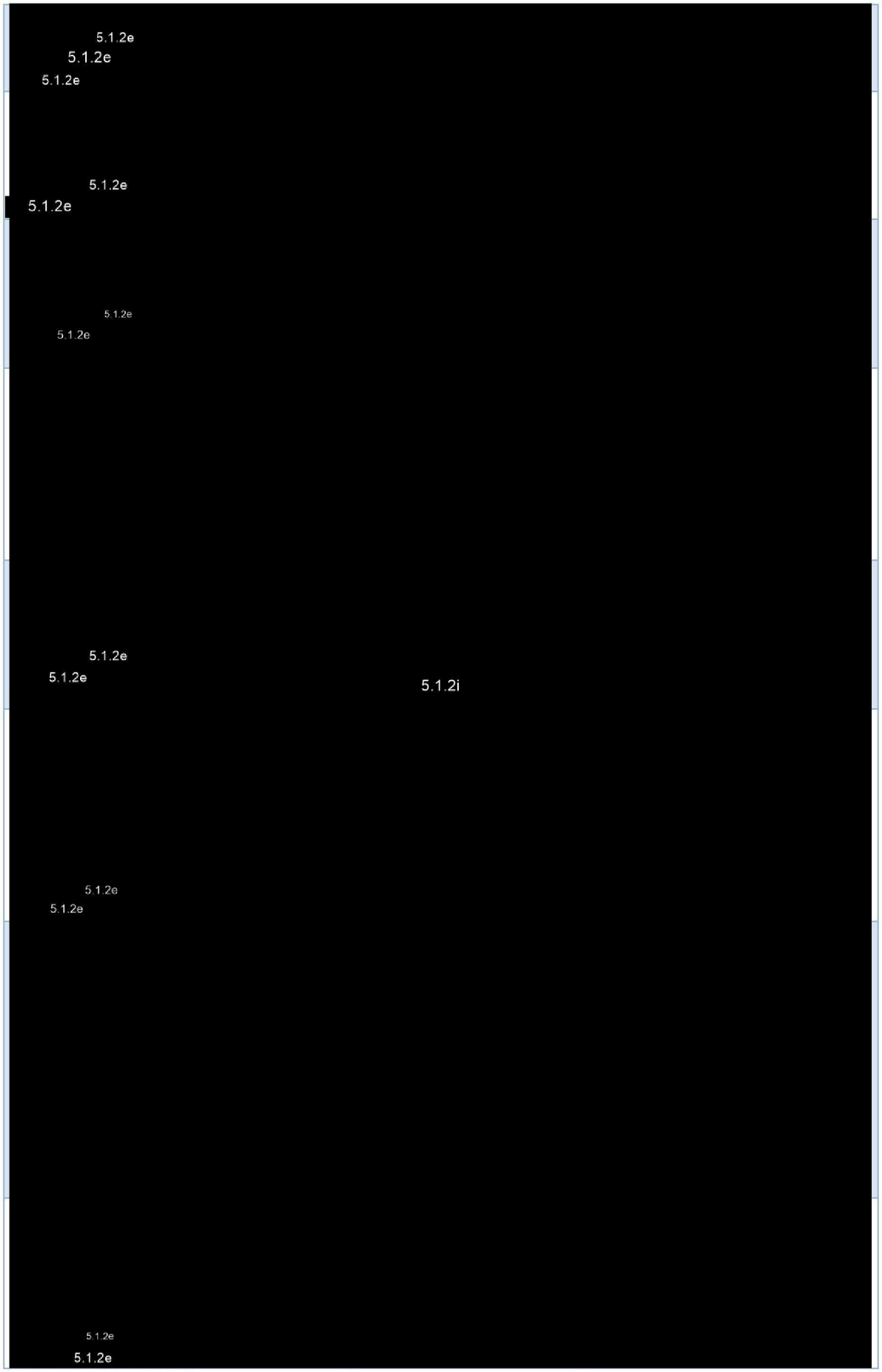
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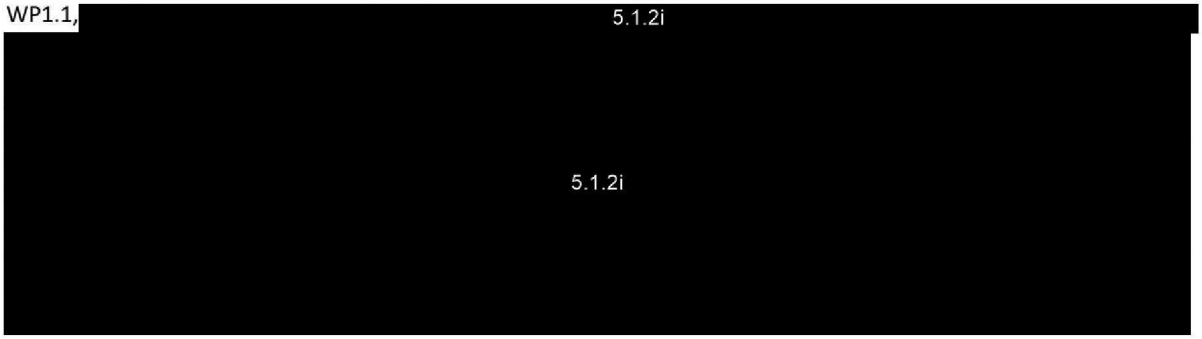
2.2 APPROACH/METHODOLOGY

The VHP for safety assessment will be developed within three interacting research lines, that involve **building** the platform, **feeding** the platform with newly generated data, and **implementing** the platform to ensure stakeholder acceptance, governance and sustainability. Each research line (RL) consists of several workpackages that are described in Chapter 4. The workpackages (WP) are inter-related, both within and between the research lines (*figure 2*). Collaboration between academia, government, industry and societal partners is also integrated within and between the RLs, to take optimal advantage of the expertise in the consortium. Together, the RLs will address the overall objectives of the project and are described below.

2.2.1 RESEARCH LINE 1: BUILDING THE VIRTUAL HUMAN PLATFORM

In short. Just like the real human body, a virtual human requires organs that work properly and are well connected. In RL1, a growing and flexible VHP will be built, by collecting relevant data of well-defined quality in an interoperable format, thereby developing a knowledge research environment that will dynamically integrate data and model data in a way that represents human biology. RL1 will develop and apply the models that describe the behaviour (toxicokinetic) and the potential adverse health effects (toxicodynamics) of chemicals and pharmaceuticals in the human body based on qAOPs. It develops and applies models that will translate exposure concentrations within *in vitro* human systems to concentrations within the human body (i.e. quantitative *in vitro* to *in vivo* extrapolation (QIVIVE)), thus enabling the exploitation of *in vitro* bioassay data in human safety assessment. Ultimately, RL1 will provide the modelled estimates of compound safety based on human data that will be further evaluated in RL2 and RL3.

WP1.1, 5.1.2i



WP1.2, 5.1.2i

5.1.2i

WP1.3, 5.1.2i

5.1.2i

2.2.2 RESEARCH LINE 2: FEEDING THE VIRTUAL HUMAN PLATFORM

In short. In RL2, human relevant *in vitro* experimental models available in the consortium will be applied to feed the VHP in RL1 with data on exposure, kinetics including metabolism, biological processes and toxicological effects. Data both on toxicokinetics and toxicodynamics will be generated by performing well-defined experiments with the advanced in human vitro models of our partners, which are based on stem cell technology (including iPSC), organoids and (multi-) organs-on-chips for e.g. bioengineered skin, liver, lung, thyroid, gut and kidney cells (glomerular and tubular models). For human exposure data, clinical and epidemiological data will be collected and assessed. Furthermore, we will set criteria and guidelines for the human relevance of the models and the quality of the data used. RL2 is the 'home' for the experimental research in the three scenarios and associated case studies, ranging from one relatively straightforward (WP2.2), one more complex (WP2.3) to one ambitious case study involving multiple organs (WP2.4), which are described below. In addition, safety and risk assessment of chemicals within the case studies is performed in RL2, using outcomes from modelling in RL1, and criteria established in RL3.

WP2.1, 5.1.2i

5.1.2i

WP2.2, 5.1.2i

5.1.2i

WP 2.3, 5.1.2i

5.1.2i

5.1.2i

WP2.4, 5.1.2i

5.1.2i

2.2.3 RESEARCH LINE 3: IMPLEMENTING THE VIRTUAL HUMAN PLATFORM

In short: Technological developments in data science and toxicology will not automatically be adopted in the current practice of safety assessment. Stakeholders have their own individual motivations for sticking to animal testing such as development routines, lack of incentives and liability issues, risk aversion and reputation, as well as scientific uncertainties and complexities associated with innovative animal-free approaches. While these motivations can be understood in isolation, they contribute to systemic lock-in and compromise our collective ability to ensure a transition towards animal free safety assessment [15]. The VHP is a revolutionary approach that breaks out of this lock-in and proposes human biology and physiology as the basis and new reference for human safety assessment. The pathways to widespread acceptance of this revolutionary approach, however, are uncertain and require participatory approaches to platform development as well as active management of the transition towards animal-free safety assessment. RL3 focusses on the implementation of the VHP and aims to provide insight in how a transition towards animal free safety assessment can be realized starting from the needs, responsibilities, and interests of stakeholders. RL3 also includes education and training as a crucial aspect to consolidate the strength of our project to innovate current safety assessment.

WP3.1, 5.1.2i

5.1.2i

WP3.2, 5.1.2i

5.1.2i

WP3.3, 5.1.2i

5.1.2i

Finally, WP4, **Project Coordination, Impact and Data Management**, encompasses all the RLs, and is an overarching WP which provides both strategic and operational management of the entire project, ensuring the successful completion of the project within the timescales and resources provided, as well as effectively coordinates the impact (knowledge utilisation) and data management activities in the project.

2.3 KNOWLEDGE UTILISATION

We are at the start of a new era, the transition towards animal-free safety assessment of chemicals and pharmaceuticals, where the mechanistic human based approach is at the center. There are several initiatives covering different aspects of this area. However, the fragmented nature of these initiatives prevents us as a society from reaching our goal. Our project is laying the corner stone to solving the next challenge, the concrete integration of innovations in toxicology with recent developments in data science, human disease modelling and transition management. While the potential of this integrated approach is clear, our consortium acknowledges that VHP can only become a driver of the transition towards human-based safety assessment, if it is accepted by all key stakeholders. Only acceptance can create the changes needed for a successful implementation in the broader regulatory, economic and societal environments. Therefore, in its core design, the VHP project integrates a robust knowledge utilization and impact strategy to spearhead the transition to human-based safety assessment. This strategy combines the development of actionable knowledge on the drivers and barriers of a transition to human-based safety assessment (WP 3.2) with active co-creation of the VHP by societal stakeholders (WP 3.1) and training and education of the consortium partners and the next generation of scientists in a participatory way (WP 3.3.) This impact strategy builds upon the VHP output on human disease modelling (WP2.1-2.4), and closely interacts with the VHP platform itself (WP1.1-1.3). The knowledge developed within VHP on the drivers and barriers of transitions towards animal-free safety assessment within RL3 will further contribute to improved preparedness for socio-economic and regulatory changes that are needed for the paradigm shift to occur. It will also provide important insights into impact strategies that align the VHP project with the increased societal demand for reduced animal-use and better safety assessment approaches.

2.3.1 PROJECT DELIVERABLES (OUTPUT)

- Proof of concept of the VHP and user-interface which incorporates both technical aspects and feedback from end-users (scientists, industry, regulators)
- Integration of available human databases and demonstration of how they can be used in a transparent and secure way
- Demonstration of the VHP based on safety estimates generated from the case studies that will give insight into its design and how it can be used.
- Roadmap for further development of the VHP, including its future governance, acceptance and implementation

2.3.2 PROJECT OUTCOMES & IMPACT

To achieve the ultimate and intended impact of the VHP on the safety assessment, the output of this project needs to be embraced, not only by the members of the project consortium, but also by other national and international stakeholders. Therefore, various dissemination activities are described in the utilization plan (table 5). As a result of these activities and the active exploitation of the VHP by the consortium partners, the following outcomes are foreseen:

- Scientifically sound, practicably implementable non-animal solutions, readily deployable to aid in meaningful safety assessment of chemicals and pharmaceuticals
- More (inter)national regulatory bodies recognize VHP and use results in their daily practise
- Uptake by other industries (e.g., food, medical devices) and exploitation of the application of the VHP to broader scientific disciplines (e.g. cardiovascular disease, diabetes)
- Awareness of the added value of VHP in the knowledge chain, by integrating data from other (inter)national initiatives into VHP

- The Netherlands recognised as the leading country in Europe in the transition to animal free innovations and in data driven regulatory science

Through these project outcomes, we are working towards the following expected (long-term) impact:

- Human physiology and biology as the new paradigm for chemical and pharmaceutical safety assessment
- State of the art data science and computational modelling in combination with advanced *in vitro* tools are the driving forces of safety assessment
- International safety regulations completely based on human physiology and biology
- Personalised treatment of diseases and safety assessment
- Experimental animal testing will become redundant

As stated in the overall objective (paragraph 2.1.5), the VHP project has the mission to innovate safety testing of chemicals and pharmaceuticals in such a way that it is fully based on human data, taking human-relevant scenarios such as age, gender, disease and life course exposure into consideration. The VHP thereby provides relevant output for the real-life human situation, making animal testing redundant. The relevant target groups have all been identified in the various VHP stakeholder workshops held in 2019 while preparing this proposal and are part of the VHP consortium. There is a high degree of involvement and commitment from the private and public sector (via in-kind and in-cash co-funding). Also, a scientific advisory board with international scientists will be installed. In the collaborative effort of the VHP project, each stakeholder from academia, government, industry and society provides a unique piece of the puzzle from their own unique perspective (see list of co-applicants, co-financers and cooperation partners). This is why we believe that our consortium can truly make a difference.

2.3.3 UTILISATION PLAN

The VHP activities towards knowledge utilization are based on: (1) an integrated strategy of co-creation and knowledge sharing and utilisation while building, feeding and implementing the VHP platform, (2) emphasis on productive interactions and knowledge sharing with stakeholders, including scientists, industry, regulators, policy makers, clinicians and patients throughout the course of the project, and (3) a wide dissemination of its results through media, website, social feeds and the networks of the involved stakeholders. The VHP project consortium already represents the most relevant stakeholders (knowledge users) in the safety assessment knowledge chain (see Table 2). As human safety assessment is increasingly important worldwide, we expect a large range of stakeholders to benefit from VHP:

Table 2: Groups, organisations and sectors impacted by our project

STAKEHOLDERS	HOW WILL THE VHP IMPROVE THEIR PRACTICE?
Civil Society/Consumers	[redacted]
NGOs	
Patients/Health Foundations	
Regulatory bodies / policy	
Industry	
Researchers / next generation of scientists	

5.1.2i

In this project we will take into account drives, such as communication, collaboration, commitment and coordination to accelerate the transition towards animal-free safety assessment [17]. We also acknowledge the barriers, our strategy to overcome these barriers are listed in Table 3.

Table 3: Barriers and strategies to overcome barriers

BARRIER	STRATEGY TO OVERCOME BARRIER
Poor adoption of project results by the end-users	• [redacted]
Fragmented and lack of policy goals: Multiple actors may have conflicting agendas and different needs	• [redacted]
(International) regulatory approval of the VHP	• [redacted]
Public acceptance and societal risk aversion	• [redacted]

5.1.2i

2.3.3.1 Activities within the VHP consortium to maximise impact

In the collaborative effort of the VHP project, we have a very well-balanced consortium with stakeholders from academia, industry, government, and society, where each stakeholder provides a unique piece of the puzzle from their own unique perspective (Table 6-9). This is why we believe that our consortium can truly make a difference. The VHP consortium unites all the necessary, complementary expertise and exchange knowledge to (1) build, test and evaluate the VHP platform, and (2) to promote the proofs of concepts and institutional insights in real-life settings, both important towards realizing the knowledge utilization potential. Knowledge exchange within the consortium is maximised through joint research with frequent exchange of personnel between partners (section 4.1), through regular consortium meetings and through teaching and training actions. A kick-off meeting and annual progress meetings for all VHP researchers and partners will be complemented with an annual retreat, set-up as interactive workshops for the entire VHP community, in which the young researchers, user representatives, advisory board members, industrial partners, regulatory bodies and invited specialist speakers can extensively discuss the research and societal implications. The user feedback from both annual meetings will iteratively direct the experimental VHP approaches, project planning and facilitate utilization. At each user meeting, utilisation (incl. IP issues) concerning new findings will be assessed. Moreover, there is a high degree of involvement and commitment from the private and public sector (via in-kind and in-cash co-funding).

2.3.3.2 Activities of the VHP consortium with external stakeholders to maximise impact

5.1.2i

Table 4: Impact plan

ACTIVITY	PURPOSE
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

5.1.2i

5.1.2i

- 5.1.2i
- 5.1.2i

2.3.4 DISSEMINATION PLAN

The key target groups are categorised into the internal (VHP consortium) and external target audience (beyond the VHP consortium). The VHP consortium partners will be the first users. They are also key-opinion-leaders in their respective fields and therefore present a channel for disseminating the project results to other potential users. Our dissemination activities (Table 5) therefore rely on the VHP consortium partners acting as ambassadors and exploiting project results to their respective networks, business partners and customers.

Table 5: Overview of VHP-dissemination activities

DISSEMINATION CHANNEL	TARGET AUDIENCE	EXPECTED IMPACT
5.1.2i		

3 THE CONSORTIUM

3.1 DESCRIPTION OF THE CONSORTIUM

The VHP community is an interdisciplinary consortium consisting of 12 co-applicant organisations with leading scientific groups from **Dutch universities** (UU, MU, UL, WU, VU), university medical centres (UMCU, VUMC, EMC), **public health institutes** (RIVM) and **applied research organisations** (HU, TNO, WFSR), with expertise spanning the technological, biological, chemical, medical as well as the social sciences. The expertise of the main and co-applicants is shown in table 8 and table 9.

In addition to the co-applicants, the co-funders and cooperation partners ensure the active involvement of diverse academic, regulatory, industrial and societal partners to the project throughout the entire **safety assessment knowledge chain**. The safety assessment knowledge chain is comprised of: 1) the building of a transparent, secure and sustainable ICT infrastructure and modelling and integration of data (ORTEC, Uppsala Universitet, Certara, SURFsara, VHP, DTL); 2) the development of innovative advanced *in vitro* and disease models (hDMT); 3) the testing of compounds by chemical and pharmaceutical manufacturers (Unilever, Shell, Bayer, Galapagos), trade organizations (Cosmetics Europe, Association Innovative Medicines (VIG), Watercycle Research Institute (KWR)) and contract research organizations (Charles River Laboratories); 4), the assessment of compounds for use in humans and the development of guidelines and regulatory frameworks for safety assessment (Dutch Medicines Evaluation Board (CBG-MEB), US Environmental Protection Agency (US-EPA)); 5) policy making concerning animal welfare (Ministry of Agriculture, Nature and Food Quality (LNV)); and 6) the alignment of safety assessment requirements and consumer needs with the values and preferences of citizens and patients (Proefdiervrij, Brandwondenstichting, Nierstichting). The co-funders and cooperation partners are active in different sectors that have their own regulatory needs and assessment routines (e.g. cosmetics, chemicals, pharmaceuticals, food). All partners have ample experience with operating in public-private partnerships and translating and utilizing the developed knowledge and outcomes in their safety assessment practices. The expertise and contribution of the co-funders and cooperation partners brought to the VHP is shown in Table 6 and Table 7.

Table 6: Co-funder position in safety assessment knowledge chain and contribution to VHP

CO-FUNDERS	DUTCH (NL) /INTERNATIONAL (I)	POSITION IN SAFETY ASSESSMENT KNOWLEDGE CHAIN	CONTRIBUTION TO RESEARCH LINE
5.1.2e	5.1.2i		
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			

Table 7: Co-operation partner position in safety assessment knowledge chain and contribution to VHP

COOPERATION PARTNERS	DUTCH (NL) OR INTERNATIONAL (I)	POSITION IN SAFETY ASSESSMENT KNOWLEDGE CHAIN	CONTRIBUTION TO RESEARCH LINE
5.1.2e	5.1.2i		
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			
5.1.2e			

3.2 DIVERSITY OF THE CONSORTIUM

The consortium is made up of a diverse group of individuals with different cultural backgrounds and gender diversity. Of the co-applicants, researchers originate from various countries (Netherlands, Belgium, Germany, Sweden, UK, Ireland, USA, Canada, Italy). It is expected that 50% of PhDs and postdoctoral researchers will come from countries outside the Netherlands. The coordination team is made up of three women, and of the principal investigators, 7 out of 12 are women.

3.3 PLAN FOR INVOLVEMENT AND DEVELOPMENT OF MID-LEVEL RESEARCHERS

In this project we will hire young professionals, namely 12 PhD students, 9 post-docs and 2 technicians. While PhDs will participate in established graduate schools, the consortium is aware that the professional development of postdoctoral mid-career level researchers is often problematic at scientific institutions. Therefore, we are focussing on fostering the development of mid-career postdoctoral researchers in particular during VHP, even more so, as we need more well-educated professionals for the transition to animal free innovations. Those newly educated people, with an ambition to change the scientific, regulatory and industrial community, will help to accelerate the transition and to become the leading experts of tomorrow. The young scientists will be supervised by highly experienced leading senior researchers in their field and coached by a PI, who will support the development of a personal career development plan. This plan will be developed by the young scientists within the first year of the project and adjusted on a yearly basis. It will include personal and professional development goals and the plan to achieve them by e.g. 1) participating at courses teaching transferable skills aiming at communication, leadership and management and personal effectiveness to name but a few available at Utrecht University, 2) making use of the Research Support Offices of the partners, and developing an entrepreneurial mindset through 3) the interaction with industry (secondments will be encouraged). The young scientists will become actively part of the project management team (rotating) to train their managerial skills. Their collaboration and interaction with different disciplines will enable them to communicate with researchers from different disciplines, train them to discuss intersectoral (academia-industry), as well as provide them with a network across different fields and sectors – all important for a career in academia or industry.

3.4 LIST MAIN-APPLICANT, CO-APPLICANTS, ORGANISATION AND EXPERTISE

Table 8: Main applicant and her expertise

Main applicant			
NAME, TITLE(S)	ORGANISATION	POSITION	EXPERTISE
5.1.2e	Utrecht University (UU) Institute for Risk Assessment Sciences	5.1.2e	5.1.2e

Table 9: Co-applicants and expertise

Co-Applicant(s)				
WP involved	NAME, TITLE(S)	ORGANISATION	POSITION	EXPERTISE
1.1/1.3	5.1.2e	Maastricht University (UM)	5.1.2e	5.1.2e
1.1		Maastricht University (UM)		
1.3		Leiden University (UL) LACDR		
1.3		Leiden University (UL), LACDR		
1.1/1.3 4		University of Applied Sciences Utrecht (HU)		
1.3		Universiteit Leiden (UL)		
1.2/1.3		TNO		
1.3/ 2.1		Vrije Universiteit Amsterdam (VU)		
1.3		National Institute for Public Health and the Environment (RIVM)		
1.2		Utrecht University (UU), Institute for Risk Assessment Sciences (IRAS)		
1.2		Wageningen University & research (WUR)		
1.2		(WSFR)		
1.2		Wageningen University		
1.3/2.1		Maastricht University (UM)		
2.1		Utrecht University (UU), IRAS & (HU)		
2.1		VU Medical Center (VUMC)		
2.1		TNO		
2.2		Utrecht University (UU)		

2.2	5.1.2e	University Medical Centre Utrecht (UMCU)	5.1.2e	5.1.2e
2.3 3.1/3.2		RIVM, Centre for Safety of Substances and Products		
2.3		Utrecht University (UU), IRAS		
2.3		Utrecht University (UU), IRAS		
2.4		RIVM, Centre for Health Protection & IRAS		
2.4		Erasmus MC (EUR)		
3.1		Utrecht University (UU), Copernicus Institute		
3.2		(RIVM) , Centre for Health Protection		
3.1-3.3 4		University Applied Sciences Utrecht (HU)		
3.1- 3.3		Utrecht University (UU)		
3.1/3.2	5.1.2e	RIVM		
3.1		Utrecht University (UU), Copernicus Institute		
3.1/3.3		Utrecht University (UU), Copernicus Institute		

4 THE WORK PLAN

4.1 OVERALL WORK PLAN

We present the overall structure of the workplan in the PERT chart in *Figure 2*, showing the interaction among research lines and work packages. Research line 1, building the VHP, is in the heart of the project, in which we will develop the ICT infrastructure (WP1.1) and integrate *in silico* tools for toxicokinetics (WP1.2) and toxicodynamics.(WP1.3). We will feed research line 1 with human data from *in vitro* toxicokinetics (WP2.1) and three scenarios (WP2.2-2.4). We will implement all elements of the VHP in research line 3 (WP3.1-3.3). WP4, Coordination, Impact and data management is an overarching WP that covers all aspects of the project.

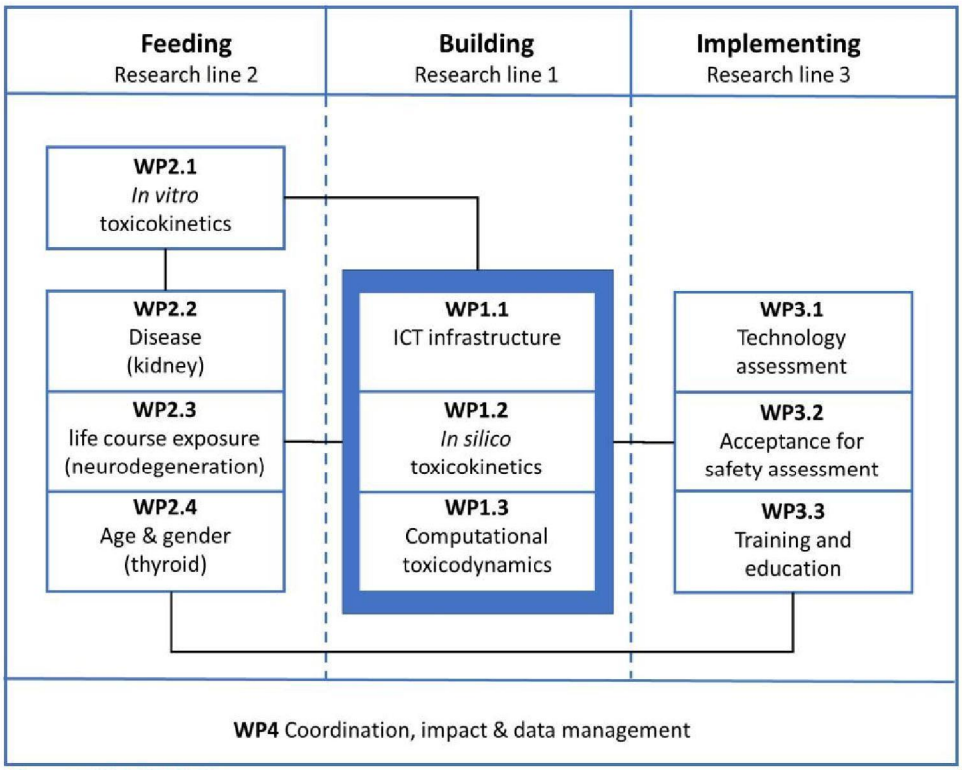


Figure 2: PERT CHART

4.2 WORK PACKAGES

Work package number	1.1
Work package title	Building the ICT infrastructure for the VHP
Work package leader	5.1.2e
Involved partners	5.1.2e
Start date	Month 1
End date	Month 60

Objectives

1.1.1 To develop the technical infrastructure for the VHP;

1.1.2 To set up a basic predictive platform based on human physiology and biology ;

1.1.3 To develop data analysis workflows based on the VHP;

1.1.4 To make services (tools, data, knowledge) available for all project partners;

1.1.5 To continuously support VHP with interoperability tools;

Description of activities

5.1.2e

5.1.2e

5.1.2e

5.1.2e

5.1.2i

5.1.2e

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	1.2
Work package title	*In silico* toxicokinetics
Work package leader	5.1.2e
Involved partners	5.1.2e Certara,
Start date	Month 1
End date	Month 60

Objectives

1.2.1 To define parameters required for physiologically based kinetic (PBK) modelling;

1.2.2 To develop and adapt generic PBK models to be integrated in VHP;

1.2.3 To provide guidance for quantitative *in vitro* to *in vivo* extrapolations to be integrated in VHP.

Description of activities

5.1.2e

5.1.2i

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	1.3
Work package title	Computational toxicodynamics
Work package leader	5.1.2e
Involved partners	5.1.2e 5.1.2e, participants WP2.1-2.4
Start date	Month 1
End date	Month 60

Objectives

1.3.1. To develop QSAR and PCM models for molecular initiation;

1.3.2. To develop quantitative AOP models;

1.3.3. To test the VHP by integrating *in silico* models and data;

1.3.4. To generate safety estimates by running the VHP.

Description of activities

5.1.2e

5.1.2e

5.1.2e

5.1.2i

5.1.2e

Expected output

5.1.2i

Work package number	2.1
Work package title	*In vitro* models to provide toxicokinetics & toxicodynamics parameters
Work package leader	5.1.2e
Involved partners	5.1.2e
Start date	Month 1
End date	Month 60

Objectives

2.1.1. To verify *in vitro* models relevant for ADME modelling in WP1.2 and local toxicity, using well defined concentration ranges with training sets of known compounds;

2.1.2. To obtain *in vitro* parameters for PBK modelling following human relevant exposure of selected compounds used in the case studies;

2.1.3. To test the applicability domain of iPSC models to generate personalized parameters for adsorption and metabolism.

Description of activities

5.1.2e

5.1.2i

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	2.2
Work package title	Disease state: Case study chronic kidney disease
Work package leader	5.1.2e
Involved partners	5.1.2e 5.1.2e Nierstichting
Start date	Month 1
End date	Month 60

Objectives

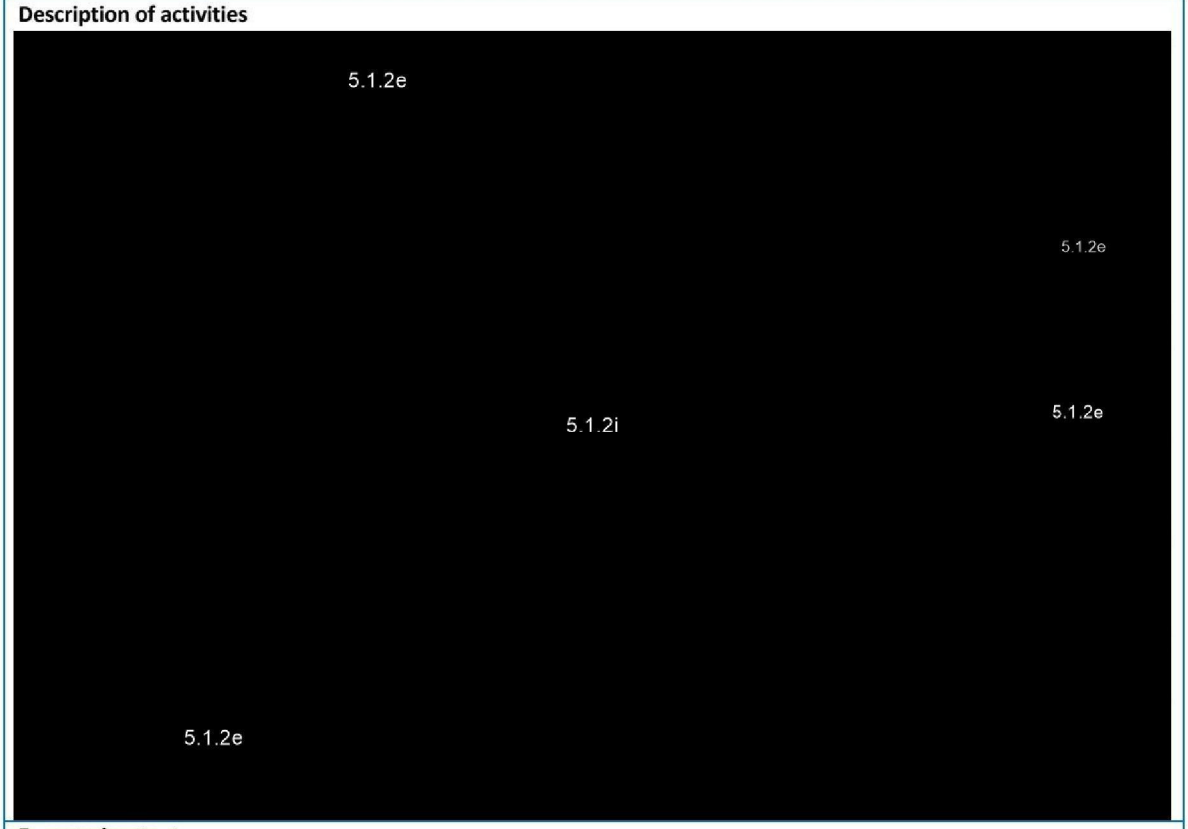
2.2.1 To identify critical physiological pathways and mechanisms in chronic kidney disease originating from drug-induced kidney injury;

2.2.2 To develop the AOP networks of chronic kidney disease focusing on mechanisms related to drug-induced kidney injury;

2.2.3 To test the toxicity and dose response relationships of selected drugs in advanced *in vitro* models following human relevant exposure;

2.2.4 To assess the safety of selected drugs with respect to chronic kidney disease in humans using the VHP.

Description of activities



Expected output

Work package number	2.3.
Work package title	Life course exposure: Case study neurodegenerative disease and life course exposure to chemicals
Work package leader	5.1.2e
Involved partners	5.1.2e
Start date	Month 1
End date	Month 60

Objectives

2.3.1 To identify critical biological, physiological processes in relation to Parkinson's disease;

2.3.2 To model the life course exposure in human populations;

2.3.3 To develop descriptive AOP networks of Parkinson's disease;

2.3.4 To determine the toxicity and dose response relationships in advanced *in vitro* models;

2.3.5 To assess the safety in relation to human life course exposure and development of Parkinson's disease.

Description of activities

5.1.2e

5.1.2e

5.1.2e

5.1.2i

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	2.4.
Work package title	Age and gender specific safety: Case study Thyroid mediated developmental neurotoxicity
Work package leader	5.1.2e
Involved partners	5.1.2e
Start date	Month 1
End date	Month 60

Objectives

2.4.1. To collect existing mechanistic physiological data;

2.4.2. To determine critical physiological pathways and mechanisms in normal biology of thyroid homeostasis and its role in development of the central nervous system based on the available and new data;

2.4.3. To establish a quantitative AOP network;

2.4.4. To identify age and gender specific sensitivities of compound effects on key events in the qAOP network;

2.4.5. To identify compound induced thyroid disruption and related effects in human advanced *in vitro* models, discriminated by age and gender.

2.4.6. To assess the safety of compound exposure in relation to age and gender and thyroid disruption.

Description of activities

5.1.2e

5.1.2e

5.1.2e

5.1.2i

5.1.2e

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	3.1.
Work package title	Technology Assessment of VHP
Work package leader	5.1.2e
Involved partners	5.1.2e CRL, Galapagos, Bayer, ORTEC, Unilever, KWR, hDMT, VIG
Start date	Month 0
End date	Month 60

Objectives:

3.1.1. To perform state-of-the art technology assessment (TA) to align the work;

3.1.2. To empirically study the initiation, development and implementation of VHP as an innovation journey;

3.1.3. To analyse and actively influence event sequences in the innovation journey;

3.1.4. To specify performance criteria for VHP.

Description of activities

5.1.2e

5.1.2e

5.1.2i

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	3.2.
Work package title	Acceptance of VHP for safety assessment
Work package leader	5.1.2e
Involved partners	5.1.2e 5.1.2e Brandwondenstichting, CRL, Ministerie LNV, Unilever, Shell, KWR, Cosmetics Europe, CBG, hDMT, VIG
Start date	M0
End date	M60

Objectives:

3.2.1. To position VHP in the transition to animal-free safety assessmen;

3.2.2. To raise awareness for the use of VHP as an automated decision-making support tool;

3.2.3. To investigate uncertainties of elements within the VHP;

3.2.4. To investigate acceptance of safety assessment output of the VHP for the different scenario's.

Description of activities

5.1.2e

5.1.2e

5.1.2i

5.1.2e

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	3.3.
Work package title	Training and Education
Work package leader	5.1.2e
Involved partners	5.1.2e RIVM, CBG, 5.1.2e, Shell, Cosmetic Europe, DTL, SURFSara
Start date	Month 0
End date	Month 60

Objectives:

3.3.1. To promote interdisciplinary collaboration between scientific disciplines within the consortium;

3.3.2. To facilitate transferability of advanced *in vitro* methods, as well as *in silico* tools;

3.3.3. Implementing new teaching/learning modules (bachelor, master, PhD, postdoc);

3.3.4. To promote capacity building and awareness of stakeholders towards use, acceptance and implementation of VHP;

3.3.5. To improve professional skills regarding risk communication.

Description of activities

5.1.2e

5.1.2e

5.1.2e

5.1.2i

5.1.2e

5.1.2e

Expected output

5.1.2i

Work package number	4
Work package title	Project Coordination, Impact and Data Management
Work package leader	5.1.2e
Involved partners	5.1.2e
Start date	0
End date	60

Objectives:

4.1. To ensure that the project objectives are achieved and to make sure that the deliverables are completed according to the allocated time and budget;

4.2. To manage the overall knowledge utilisation of the project, including communication, dissemination and impact;

4.3. To provide effective and sustainable data management.

5.1.2e

5.1.2i

5.1.2e

5.1.2e

Expected output

5.1.2i

4.3 TIMELINE AND MILESTONES

Figure 5: GANTT chart of the project

Depicted is the time schedule of the tasks as described in the work packages. The different colors represent the different research lines, research line 1 (blue), research line 2 (green), research line 3 (yellow). Project management, impact management and data management (WP4) will be a continuous task during the whole project. Besides deliverables, milestones (M1-5) are depicted.

During the project several **milestones (M)** are defined. All milestones are important achievements during the project that will be used to monitor progress.

- **M1** is reached when all partners signed the consortium agreements, all personnel is hired and the kick off has taken place.
- **M2** is reached when the first version of the VHP is operational and data can used in the platform and evaluation can start.
- **M3** is the implementation of new and existing data, PBK and QIVIVE modelling and qAOP in the VHP. This innovative integration of data and computational tools using artificial intelligence, machine learning, in the VHP is tested and evaluated.
- At **M4** final adjustments to VHP can be made and a final test VHP in safety testing has taken place. At this point also the first VHP training for stakeholders outside the project takes place.
- At **M5** the international launch of VHP will take place at the final symposium and represents the final output of the project.

4.4 RISK ASSESSMENT

Table 11: Risk assessment and action to mitigate risks.

#	WP	DESCRIPTION	HOW TO MITIGATE?
1	all	[redacted]	[redacted]
2	all		
3	all		
4	1.1		
5	2.2-2.5		
6	2.2-2.5	5.1.2i	5.1.2i
7	3.2		
8	1.1-3.2		
9	3.1-3.2		
10	3.1-3.3		
11	4		

4.5 MANAGEMENT STRUCTURE

4.5.1 GENERAL

The VHP consortium comprises a diverse group of parties, including co-applicants, co-funders and cooperation partners, who will collectively undertake a complex programme of innovation. A comprehensive project management structure and the implementation of specific procedures will grant effective and optimised collaboration. The overall management objective of WP 4 is to provide both strategic and operational management, ensuring the successful completion of the project within the timescales and resources provided. The formal project management procedures will be finalised and implemented at the start of the project. The management structure is given (*Figure 6*)

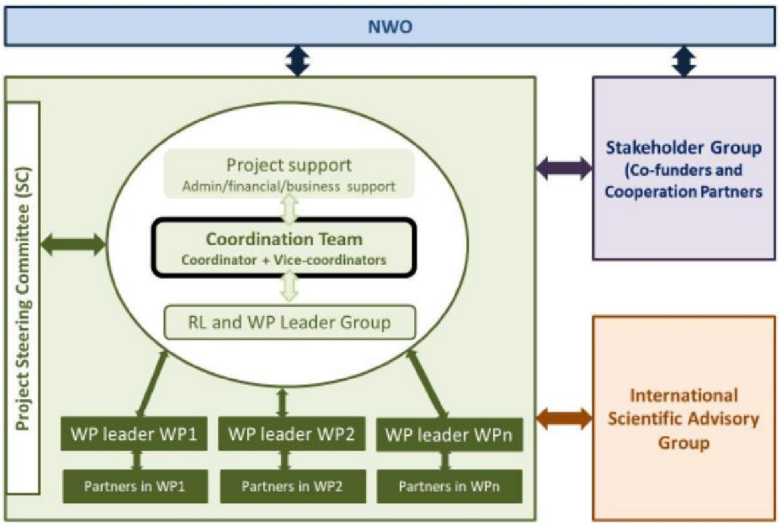


Figure 6: Management structure of the VHP project

The VHP project will have three core management groups: The Project Steering Committee (SC), the Coordination Team (CT) and the Research Line/Work Package Leader Group.

4.5.2 PROJECT STEERING COMMITTEE (SC)

Role: With overall responsibility for the project, the SC will be the main decision-making body. The SC will ensure governance and overall cohesion and quality of the project, and has the following responsibilities:

- Review the project's overall progress and identify, review and propose solutions to any project risks
- Review and agree any changes to the Consortium Agreement; entry of a new partner; exit of an existing partner; change in budget;
- Oversee compliance to the Consortium Agreement;
- Meet with, and consider advice from, the Stakeholder Group (see below)

Leadership: The coordinator will act as chair. 5.1.2e

5.1.2e

Members: The SC will include one representative from each co-applicant. When the SC is required to make decisions, each member will have one vote.

4.5.3 COORDINATION TEAM (CT)

Role: The CT consists of the Project Coordinator (PC), the Vice-Coordinator for Science (VC-Science) and Vice-Coordinator for Impact (VC-Impact). The PC will be the single point of contact between the project and NWO. The PC will have overall responsibility for monitoring project progress and compliance including:

- Finalising and implementing the Project Management Structure;
- Developing and implementing, with partner agreement, management procedures to monitor the overall project performance in terms of budget, tasks, deliverables, milestones, quality, risks and reporting, to ensure any underperformance or issues are promptly addressed;
- Preparing and circulating regular internal project communications.

The VC-Science oversees the scientific progress of the project and chairs the RL/WP leader group meetings. She is responsible for overseeing the input from the International Scientific Advisory Group.

The VC-Impact oversees knowledge utilization and stakeholder participation and chairs the Stakeholder Group meetings.

Leadership: The PC role will be undertaken by 5.1.2e The VC-Science role will be undertaken by 5.1.2e 5.1.2e. The VC-Impact role will be undertaken by 5.1.2e The CT will be supported by a project support team. UU and HU will hire a project manager at 0.3 FTE for the duration of the project to assist in daily management of the project. UU will also provide administrative, financial, communication and IP/business development support.

4.5.4 Research Line and Work Package Leader Group

Role: Each RL leader is responsible for overseeing the work within his/her research line, which is made up of 3-4 WPs. The WP Leader will be responsible for coordinating the partners in their WPs to achieve the tasks and deliverables within the timescales and resources available. RL and WP leaders will regularly communicate with each other regarding the project's technical and societal implementation, and each Leader will ensure their WP is successfully aligned with (and links to) other WP. The Leaders will also report WP progress to the CT as required.
Leadership: The Chair will be the VC-Science.
Members: RL leaders and one named Leader from each Work Package.

4.5.5 Stakeholder Group (SG)

Role: SG provides input and advice on the overall project strategy and specific tasks regarding the design of the VHP and the implementation. It advises on optimal knowledge utilisation and guidance how to best translate and implement VHP.
Leadership: The Chair will be the VC-Impact.
Members: Representative of the co-funders and cooperation partners. External stakeholders may also be invited.

4.5.6 International Scientific Advisory Group (SAG)

Role: The SAG will provide advice and experience in order to support the SC during the project in terms of expert input as regards the scientific goals and strategy of the project, the scientific progress during the project and the scientific quality of the results. They will be informed of all progresses and deliverables, and their (written) comments and feedback will be incorporated in the Work Plan.
Leadership: The SAG will be chaired by the VC-Science.
Members: The SAG consists of world-renowned experts in the field of human and virtual models. A number of experts have already agreed to participate in SAG once the project is granted: 5.1.2e 5.1.2e

4.5.7 Management Procedures

The VHP consortium will develop, agree and implement project management procedures to monitor regularly the overall project performance in terms of budget, tasks, deliverables, quality, risks and reporting, to ensure any underperformance or issues are promptly addressed.

Procedures will be clarified in the **Project Work Plan –** a project plan developed at the start of the project and reviewed and updated annually. The plan will clarify to each partner their required tasks, resources, deliverables and milestones for that year of the project. A key focus of the plan will be to ensure any Work Package interdependencies are considered to help prevent any issues arising, and ensure all partners have a very clear understanding of their own role in relation to others and project progress. Ethical documentation and applications, and data transfer agreements will be reported in this plan and revised annually if necessary. The SC will ensure that this plan is implemented, and support partners to resolve any technical and financial issues.

4.5.8 Consortium Governance

A **Consortium Agreement** will be signed by all co-applicants at the commencement of the project. This Consortium Agreement will be in line with this proposal and will formally outline partner responsibilities; liabilities towards each other; how partners will address ownership and dissemination of project results; governance structures; financial provisions; and conflict resolution. The SC will oversee compliance with this agreement.

Table 12: Meeting Type and Frequency

MEETING	FREQUENCY	FORMAT
VHP Consortium Meeting	Annual	Two-day event which will incorporate parallel meetings (e.g. Steering Committee, WP leaders, SAG)
Project Steering Committee	Annual	Within Consortium meeting
Coordination team (CT)	At least once per month	Face2Face or Teleconferences
RL and WP Leader Group	Quarterly	Within Consortium meeting and virtual (teleconferences/skype)
Stakeholder Group	Annual meetings and/or thematic meetings	Half to one day event added on to the Consortium meeting
Scientific Advisory Group	Annual or ad hoc at request of the WP leaders	Concurrent with the Consortium meeting

4.6 JUSTIFICATION OF PROJECT BUDGET

The total budget of this project is 5.1.2b,5.1.2f is contributed by our co-funding and cooperation partners. The subsidy requested from NWO is 5.1.2b,5.1.2f The breakdown of requested subsidy is: VSNU (universities): 5.1.2b,5.1.2f NFU (academic hospitals): 5.1.2b,5.1.2f ; and other organisations including applied science organisations (5.1.2b,5.1.2f and governmental institutions (RIVM: 5.1.2b,5.1.2f .

The **personnel costs** of the project are 5.1.2b,5.1.2f The breakdown of (scientific) staff per organization is shown in table 13 below. The number of cofounding partners and cooperation partners per work package is also shown below. Although we are using the NWO subsidiary mainly for hiring Post-docs and PhDs in research lines 1 and 2, the number of personnel is balanced between the different research lines by the large contribution of the co-funders and cooperation partners in research line 3. A portion of the personnel costs of UM, RIVM and HU will be used to hire staff (system administrators, technicians) to provide technical IT support to the whole consortium (see section 5.1.4).

A total of 23,3 FTE will be working on the project on the budget requested. Bench fee costs 5.1.2b,5.1.2 have been reserved for the stimulation of the scientific career of the PhD and postdoctoral researchers (see section 4.5).

Table 13: Distribution of personnel (FTE) per partner, per WP and the distribution of the co-funders and cooperation partners.

Partner/WP	WP 1.1	WP 1.2	WP 1.3	WP 2.1	WP 2.2	WP 2.3	WP 2.4	WP 3.1	WP 3.2	WP 3.3	Total
Erasmus MC							**0,5**				**0,5**
Postdoc							0,5				0,5
HU	**0,6**			**1,7**						**0,7**	**3**
Analist				1							1
Postdoc	0,6			0,7						0,7	2
UL			**2**								**2**
PhD			2								2
RIVM	**1**					**1**	**1**				**3**
PhD	1					1	1				3
TNO			**1**								**1**
Postdoc			1								1
UM	**2**	**1**									**3**
PhD	1										1
Postdoc	1	1									2
UMCU					**1**						**1**
PhD					1						1
UU-Copernicus								**1**	**1**		**2**
PhD								1			1
Postdoc									1		1
UU-IRAS		**0,8**		**1,75**		**0,75**					**3,3**
Analist				0,75							0,75
PhD				1		0,25					1,25
Postdoc		0,8				0,5					1,3
UU-UIPS					**1**						**1**
Postdoc					1						1
VU			**0,5**	**1**							**1,5**
PhD				1							1
Postdoc			0,5								0,5
VUMC				**1**							**1**
PhD				1							1
WUR		**0,5**	**0,5**								**1**
PhD		0,5	0,5								1
Total FTE	**3,6**	**2,3**	**4**	**5,45**	**2**	**1,75**	**1,5**	**1**	**1**	**0,7**	**23,3**
number of cofunding and cooperation partners in WP	5	3	1	5	1	1	2	13	8	3	

5.1.2b,5.1.2f

[redacted]

[redacted]

[redacted]

5 DATA MANAGEMENT AND ETHICAL ASPECTS

5.1 DATA MANAGEMENT

- A Data Management Plan (DMP) will be developed using the DMP online tool of the Utrecht University (https://www.uu.nl/en/research/research-data-management/tools-services/tool-to-create-your-dmp-online). This will ensure traceability of data sources used, ability to reuse the data and will enforce accurate and standardized meta data annotation of all data collected and generated in the project. The DMP will also provide guidelines and a style sheet for computer code that will be produced during the project. To stimulate collaboration and to enable compliance to the DMP by all partners involved an iRODS instance will initiated by SURF. This platform will be continued to serve as the collective data management system during the project. Curated datasets and code will be properly annotated and archived. iRODS also enables the creation of computational pipelines which will be integrated in the project's data workflow. All researchers in the project that will work with the DMP systems will be trained during hands-on workshop at the start of the project (WP3.3).
- To ensure alignment of the data-management workflow and the computational work in the rest of the project all data, source code and metadata will be put under version control. This will ensure that data used in the VHP platform will be traceable to the individual data-point level. All datasets used in this project will be accompanied by a digital object (DOI) and a licence, provisioned by the iRODS DMP system. All data used in this project will be made FAIR as explained below.
- The coordination team assisted by the DMP team (5.1.2e 5.1.2e will be in charge of drafting and implementing the DMP. Furthermore, the DMP team will coordinate the training workshops and provide further help in using the DMP system. Through our collaboration partner DTL we will also organize a workshop for associated project teams, with supported access to the Data Stewardship Wizard developed in ELIXIR, to assist in further detailing the project DMP and data access governance.
- The DMP will be updated over the course of the project with every periodic evaluation of the project or whenever significant changes required updating, such as changes in consortium policies or composition (WP4).

5.1.1 REUSE OF DATA

Data collected during this project will be derived mostly from public databases. Some publicly accessible databases must have a licence agreement in place, before data is allowed to be reused in the project and beyond. For those data-sources we will make arrangements for suitable reuse of the data after the project is finished. For data and tools that fall under a publication embargo, as described in the consortium agreement, an embargo period as short as possible will be applicable. Data and tools in this category will be made available after the embargo has been lifted. Curated and reused data will be made available through appropriate data repositories. Furthermore, data can be made available as stand-alone data packages for commonly used Data Science programming languages such as R and Python.

5.1.2 STORAGE OF DATA

All data collected during the project that is newly generated or data from public datastores that need to be stored for performance purposes will be stored in a central data-ware house. Terms of storage for data from third parties will be arranged in the licence-agreements, when applicable. The partner that will be responsible for setting up the data warehouse is ORTEC. To ensure data governance, traceability and reproducibility an ETL (Extract, Transform and Load) system will be put in place.

5.1.3 DATA AFTER THE PROJECT

To ensure the project's legacy is available for future users, the VHP as a whole will be governed and continued in alliance with 5.1.2i (to be established during the project, see WP4). A VHP foundation will be established to address legal, licensing, quality issues as is common in the Open Source Software community (e.g. European ELIXIR infrastructure (https://elixir-europe.org). We envision the VHP foundation to ensure accessibility of the platform by:

- Provide a reference point for individuals, institutions or commercial enterprises that want to support or interact with the VHP development community.
- Hold and administer the copyright of the VHP software, IP (if any) and documentation.
- Maintain (or delegate) the official repository for the deposition of the VHP software and guarantee the quality of add-ons through an online review process (quality control).
- Supporting research in the further development of VHP.
- Harmonizing and empowering other initiatives regarding *in silico* prediction of safety of chemicals with VHP.

Governance by the VHP foundation will ensure availability of the software, innovation and the possibility to extend and build-upon existing VHP. It will be part of the VHP project to assess and formulate the specifics on how the exact structure will be (WP4 and utilization plan).

We aim to work with standardized release terms of software, updating it as we move through the project and under governance of the VHP Association, after the project is finished. An agile workflow implementing short sprints to the next release will enforce regular updates on functionality and stability of the software.

- **All data in the VHP project will be made FAIR:** The data contained within the project will be made to adhere to the FAIR principles. This means that:
- **Data will be made Findable** by assigning a DOI and a licence to each dataset, code(packages) and workflow collected or created in the project. This is provisioned by including iRODS in the data-management workflow of the project. Ontologies (standardized vocabulary in biology and toxicology) will be used as well as most commonly used identifiers (Uniprot for proteins, SMILES, INCHI(keys) or CHEBI for molecules). Datasets and related metadata may undergo curation and modifications. To ensure traceability of these changes a versioning system (Git) will be used and set up. Developers and computational experts of the VHP team will be provided with access to the repositories. If applicable they will receive training on how to collaborate with Git (see WP3.3 Education & training). Furthermore, to keep track of (pre)processing and curation, code that is used to achieve this will be stored alongside the data.
- **Data will be made Accessible** by using public repositories as much as possible to grant public access to the data (e.g. Gene Expression Omnibus for transcriptomics data). Open Source software policy (GNU-GPL like) will be used according to the licencing of the libraries/packages used and will be deposited in Git repositories. Newly developed software and data packages will be accompanied by GNU-GPL like licence as well.
- **Data will be made Interoperable** by storing data and metadata as much as possible in dedicated and computer readable formats (e.g. ISA-tab or dedicated XML formats). By defining data protocol documents where all required standards, vocabularies and metadata are defined. Workflow systems (KNIME, Galaxy, Docker) will be used within the consortium since they allow an enhance reproducibility in science.
- **Data Reusability** will also be a central objective. Along with the data, workflows and ETL tools as well as artificial intelligence, machine learning implementations and trained models will be made available as a set of Docker container images in a repository (e.g. Docker Hub). Code produced during the project will be assembled in libraries (Python) or packages (R) as much as possible to increase the legacy of the project. Curated and annotated datasets will be deposited in appropriate repositories (e.g. DANS, GEO, etc.).

5.1.4 NEEDED FACILITIES

A **dedicated budget** will be reserved in WP4 to ensure data storage and open access policy (e.g. for journals). This budget will also be dedicated to hiring cloud computing infrastructure and web server hosting. ICT system administrators (2 FTE) will be hired for the project. **Data security and transparency** will be set up in the first 3 months and audited during the project to gather all the information provided by the research groups and list down in the Data Management Plan (month 6).

Figure 7: Concept scheme ICT infrastructure of the VHP.

5.2 ETHICAL ASPECTS

Table 14: Ethics in the VHP project

	NOT APPLICABLE	NOT YET APPLIED FOR	APPLIED FOR	RECEIVED
Approval from a recognised (medical) ethics review committee	☐	☒	☐	☐
Approval from an animal experiments committee	☒	☐	☐	☐
Permission for research with the population screening Act	☒	☐	☐	☐

The VHP project will conduct a series of investigations that include data from human studies, *in vitro* studies with human cell systems, induced pluripotent stem cells (iPSCs) and organoids. Therefore, the ethical issues that relate to these studies will be carefully evaluated by an ethics committee that will be coordinated by WP4 (Coordination, Impact and Data Management). The VHP partners will follow all relevant National and EU legislations relating to the conduct of human studies (I), the study and handling of biological materials (II), the management of data to protect privacy and maintain confidentiality (III). The following national and international legislations and guidelines will be followed:

5.2.1 KEY EU LEGISLATIONS FOR RESEARCH ON HUMANS

- ICH GCP International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Good Clinical Practice Guidelines;
- CIOMS: International Guidelines for Ethical Review of Epidemiological Studies (2009);
- CIOMS: International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002);
- WMA: Declaration of Helsinki (2008);
- UNESCO: Universal Declaration on Bioethics and Human Rights (2005);
- CCMO: Medical Research Involving Human Subjects Act (WMO).

5.2.2 KEY EU LEGISLATIONS FOR HUMAN TISSUE USE

- Federa: Human Tissue and Medical Research: Code of Conduct for responsible use (code Goed Gebruik) (2011);
- EC: Directive 2004/23/EC on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage, and Distribution of Human Tissues and Cells;
- WHO: Guideline for Obtaining Informed Consent for the Procurement and Use of Human Tissues, Cells, and Fluids in Research (2003);
- ITA: Infectious Substances and Diagnostic Specimens Shipping Guidelines (2005);
- ISBER: Best Practices for Repositories I: Collection, Storage and Retrieval of Human Biological Materials for Research (2005);
- EC: Good Cell Culture Practice guidance (2011).

5.2.3 KEY EU LEGISLATIONS FOR HUMAN DATA USE

- General Data Protection Regulation Directive 2016/679/EC of the European Parliament and of the Council (2016);
- Netherlands Code of Conduct for Research Integrity –NOW-VSNU-VH (2018);
- Declaration on Ethical Considerations Regarding Health Databases (2002).

5.2.4 ETHICS COMMITTEE

The project will obtain Ethics Committee approval for all activities involving human biomaterials and comply with all National and international (European) related guidelines. Each partner signing the consortium agreement has the responsibility to adhere to the legislation outlined in the agreement.
Compliance to ethics regulations will be secured by the following actions:

- Work package leaders will be responsible to ensure that all partners conducting research in their WP comply with the relevant guidelines and any specific Standard Operating Procedures generated by the VHP consortium. Any concerns will be discussed within the project steering committee.
- The Ethics Committee will be consulted as required for advice, and will support partners, by providing advice on ethical use of human samples and/or data and conduct studies. The Ethics Committee will conduct regular reviews of all studies to ensure that partners have remained in compliance with EU and national legislation.

6 OTHER

6.1 PUBLIC SUMMARY

6.1.1 ENGLISH SUMMARY

Through co-creation with stakeholders, we will develop the world's first Virtual Human Platform to determine the safety of chemicals and pharmaceuticals for human health based solely on human biology. By integrating innovations in data science, human tissue culture models and transition management, we will spearhead the transition to animal-free safety assessment.

6.1.2 DUTCH SUMMARY

In co-creatie met stakeholders ontwikkelen wij 's werelds eerste Virtual Human Platform voor de beoordeling van de veiligheid van chemicaliën en geneesmiddelen, uitsluitend op basis van de biologie van de mens. Door innovaties in datawetenschappen, menselijke weefselkweekmodellen en transitiemanagement te integreren, brengen we de transitie naar proefdiervrije veiligheidsbeoordeling in een stroomversnelling.

6.2 SIGNATURE

☒ By submitting this form, I declare that I satisfy the nationally and internationally accepted standards for scientific conduct as stated in the Netherlands Code of Conduct for Research Integrity (Association of Universities in the Netherlands).

Main applicant: 5.1.2e
Place : Utrecht
Date: 30 January 2020

Signature: 5.1.2e

6.3 LITERATURE REFERENCES

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Annex 3
Grant Award Decision and total budget of the Project, in-cash and in-kind contributions

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Date 19 December 2020
File no. NWA.1292.19.272
Corresp.no. 2020/NWA/00992784
Budget no. 11656
Please include date, file number and correspondence number in any reply

Phone +31 (0)70 - 5.1.2e
Email nwa-projectbeheer@nwo.nl

Subject Grant award NWA-ORC 2019

Dear 5.1.2e

With reference to the correspondence in which I informed you, on behalf of the NWO Executive board, of the granting of your NWA-ORC 2019 application titled: 'The Virtual Human Platform for Safety Assessment' (file number NWA.1292.19.272), it is my pleasure to award the grant under the terms and conditions set out in this letter.

The maximum amount granted by NWO for this project is 5.1.2b,5.1.2f corresponding with the amount you requested in your (corrected) budget (financial overview, see appendix 1). The in-kind and cash cofunding of your partner(s) amounts to respectively 5.1.2b,5.1.2f corresponding with the (corrected) budget and letters of support. Payment of the cash cofunding runs via NWO. The total amount paid to you bij NWO is therefore 5.1.2b,5.1.2f. This amount will be paid annualy by NWO according to the instalments as identified in the start form (see appendix 2).

The project should start no later than 19 June, 2021. The maximum duration of your project is 5 years.

What are the conditions?
The granting of your project is subject to a number of obligations and conditions. Please note that The Dutch General Administrative Law Act, the NWO Grant Rules 2017 (www.nwo.nl/grantrules) as well as the call for proposals NWA-ORC 2019 apply to this grant. Also, the cash contribution committed by Stichting dierproefvrij, Unilever, Nierstichting, Brandwondenstichting, Charles River and Galapagos should be paid.

In particular, I draw your attention to the fact that project cannot start until a number of specific conditions have been met and NWO has received the following documents (via your ISAAC account):

A. A completed and signed start form (appendix 2) indicating when your research project will start. This form also includes payment instalments of the grant by NWO. Your project must start within six months after

the awarding of the grant. By signing the start form you indicate that you accept the grant under the conditions mentioned above.

B. A completed data management plan in which you inform NWO of your data management plans for the project. You can download the data plan format from the NWO website: (https://www.nwo.nl/en/research-data-management).
C. The written confirmations of the committed cash contributions of the co-financiers (a format will be sent to you by email).
D. A signed consortium agreement. A format for this can be downloaded via ISAAC, on the tab 'project forms'.

The above mentioned documents should be submitted to NWO within six months after the awarding of the grant. You submit the documents via ISAAC, in the tab page 'project documents. If you do not meet the above mentioned conditions, the grant may be withdrawn.

After NWO has approved your starting documents, you need to add the complete information of the project member(s) involved in your project in ISAAC.

With regard to the administrative side of the project we advise you to contact the administrator of your institution and possibly delegate certain powers to him or her. You will find the instructions and the authorisation form on the NWO website: https://www.nwo.nl/en/news/new-isaac-authorisation-scheme-project-managers. The final responsibility for the project and the grant remains with you.

Project Management

On the side of NWO, the management of your project is taken care of by the NWA program agency. For further information you can contact us by emailing nwa-projectbeheer@nwo.nl (please state your project number) or by telephone via 070 – 344 07 54. (Change) requests can be submitted via your account in ISAAC.

Additional requirements and points of action in the context of the NWA-ORC program

Your project is awarded within the NWA-ORC program. This results in a number of additional conditions and action points.

- Attending the kick-off meeting of the program on **March 5**, 2021 (see below).
- A startup meeting between NWO and the project leader.
- Setting up an advisory committee.
- Jointly drawing up an impact plan
- Organizing a kick-off meeting of the project.

More information can be found in the concise 'stappenplan na honorering' in appendix 3. Please note that the activities do not necessarily take place in the order mentioned.

Kick-off meeting

I would like to announce that NWO is organizing a kick-off meeting on **March 5, 2021** for the project leaders of the awarded NWA-ORC 2019 projects. During this meeting we will inform you about, among other things, how the substantive monitoring and supervision of the projects will take place, as well as the annual reporting obligations. Your presence at this meeting is mandatory. You will soon receive more information about the location and the program.

Open Access
The Dutch government has set the target that by 2020 100% of scientific publications financed with public funds will be open access. All publications that partly result from research funded by NWO must therefore be made available in Open Access immediately upon publication. NWO does not accept embargo terms in this respect. Publications include both (peer-reviewed) articles and books (monographs, edited volumes, proceedings and chapters). There are different routes to comply with NWO's Open Access policy:

1) Publication in a full gold Open Access journal. Journals must in that case be registered in the Directory of Open Access Journals (DOAJ) (https://doaj.org/).
2) Publication in a hybrid journal.
3) Deposit of a version of the article in a repository. In that case it must be registered in the Directory of Open Access Repositories (http://v2.sherpa.ac.uk/opendoar/).

NWO will only reimburse publication costs for full gold open access journals. For hybrid journals the VSNU has agreements with many of the major publishers that enable researchers affiliated with Dutch universities to do so at no extra cost. For an overview of these agreements see www.openaccess.nl.
More information and further conditions can be found at: www.nwo.nl/openscience.

Integrity
The NWO Grant Rules 2017 specify that research funded by NWO must be carried out in accordance with nationally and internationally accepted standards of scientific conduct as laid down in the Netherlands Code of Conduct for Research Integrity (2018). In the event of a (possible) breach of the above-mentioned standards in research funded by NWO, the applicant must inform NWO immediately and submit all relevant documents to NWO. More information about the NWO code of conduct and policy on research integrity can be found on the website: www.nwo.nl/integrity.

I wish you every success in carrying out your research.

On behalf of the board of directors of the Dutch Research Council (NWO),

Your sincerely,

prof. dr. C.C.A.M. Gielen
Chair of the NWO Executive board

Appendices:

1. Financial overview
2. Start form
3. Stappenplan na honorering (only available in Dutch)

You have the right to lodge an objection to this decision within six weeks of the date of the decision letter. Your objection should be sent in writing or by mail to the NWO Executive Board, P.O. Box 93138, 2509 AC The Hague. It must be signed and dated, must specify your name and address, and must state the reasons why you object to the decision. A copy of this decision letter should be enclosed with your written objection. Further information about the objections procedure can be found on the NWO website.

You can also file your objection digitally. To do so, you can only use the email address that is provided by NWO for this: bezwaar@nwo.nl. Your digital objection must satisfy the same requirements as a written objection. Make sure that you scan your written objection or add a scanned signature in your objection.

Dossiernr. NWA.1292.19.272
Corresp.nr. 2020/NWA/00992784

Appendix 1: financial overview[1]

Project : NWA.1292.19.272
Main applicant : 5.1.2e
Title : The Virtual Human Platform for Safety Assessment
Budget number : 11656

Grant awarded by NWO

The maximum amount granted for this project is 5.1.2b,5.1.2f 5.1.2b,5.1.2f The maximum amount granted by NWO is 5.1.2b,5.1.2f
The total financial contribution is 5.1.2b,5.1.2f and is divided over the following items[2]

Personnel[3]

category	fte	months	Benchfee[4]	amount
VSNU PhD/PDEng/MD PhD	1	48		
VSNU PhD/PDEng/MD PhD	1	48		
VSNU PhD/PDEng/MD PhD	1	48		
NFU PhD/PDEng/MD/PhD	1	48		
VSNU PhD/PDEng/MD PhD	1	48		
VSNU PhD/PDEng/MD PhD	1	48		
VSNU PhD/PDEng/MD PhD	1	48		
VSNU PhD/PDEng/MD PhD	0,25	48		
NFU PhD/PDEng/MD/PhD	1	48	5.1.2b,5.1.2f	5.1.2b,5.1.2f
VSNU PhD/PDEng/MD PhD	1	48		
VSNU Non-scientific personnel (HBO)	0,75	60		
NFU Postdoc	0,5	36		
VSNU Postdoc	1	48		
VSNU Postdoc	1	48		
VSNU Postdoc	1	48		
VSNU Postdoc	0,8	60		
VSNU Postdoc	1	48		
VSNU Postdoc	0,5	48		
VSNU Postdoc	0,5	28		

VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
VSNU Research leave	1	5		
NFU Research leave	1	5		
NFU Research leave	1	5		
NFU Research leave	1	5		
Subtotal				

category	hours	hour rate	amount
Medior researcher PD-level	6100		
Supporting staff NWP HBO	6100		
Medior researcher PhD-level	14640		
Medior researcher Postdoc-level	6600		
Medior researcher Postdoc-level	6100		
Subtotal Personnel			

Material costs[3]

category	amount
Project related goods/services	
Implementation costs	
Subtotal material costs	

Other costs[3]

description	amount
Knowledge utilisayion	
Entrepreneurship	
Internationalisation	
Subtotal other costs	

Projectmanagement[3]

description	amount	
Progress reports, large meetings, monitoring progress	5.1.2b,5.1.2f	
Subtotal projectmanagement		5.1.2b,5.1.2f
TOTAL		5.1.2b,5.1.2f

Co-funding

organisation	type co-funding	amount
ORTEC	In kind	5.1.2b,5.1.2f
ORTEC	In kind	
ORTEC	In kind	
Unilever	In kind	
Cosmetics Europe	In kind	
Cosmetics Europe	In kind	
Cosmetics Europe	In kind	
Bayer	In kind	
Shell	In kind	
Shell	In kind	
Shell	In kind	
Min LNV	In kind	
Min LNV	In kind	
Min LNV	In kind	
Min LNV	In kind	
Brandwondenstichting	In kind	
VIG	In kind	
VIG	In kind	
KWR	In kind	
KWR	In kind	
KWR	In kind	
Charles River	In kind	
Charles River	In kind	
Certara	In kind	
Stichting dierproefvrij	In cash	
Unilever	In cash	
Nierstichting	In cash	
Nierstichting	In cash	

Brandwondenstichting	In cash	5.1.2b,5.1.2f	
Charles River	In cash		
Galapagos	In cash		
Subtotal co-funding			5.1.2b,5.1.2f

1 In principle, NWO pays the allocated project budget in (annual) tranches (see start form). The first instalment is paid when the conditions set out in this letter have been met. You will receive the final instalment upon receipt and approval of the final report and financial statements.
2 Any substantial deviation or change to the project plan and/or budget requires NWO's prior approval. You can submit a request through ISAAC or contact your contact person.
3 The amounts for personnel and credits include cash contributions from third parties. PPP projects can only start after receipt of the first tranche of the money from third parties. Full availability of these budgets is only possible when NWO has received the full amount from third parties mentioned under 'Co-funding' on the project budget (where applicable). For this reason, the amounts in the case of co-financing 'in cash' are shown negatively. If the private partner/party does not, or not fully, meet its financial obligation, this may have consequences for the amount of the grant when the grant is determined.
4 The personal bench fee is intended for the project employees to be appointed, intended to stimulate their scientific career. The bench fee can be used to defray inter alia expenses for taking a doctorate and visits to conferences (including foreign ones).
5 The personnel component of the grant has been determined in accordance with the VSNU salary table as of July 1, 2020, NFU salary tables as of January 1, 2020 and the HOT tables 2017.

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Appendix 2: Start form

Please fill in all fields and upload the start form via your account at www.isaac.nwo.nl

File number: NWA.1292.19.272	Budget number: 11656
Name [redacted]	
Organization: University Utrecht	
Department: Faculty Veterinary Medicine	
Start date project: 01 June 2021	
End date project: 01 June 2026	

Payment instalment: duration project is 5 years.

Total		[redacted]	Percentage
Per start date	**Instalment 1**		20%
1 year after start	**Instalment 2**		15%
2 years after start	**Instalment 3**		15%
3 years after start	**Instalment 4**		15%
4 years after start	**Instalment 5**		20%
After financial and scientific completion	**Last instalment**		15%

IBAN: NL02 ABNA 0461 8692 25	
Name account holder: Universiteit Utrecht	
Payment reference: DR.530004.1	

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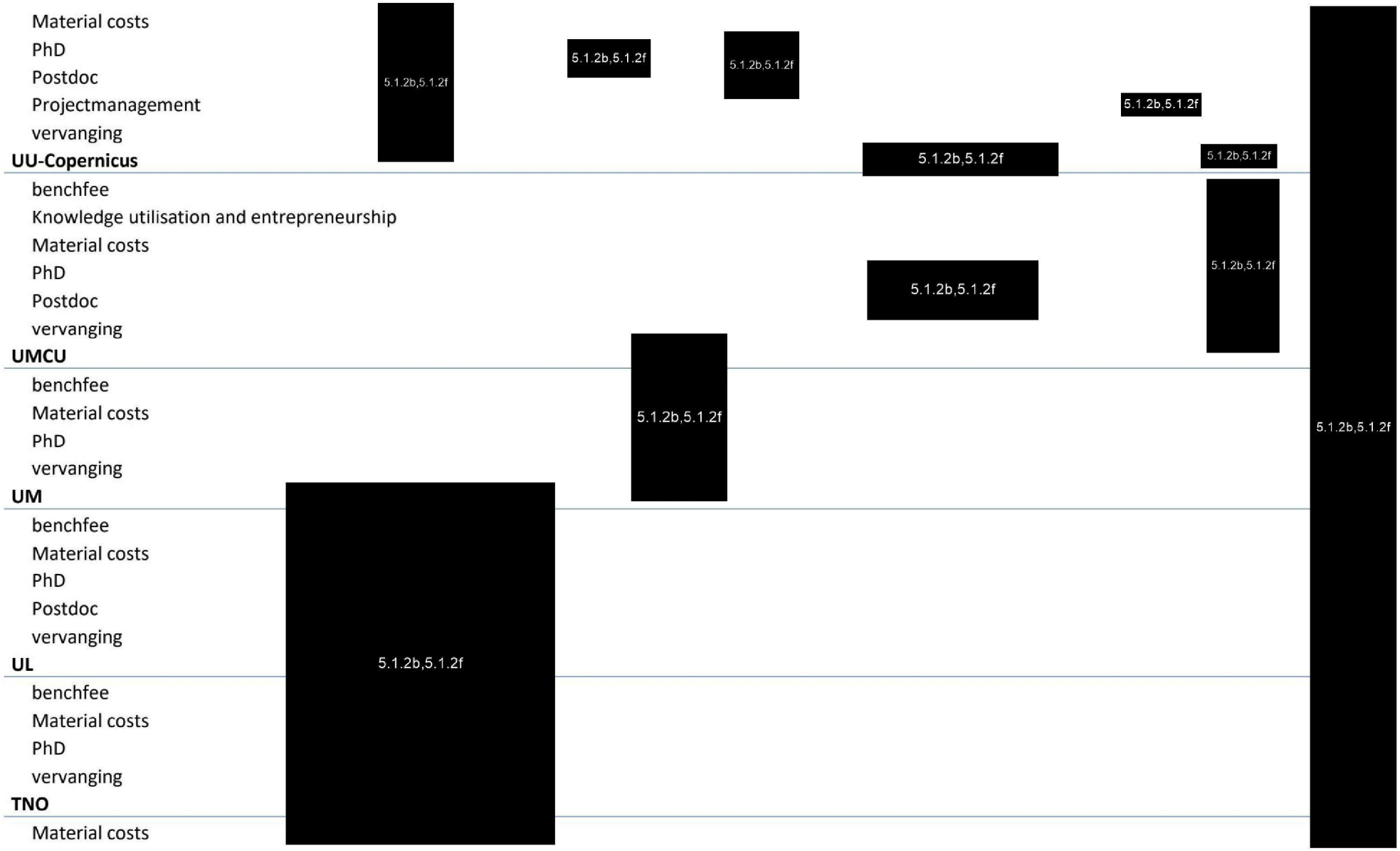
Corresp.nr. 2020/NWA/00992784

Name financial contact institution:	5.1.2e
Email address:	5.1.2e @uu.nl
Telephone number:	+31-30- 5.1.2e

For approval	Name:	Signature:
5.1.2e	5.1.2e	5.1.2e
Administrator institution:	5.1.2e	

Table : Budget in euro's per applicant per post and per workpackage

Row Labels	WP 1.1	WP 1.2	WP 1.3	WP 2.1	WP 2.2	WP 2.3	WP 2.4	WP 3.1	WP 3.2	WP 3.3	WP 4	WP3	Grand Total
WUR													
benchfee		5.1.2b,5.1.2f											
Material costs													
PhD													
vervanging													
VUMC													
benchfee													
Material costs													
PhD													
vervanging													
VUA													
benchfee													
Material costs			5.1.2b,5.1.2f	5.1.2b,5.1.2f									
PhD													
Postdoc													
vervanging													
UU-UIPS													
benchfee													
Knowledge utilisation and entrepreneurship													
Material costs					5.1.2b,5.1.2f								
Postdoc													
vervanging													
UU-IRAS											5.1.2b,5.1.2f		
analist		5.1.2b,5.1.2f											
benchfee													
Internationalisation													
Knowledge utilisation and entrepreneurship													


Material costs
PhD
Postdoc
Projectmanagement
vervanging
UU-Copernicus
benchfee
Knowledge utilisation and entrepreneurship
Material costs
PhD
Postdoc
vervanging
UMCU
benchfee
Material costs
PhD
vervanging
UM
benchfee
Material costs
PhD
Postdoc
vervanging
UL
benchfee
Material costs
PhD
vervanging
TNO
Material costs
5.1.2b,5.1.2f

Postdoc		5.1.2b,5.1.2f
RIVM		
Internationalisation		
Knowledge utilisation and entrepreneurship		
Material costs		
PhD	5.1.2b,5.1.2f	
Projectmanagement		
HU		
analist		
Knowledge utilisation and entrepreneurship		5.1.2b,5.1.2f
Material costs		
Postdoc	5.1.2b,5.1.2f	
Projectmanagement		
Erasmus MC		
benchfee		
Material costs		
Postdoc		
vervanging		
Grand Total		5.1.2b,5.1.2f

TTable : Contribution in euro's per Co-funder per research line

Party	RL1	RL2	RL3	Grand Total
VIG			x	
in kind				
Unilever		x	x	
cash				
in kind				
ST Proefdiervrij			x	
cash				
Shell		x	x	
in kind				
ORTEC	x		x	
in kind				
Nierstichting			x	
cash				
Min LNV		x		
in kind				
KWR			x	
in kind				
Galapagos			x	
cash				
Costmetic Europe			x	
in kind				
Charles River		x	x	
cash				
in kind				
Certara				
in kind	x			
Brandwonden stichting			x	
cash				
in kind				
Bayer		x	x	
in kind				
Grand Total				

5.1.2b,5.1.2f

Annex 4

Accession document

ACCESSION of a new Party to

Virtual Human Project for safety Assessment Consortium Agreement, version […, YYYY-MM-DD]

[OFFICIAL NAME OF THE NEW PARTY]

hereby consents to become a Party to the Consortium Agreement identified above and accepts all the rights and obligations of a Party starting [date].

Prof. dr. A. Pijpers A.

hereby certifies that the consortium has accepted in the meeting held on [date] the accession of [the name of the new Party] to the consortium starting [date].

This Accession document has been done in 2 originals to be duly signed by the undersigned authorised representatives.

[Date and Place]

[INSERT NAME OF THE NEW PARTY]
Signature(s)
Name(s)
Title(s)

[Date and Place]

Signature

Prof. dr. A. Pijpers. Pijpers

Annex 5

Invention Disclosure Form

Title of the invention:

Date:
Submitted by (name and affiliation):

Part A. Description of the Invention

Background of the invention (state of the art); why is the invention required, what problem is solved? Has it been tried to solve this problem before or by different means?

- Describe the background of the invention (3-4 paragraphs):
- Describe the problem(s) solved by the invention:
- Describe the differences from the state of the art:
- Has any patent search been carried out? If so, provide results.

Give a short description of the invention and the inventive steps (i.e. non-obvious steps which are crucial in obtaining the benefits of the invention).

- Description of the invention (3-4 paragraphs):
- Indicate the inventive steps:
- Describe the benefits of the invention:

Description of the research that resulted in the invention. Is it a result of a main project of the group? Is further research going to be conducted in the next twelve months? Will this research further contribute to the invention?

- Description of how invention has originated:
- In case of result from research project/theme give here the description of project/theme:
- Does the research continue in next 12 months?:
- Does the further research contribute to invention? How?:

Describe the development stage (how much further development is required for commercialization). Is funding needed?

- Describe the development stage (concept, proof of concept, prototype, etc.):
- Is further research or development required?
- Is funding needed?

When was the invention made? When was the first written record of the invention made? When was the first experimental demonstration of the invention (proof of concept) or how much time is needed to deliver proof of concept?

- Invention made (date):
- First written record of invention (date):
- Time needed for proof of concept (months):

Part B: Inventor details

Name only those who contributed intellectually in the inventive step of the invention. Please note that inventorship is not the same as authorship and has important legal implication in the

procedure for acquiring patent protection. An inventor is somebody who contributes intellectually to the invention. It does not concern those who only perform the work or those who made the work possible.

Inventor 1:
Full Name:
Affiliation within [organisation X]:
Function Title:
Details of third party payment covering employment:

Inventor 2:
Full Name:
Affiliation within [organization X]:
Function Title:
Details of third party payment covering employment:

Inventor 3:
Full Name:
Affiliation within [organisation X]:
Function Title:
Details of third party payment covering employment:

Inventor 4:
Full Name:
Affiliation within [organisation X]:
Function Title:
Details of third party payment covering employment:

If more inventors are involved, please add all names.
In case of more than 4 inventors, please add all names and details and also in the right order of first inventor, second, etc

Part C: Intellectual Property information

Give full details of funding sources of the research that led to the invention, including funding from within [organisation X]. Research contract details, terms of the contract covering Intellectual Property (provide copies if applicable). This information is needed to establish third party rights.

- Give details of funding sources of the research, including funding from within WUR:
- Give research contract details:
- Give terms of the contract concerning IP (provide copy):

Give full details of the materials used in the research (including for instance special software programs) and any Material Transfer Agreements (MTA) that are applicable.

- Details used materials:
- Details used software programs:
- Details of MTA (provide copies where applicable):

Part D: Disclosure

Please list any previous or anticipated disclosures of information that could be relevant for the invention. This includes publications, abstracts, posters, lectures in public meetings as well as disclosures to colleagues from other organizations. These may affect the patentability and the time of filing. Please, provide information of all relevant publications in the field of invention, including background publications, conference abstracts, relevant patents or patent applications, etc.

- Previous or planned disclosures of information:
- Relevant publications:
- Disclosures to others:
- Patents:
- Key words for searching databases and markets

Part E: Commercial information

Provide any details that may help to assess the commercial potential of the invention. In particular list any companies that you know use or exploit the type of technology and detail any interest they may have (shown) in your research.

- Describe commercial perspectives for the invention:
- For what market segment is the invention relevant (e.g. agro-chemical; food; medical; pharma; plant breeding; veterinary; etc.)
- Give names of companies that could be interested:
- Give names of any research group working in the same area:

List any thoughts you have as to how the invention could be exploited. I.e. will it lead to new research projects that could be funded externally, can the technology/product be sold in the next years, is the invention suitable for a spin-off company?

- Perspectives for commercialization:
- Interest in new research to be funded externally:
- Interest in selling the invention :
- Interest in using the invention for spin-off

Annex 6

Members of the International Scientific Advisory Group and Cooperation Partners

International Scientific Advisory Group:

[redacted]

Cooperation Partners:

[redacted]