Controlled Human Infection Studies in the Netherlands ROADMAP
Controlled Human Infection Studies in the Netherlands

ROADMAP

2023
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Version 2.0 – 2023-05-23
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Summary

Controlled human infection models, also known as human challenge models, are carefully managed medical research studies in which volunteers are deliberately exposed to a pathogen in a careful and controlled manner, with the purpose of assessing clinical, microbiological and immunological endpoints. Human challenge models have the potential to speed up the development of products to prevent or treat infectious diseases by evaluating proof of efficacy at an early stage. Controlled human infection studies are increasingly used to evaluate medicinal products to treat and prevent disease (e.g. the RSV vaccine), and to generate knowledge about host-pathogen interactions.

A COVID-19 human challenge model was successfully established in the United Kingdom in 2021. Despite extensive experience with human challenge studies in the Netherlands and efforts to establish such a model in the Netherlands during the COVID-19 pandemic, to date this has not been successful. The ability to rapidly and successfully establish a ‘pandemic controlled human infection model’ heavily depends on a country’s research ecosystem, with prior experience in conducting human challenge studies, effective communication between critical stakeholders and available capacity critical factors for success. In the context of pandemic preparedness, we first review current practice in the Netherlands with regards to controlled human infection studies and provide a general framework for the regulatory, ethical and scientific aspects of such studies in the Netherlands. Finally, for contingency and response planning, we outline five priority approaches and associated key activities that will help to ensure meaningful impact of a pandemic controlled human infection model in accelerating licensure of new medicinal products and/or address key public health questions in the shortest possible timeframe possible. This roadmap should be seen in the context of a wider (inter)national effort to accelerate vaccine and drug development, including investments in platform technologies such as mRNA vaccines, increased production capacity and discussions to optimize regulatory evaluation processes.
1. Introduction and scope
A roadmap is being presented with regards to the development and use of controlled human infection studies (CHIS) in the Netherlands, with specific attention to pandemic CHIS. This roadmap has been commissioned by the Netherlands Organisation for Health Research and Development (ZonMw).

1.1. Definition of controlled human infection studies
Controlled human infection studies are studies that involve the deliberate exposure of research participants to infectious agents for the primary purposes of:
   a. developing models of infection or disease - that is, rigorous and reproducible methods of infecting participants with specific microorganisms and/or
   b. generating knowledge about host-pathogen interactions (including pathogenesis and correlates of infection, transmission and immunity) and/or
   c. testing (novel) vaccines and therapeutics

and the exposure takes place in a controlled manner in which:
   a. the microorganism strain(s), and the timing, route, and/or dose of the infectious agent are known, and
   b. the risks and burdens associated with a resulting infection are (relatively) minor, monitored, managed and minimized

1.2. Background of the roadmap
Discussions about the possibility to establish a controlled human infection model for COVID-19 began very soon after the start of the COVID-19 pandemic early 2020. Although development of multiple candidate COVID-19 vaccines had started immediately after the SARS-CoV-2 viral genome was made public, there was significant uncertainty at that time whether these candidate vaccines would be effective. Additionally, many countries had enforced lockdowns to reduce viral transmission and there was concern that these lockdowns would reduce COVID-19 disease incidence to such a low level that phase III efficacy vaccine studies would become very difficult to plan and execute. Although in hindsight placebo-controlled phase III studies were indeed possible and successfully demonstrated the safety and efficacy of COVID-19 vaccines, at that time of the pandemic it was considered that a controlled human infection model for COVID-19 could potentially be used to assess vaccine efficacy in case large scale field studies were not feasible, or identify vaccine targets in case the first COVID-19 vaccine candidates were not effective. Henceforth, preparations for a SARS-CoV-2 controlled human infection model began in the UK, the USA and in the Netherlands by early 2020. This led to intensive discussion amongst the scientific community, given that the SARS-CoV-2 virus that causes COVID-19 was a newly emerged virus and not much was known about the potential risks of infection to participants.

Key factors that influenced this risk were the lack of:
1. pre-existing immunity in the population
2. knowledge about the clinical course of COVID-19 and the main risk factors for (severe) disease
3. knowledge about best practices for clinical management, including knowledge about, and access to effective medication
4. knowledge about long-term sequelae

In April 2020, the WHO installed a multidisciplinary advisory committee of international experts to provide a framework for a SARS-CoV-2 CHIS, addressing its intended use, scientific and social value and ethical framework. Following initial discussions with Leiden University Medical Center (LUMC), ZonMw commissioned the development of a clinical protocol for a SARS-CoV-2 human challenge study by LUMC in September 2020. This protocol was finalized by the end of October 2020, after which it was discussed with several parties. Due to the absence of a clear funding path, questions about the necessity and value of the model, and the need to define the main research question(s) and associated research activities, LUMC was requested to prepare and submit a ZonMw research proposal to obtain funding. Because of the high complexity of this study, a special committee was installed by ZonMw to evaluate the proposal, with a specific focus on its necessity and value. The results of this evaluation are described in the report ‘Advies over nut en noodzaak Controlled Human Infection Model voor COVID-19 in Nederland’, which was published in September 2021. Although the value of the model and the high quality of the proposal were generally acknowledged, concerns remained about long-term sequelae (i.e. ‘long COVID’ or ‘post-COVID’) and there was disagreement among committee members on the necessity of the model given that COVID-19 vaccines had become increasingly available in the Netherlands from January 2021 onwards. Based on the committee’s evaluation report, the proposal was not funded and the protocol was not submitted to an ethical committee for formal evaluation. At present, no SARS-CoV-2 CHIS has been established in the Netherlands.

Whereas parallel efforts in the USA to establish a SARS-CoV-2 CHIS were abandoned, the UK followed a different trajectory. A consortium of academic and industry partners, together with the British government, was established early in 2020 and was funded through the Human Challenge Programme of the UK Vaccines Taskforce. This consortium proceeded to address the technical, funding and ethical considerations for a COVID-19 human challenge model. The observation that the clinical course of COVID-19 was generally mild or asymptomatic, and that COVID-19 was mostly a self-limited disease in young adults without co-morbidities supported the decision to proceed with establishing the model. A unique, first-in-human SARS-CoV-2 challenge study, led by Imperial College London, was performed between 6 March and 8 July 2021. The primary aim of the study was to identify the safe minimum inoculation dose at which >50% of volunteers were infected. In total, 36 volunteers aged 18-29 years, with no prior immunity were inoculated with wild-type SARS-CoV-2 (Wuhan-Hu-1), the results of which have been published. At the time of writing,
multiple follow-up COVID-19 human challenge studies are ongoing in the UK, including with other SARS-CoV-2 variants.

1.3. Scope of the roadmap
This roadmap was initially commissioned to provide guidance on the establishment and role of a CHIS during a pandemic in the Netherlands. During the development of this roadmap it became clear that the main criterion for establishing a CHIS during a pandemic is the pre-existence of expertise, infrastructure and capacity for controlled human infection studies in general. We therefore first review current practice in the Netherlands with regards to controlled human infection studies and provide a general framework for the regulatory, ethical and scientific aspects of CHIS in the Netherlands. Finally, we identify a number of priority activities that are necessary for performing controlled human infection studies for pandemic threats.

1.4. Resources
For this roadmap, we interviewed several national and international experts and stakeholders, including:

- Prof. Andrew Pollard, Director of the Oxford Vaccine Group in the Department of Paediatrics at the University of Oxford, consultant paediatrician at Oxford Children’s Hospital and Fellow of St Cross College, UK
- Prof. Daniela Ferreira, Professor of Respiratory Infection and Vaccinology at the Oxford Vaccine Group in the Department of Paediatrics at the University of Oxford and the Director of the Liverpool Vaccine Group at the Liverpool School of Tropical Medicine, UK
- Prof. Benjamin Mordmüller, Professor Medical Microbiology, Radboud University, the Netherlands
- Prof. Robert Read, Director, NIHR Southampton Biomedical Research Centre (2017-2022), NIHR BRC Theme Lead for Microbiology, Immunology and Infection, Professor of Infectious Diseases and Honorary Consultant Physician, UK
- Prof. Helen McShane, Professor of vaccinology, Director, Oxford NIHR Biomedical Research Centre, Deputy Head (Translation and Personnel), Medical Sciences Division, Honorary Consultant Physician, UK
- Prof. Meta Roestenberg, Professor in vaccinology, Clinical head of the Controlled Human Infection Center Leiden University, the Netherlands
- Prof. Andrew Gorringe, Scientific Leader at Public Health England, Porton Down and a Visiting Professor at University of Bath, UK
- Prof. Robert Sauerwein, Emeritus Professor Medical Parasitology, Radboud University, the Netherlands
- Prof. Joop van Gerven, Chair of the Central Committee for Human Research (CCMO), Professor Clinical Neuropsychopharmacology, Leiden University, the Netherlands
• Prof. Marion Koopmans, Head of the Erasmus MC department of viroscience, Professor of Virological research for Public Health, Erasmus Medical Center, the Netherlands
• Dr. Corine Geurts van Kessel, Assistant Professor Clinical Virology, Erasmus Medical Center, the Netherlands
• Dr. Jeannine Hautvast, Senior researcher in Infectious Disease Control, Department of Primary and Community Care (GGD), Radboud University, the Netherlands
• Dr. Hester de Melker, Head of the Department of National Immunisation Programme and Surveillance Public Health, National Institute for Public Health (RIVM)
• Dr. Pieter Fraaij, Consultant paediatric infectious disease and immunology.
• Dr. Marcel van Bergen, Chairman BVF-platform (Dutch Biosafety Platform), Member of Scientific Working Group European Biosafety Association, BioRisk Professional Radboud UMC, the Netherlands

Although this roadmap has been developed based on discussions with consulted experts, it should be noted that this document may not necessarily reflect the individual opinion of the experts.

Besides the cited public sources, the following key international resources were also used as they address specific aspects of controlled human infection studies:

• WHO guidance on the ethical conduct of controlled human infection studies 5
• WHO, Key criteria for the ethical acceptability of COVID-19 human challenge studies 6
• Welcome Trust, Considerations on the principles of development and manufacturing qualities of challenge agents for use in human infection models 7
2. Controlled human infection studies in the Netherlands

2.1. Historical context of CHIS and current practice

Human infection studies have a long and controversial history, dating back to the 18th century. Whereas the first human infection studies were poorly controlled and did not meet modern scientific and ethical standards, human infection models have become much more rigorous, controlled and accepted, particularly in the last 50 years. Nonetheless, deliberate exposure of volunteers to pathogens remains a delicate ethical balance between the potential risks to participants and the scientific and social value of the study. Controlled human infection studies are used to: 1. develop models of infection or disease; 2. generate knowledge about host-pathogen interactions, including correlates of infection, transmission and immunity and 3. evaluate medicinal products to treat and/or prevent disease. So far, worldwide over 20 thousand individuals have been challenged in controlled human infection studies using various pathogens and serious adverse events were rare.

Decades of experience in the Netherlands with controlled human infection studies have led to well-established and widely accepted challenge models. Although the vast majority of CHIS in the Netherlands has focused on malaria (Radboudumc and LUMC), there is a growing interest for conducting human challenge studies at other Dutch university medical centres, as well as internationally. Several CHIS have been established in the Netherlands in recent years, spanning a wide range of bacterial, viral and parasitic infections, including vector-borne diseases (see Table 1).

Table 1: Controlled human infection studies in the Netherlands, based on clinical trial registries*

<table>
<thead>
<tr>
<th>Year</th>
<th>Site(s)</th>
<th>Number of volunteers</th>
<th>Study Identifier</th>
<th>Challenge agent</th>
<th>Status</th>
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<td>5</td>
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* This list may not be complete

2.2. Role of CHIS in clinical development

Infectious diseases are a major health and economic burden to society, with a disproportionately large impact in infants, older individuals and individuals with pre-existing health conditions. Fast and broad access to safe and effective vaccines, drugs
and biologicals is necessary to limit the impact of infectious disease outbreaks. At present, there is a well-known translational gap from basic scientific findings to clinical research and application in humans. **Human challenge studies have the potential to significantly accelerate clinical development of new products by providing proof-of-concept or proof-of-efficacy at an early clinical stage** 10. As an example, the demonstration of protective efficacy of the Pfizer RSV pre-fusion vaccine candidate (RSVpreF) in a phase 2a controlled human infection study 11 supported the subsequent evaluation of the RSVpreF vaccine in 51,353 adults ≥60 years of age in a phase 3 efficacy study (RENOIR) 29, as well as in 7,358 pregnant women (MATISSE) 30, the data of which is currently under review by the FDA and EMA for licensure. CHIS have also been used for vaccine registration or World Health Organisation (WHO) prequalification for Malaria, Cholera and Typhoid conjugate vaccines, as well as for licensure of antiviral drugs against influenza virus infection 12,13.

### 2.2.1. Uses and limitations of CHIS

**Human challenge studies represent a fit-for-purpose model that should always be considered alongside other means by which key questions on infectious diseases can be addressed.** CHIS are particularly relevant in settings that are either difficult to replicate in animal studies, or that would otherwise require large, costly field studies.

Field trials are often large and heterogeneous with regards to prior exposure of the study population to the pathogen of interest, as well as variability in the challenge dose and exposure rate. Conversely, CHIS are performed in a selected, more homogeneous population in which 100% of participants are exposed to infectious challenge. It is important to emphasize that CHIS can only be performed in treatable or self-limiting diseases where no irreversible pathology is likely to occur. CHIS are therefore not an appropriate model to investigate (mechanisms of) severe disease, and alternative research methods should be considered to answer questions on pathophysiology of severe disease, for instance epidemiological studies in infected patients and/or animal studies. In addition, induced infection may differ from natural infection as a consequence of e.g. differences in the trial population compared to the actual population of interest, differences in challenge strains compared to circulating strains and variation in pathogen exposure.

A crucial feature of CHIS is the ability to obtain pre-challenge information and biological samples, which makes human challenge studies highly suitable to investigate aspects related to pathogen replication, shedding and transmissibility.
3. Ethical considerations

3.1. Risks and social/scientific value

Participants in CHIS are volunteers who do not obtain direct health benefit from participation. They may, in fact, contract a disease as a result of participation, which contravenes the Hippocratic Oath and the declaration of Helsinki: 'It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject' \(^{14}\). However, if the risk of harm is \textit{minimal} and \textit{in line with what is accepted in other types of medical research}, human controlled infection studies can be ethically justified.

As in other medical research, a formal and careful risk assessment should be carried out to define the risk and level of harm. This assessment will be reviewed by the ethical committee to see if the overall risk is acceptable. Although some risk of harm might be acceptable, the foreseeable risks to the participants should be kept as low as possible. \textit{The key question is what risk of harm is acceptable?} The Royal College of Physicians guidelines \(^{15}\) provide guidance on this, stating that for those circumstances where society rather than the participant may benefit from the research, however large the benefit, to expose a participant to anything more than low risk of harm needs very careful consideration and would rarely be ethical. The quality and scientific and social value of the research should be high in order to outweigh the risk to the healthy volunteer \(^{16}\).

A guidance document on ethical questions associated with CHIS has been published by the WHO in 2022 \(^5\). This general guidance aims to inform well-considered and contextualized decisions about the ethical acceptability of proposed CHIS, including priorities for engagement and social science research to support deliberation and practice. \textit{The WHO guidance takes the position that there are no morally compelling grounds for distinguishing between the types of risks and burdens in clinical first-in-human studies of novel pharmacological agents and the ones in CHIS designs.} CHIS are therefore not, in themselves, a morally distinct form of research but instead fall within the continuum of health-related research conducted with human participants governed by relevant national and international ethics guidance and regulations.

This WHO document can be used as guidance by the medical ethical committees, regulators, funders and policymakers and researchers involved in human controlled infection studies and it addresses justification, risks, reimbursement, fair collaborations, sharing of data and governance of CHIS, among other topics.

The interests of the participant should be considered at all stages of the research process. Volunteers must be informed of all conceivable risks and have adequate time to decide on their individual participation in relation to the risks involved and financial compensation for the time and inconvenience of taking part. Financial compensation in the Netherlands is based on the ‘wage model’, which compensates participants on the basis of the time and burden associated with research participation, but not risk \(^{17}\).
In summary, although unfamiliar to some people, CHIS are not an exceptional and morally distinct form of research. They follow existing national regulations and laws. In the Netherlands, CHIS are subject to the Medical Research Involving Human Subjects Act (WMO). In addition, there are a number of other national and European laws and regulations that apply, which will be reviewed in this document.

3.2. Ethical evaluation process in the Netherlands
The local medical research ethical committees (Medisch Ethische Toetsings Commissies, or METCs), as well as the central Dutch committee for human research (Centrale Commissie Mensgebonden Onderzoek, or CCMO) are independent administrative bodies that are part of the Dutch government. As of 31 January 2023, clinical studies in the Netherlands that involve an investigational medicinal product (IMP), including e.g. intervention studies with a vaccine followed by controlled human infection, must be submitted to the EU Clinical Trial Portal and Database, according to EU Clinical Trial Regulation (CTR) No. 536/2014. In case of Dutch mono-center CHIS involving licensed IMPs, such studies will normally be referred to the local METC for evaluation. In practice, this means METCs working with research institutes at which CHIS are conducted more often will have more experience with evaluating such studies.

There are a number of specified cases, listed in Article 14 of the WMO (https://wetten.overheid.nl/BWBR0010314/2021-05-26), in which CHIS will be evaluated by the CCMO instead of the METC. These include e.g. studies in pregnant women, studies with unregistered prophylactic vaccines, studies involving a product that contains living (micro-)organisms or viruses that are directly aimed at combating disease-causing factors, and studies that develop genetically modified microorganisms (GMOs) as a product. In the Netherlands, GMOs are regulated by the Besluit genetisch gemodificeerde organismen milieubeheer 2013 and Regeling genetisch gemodificeerde organismen milieubeheer 2013, as part of the Environmental Management Act. Although CHIS involving GMOs or GMO-vaccines are not considered ‘gene therapy’ studies per se, these studies are still subject to a permit. The procedure for obtaining such permits and approval are outlined by the ‘Loket Gentherapie’ (https://www.loketgentherapie.nl/).

3.3. Risk assessment
Risks and burden of CHIS include not only risks to participants, but also risk to third parties, including staff, society and environment, due to potential unintended transmission or contamination by microorganisms.

3.3.1. Risks to participants
Risk to the participant is addressed in the study protocol and appropriate clinical data will need to be considered, as in any clinical study involving research on human subjects. The risk to the participant in human challenge studies is pathogen-specific and related to dose, time of exposure, the possibility to monitor infection and
symptoms, risk of sequelae after infection and the availability of rescue therapy. CHIS should be designed in such a way that this risk for the participant is minimised and ethically acceptable. Nonetheless, risks in a CHIS will often remain. The decision whether the provided clinical data is appropriate lies with the designated medical ethical committee.

3.3.2. Risk mitigation participants
The way risks can be minimised depends on the study design and aim of the study.

Participant selection: The risk of (severe) disease is often dependent on participant characteristics such as age, sex or comorbidities. Selecting participants with low risk factors based on an assessment of these characteristics improves the safety of the CHIS. In the case of SARS-CoV-2, the risk of becoming infected vs the risk of developing severe symptoms differed significantly between population groups and changed significantly over the course of the pandemic, due to vaccination and prior exposure. An example of a risk assessment tool is the one developed for the SARS-CoV2 human challenge study. For this purpose, several items were scored and based on the available knowledge of risk for each of these items a score was given to express the individual risk for a volunteer.

Challenge agent selection: Some strains of a pathogen might be less pathogenic than others. If the design and generalisability of the study allows, strain with lower pathogenic potential might be chosen to inoculate participants. An example of how this can be done is the selection of a Streptococcus pneumoniae serotype 3 strain.

Early diagnosis and/or treatment: The availability of effective rescue medication, for example in bacterial or protozoan CHIS, makes it possible to stop the study in case of safety concerns for the participant. Intensive monitoring of the participant and possible use of pre-symptomatic endpoints will further minimize risks.

3.3.3. Risks to third parties
Participants in CHIS who have been exposed to challenge agents may be infectious to third parties. Transmission risk to third parties is related to exposure, which is dependent on pathogen load of the challenged participant, symptoms (not always), and the nature, frequency and duration of exposure. Transmission risk is also related to susceptibility of contacts, which is dependent on immune status, age, comorbidities, etc. The European clinical trial protocol template includes a ‘structured risk assessment’ paragraph. However, the risks of spread to third parties, as well as the steps taken to mitigate such risks are currently not routinely assessed using clear criteria. Of note, knowledge and disease-specific expertise on these topics may be limited or absent among ethical committee members and the committee might request input from external, independent experts.

3.3.4. Risk mitigation third parties
Containment measures. Quarantining participants for a certain period in an inpatient facility, a designated accommodation or at home may be necessary to reduce the risk
of transmission to third parties. At the same time, this also poses a higher burden on participants and significantly increases the costs of CHIS, particularly for inpatient facilities, potentially reducing the practical feasibility of such studies. It is therefore crucial to carefully weigh the likelihood of the pathogen causing disease and/or outbreaks against the appropriate containment level.

The risk to staff and other third parties depends on the characteristics of the microorganism. In the Netherlands, the classification of biological agents is embedded in the occupational health and safety act (ARBO-wet), which provides legislation to protect workers that may be exposed to biological agents. Within the European Union, a related EC directive (2000/54/EC) has been published that classifies biological agents into four risk groups according to the following criteria: i. Agent is pathogenic to humans; ii. Agent is a hazard to employees; iii. Agent is transmissible to the community; and iv. There is effective treatment of prophylaxis available (https://osha.europa.eu/en/legislation/directives/exposure-to-biological-agents/77).

This approach distinguishes four Risk Groups with corresponding biological containment levels and measures, i.e. BioSafety Levels (BSL)-1 to 4. Current CHIS primarily make use of biological agents categorized at BSL levels 1-2. At present, SARS-CoV-2 is still classified as a Risk Group 3 human pathogen. However, it should be noted that previous human challenge studies with different challenge agents, but that belong to the same Risk Group as defined by EU Directive 2000/54/EC, have applied different containment strategies, ranging from inpatient housing of participants in clinical facilities to outpatient studies where volunteers were sent home after challenge. Outpatient studies have been - and are being - performed for multiple challenge agents, including rhinovirus, Streptococcus pneumoniae, Bordetella pertussis, Bacille Camlette-Guérin, RSV-A2, malaria, and others.20 19 21.

In the Netherlands, the National Institute for Public Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM) is tasked with the coordination of infection prevention measures at the national level. At the regional level the GGD is responsible for infectious disease control, organized into 25 regional districts. The activities of the RIVM and GGD are covered by the Public Health Act, which determines how certain professional groups must act after discovering or suspecting infectious diseases. Doctors, laboratories, or institutions in the Netherlands are legally required to notify their regional GGD if certain infectious diseases are discovered, with four different groups of notifiable diseases: A, B1, B2 and C. As many of the challenge agents used in human challenge studies are notifiable diseases, GGDs are an important stakeholder. GGDs are also mandated to impose possible legal measures aimed at containing the spread of infections in the population, in case this is deemed necessary for public health. This includes potential mandatory quarantining and/or isolation of infectious participants. Collaboration and/or alignment with public health authorities such as the Municipal Health Service (Gemeentelijke Gezondheidsdienst, GGD) is recommended or may even be necessary.
3.4. Absolute vs relative risks
Risks to participant, as well as the risk to third parties, need to be evaluated in both absolute terms as well as in terms of relative risks. Risks are not static and may change, depending on the region, age, vaccination status, time of year, available treatment options, as well as on the amount of transmission of a pathogen in the population. For example, the risk of getting infected naturally with a pathogen might be different between summer and winter, might be more common in children than in adults, and there might be specific groups that are at higher risk of severe or prolonged disease when getting infected. To make a proper assessment of the additional risk of the study, the individual risk of participants in the study should be compared to the risk of becoming infected via natural exposure when not participating in the study. In practice however, such a risk assessment may be difficult to perform as conditions can change quickly and the intensive pathogen surveillance as was performed during the COVID-19 pandemic is not common practice, meaning that data on infection risk will often be outdated and/or incomplete. Absolute and/or relative risks need to be clearly communicated to potential study participants.

3.5. Insurance of participants in human challenge studies
Individuals participating in research covered by the WMO must be insured against any potential damages incurred as a result of participating in the research. The insurance must comply with specific regulations stated in the Compulsory Insurance Decree in Medical Research Involving Human Subjects 22. However, it is important to note that insurance may not cover all aspects in human challenge studies. For instance, participant insurance only covers damages of risks of which participants were not informed about in writing in the participant information folder. Additionally, insurance may not cover damages that were likely to occur. In the case of CHIS, this presents a potential issue as it is crucial to inform participants about risks in the participant information folder. Because participants may therefore not be covered anymore by the insurance certificate for WMO research for the risks of infection in CHIS and/or long-term sequelae, liability needs to be covered by the study sponsor/funder. In addition, there is a reasonable chance that out-of-protocol testing and/or clinical care are needed in case of possible infection. To avoid study-associated costs from being covered by the participant’s own health insurance, in-house hospital financial procedures may need to be amended.

4. Challenge agent
4.1. Auxiliary medicinal products (AMP)
AMPs are defined as medicinal products that are used for the needs of a clinical trial as described in the clinical protocol, but do not classify as an investigational medicinal product. In the EU, challenge agents are considered an auxiliary medicinal product (AMP) that is used to assess end-points in the clinical trial. Thus, in the Netherlands, as well as in other EU member states, an Auxiliary Medicinal Product dossier is required for controlled human infection studies. A challenge agent needs to be selected and manufactured in such a way that it can be used safely in studies that
generate clinically relevant results. To support the production and evaluation of challenge agents, a guidance document has recently been developed by a consortium of international experts with experience in the production of challenge agents, performance of challenge studies, and/or good manufacturing practice (GMP) 7. This guidance document provides a comprehensive list of considerations.

4.2. Selection, manufacturing and release of challenge agents

Challenge agents need to be carefully selected for the purpose of the CHIS. It will be essential to document in detail why selected strains/isolates are considered genetically and phenotypically representative of pathogen strains that circulate in the target population. If CHIS are used for licensure purposes, the challenge agent should be representative for strains/isolates circulating at the time of registration of new products.

The challenge agent should be manufactured using a reliable process, according to good laboratory practice (GLP), and following local and international laboratory guidelines and standards (i.e. good manufacturing practice or GMP; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use or ICH; or International Organization for Standardization or ISO). Quality will need to be continuously documented during the manufacturing process. Defined quality attributes should be taken into account and documented before quality control release. Manufacturing should take place in a designated laboratory, preventing contamination and allowing consistency of the final formulation by following a pre-defined manufacturing process and control testing. Stability during storage of the agent should be tested before release. A challenge agent might be manufactured by a third party, which should be qualified to do so. If this is the case, a product development report should be transferred to the clinical site before use of the agent. It is recommended – and often required - to test the challenge agent for identity, purity, viability and stability, before the start of the study. Depending on the aim of the study, production facilities may need to adhere to GMP standards. If the study is likely to be part of a regulatory pathway for a drug or vaccine, a GMP produced challenge agent is preferred or may even be required. In other cases, GMP-like standards are generally accepted.

In the case of viral agents, producing a challenge agent that is suitable for use in humans presents a unique set of challenges. Virus seed stocks may be obtained directly from clinical isolates or from e.g. reverse genetics 23. Given that multiple rounds of viral replication are necessary to produce sufficient material, there is a risk that genetic mutations may arise that affect the properties of the challenge agent. Most viruses used in human challenge studies are produced using cell lines of mammalian origin. This provides a risk of potential contamination of the challenge agent with adventitious agents that could reasonably be expected to contaminate it and potentially cause a safety risk to study subjects 23. Deep sequencing has recently been explored for quality assessment and may provide a fast and accurate method to assess identity and purity of the challenge agent.
5. Capacity for controlled human infection studies

5.1. Clinical infrastructure
Participant safety is a key factor in all CHIS and care should therefore be taken to have a contingency plan available. Depending on the characteristics of the study, this may include access to the emergency room or intensive care. A clinical infectious disease team should be able to take over the care for the volunteers if post-protocol treatment is needed. All relevant clinical departments should be made aware of the study and the possibility that their involvement is needed.

Depending on the potential need for containment of the challenge agent and/or medical risk to the study participant, a CHIS may need to be performed in an inpatient setting. This requires access to a clinical infrastructure with individual rooms and appropriate containment measures (BSL-2 or BSL-3), such as ventilation and appropriate cleaning and waste management measures. In addition, such an effort requires availability of clinical staff that is sufficiently trained in infection prevention and clinical management of participants with (high) infection risk. Care should be taken that infectious participants can be safely and comfortably housed without contact with other, potentially vulnerable patients.

5.2. Laboratory infrastructure
BSL-2 or BSL-3 level laboratory facilities may be needed for processing of potentially infectious clinical samples and assessment of microbiological endpoints (e.g. pathogen detection by culture or PCR). Clinical laboratories involved in CHIS should adhere to high standards and local guidelines. As microbiological and immunological outcomes are the core of CHIS, these laboratories should have expertise with the assays and readouts used in the study. Access to clinical laboratories for participant safety testing is essential. This includes around-the-clock access to clinical biochemistry, immunology and microbiology assays to perform validated diagnostic tests for health monitoring and clinical management.

5.3. Human resources
CHIS are highly complex studies that require experienced and well-trained clinical staff to assure quality of the study and safety to study participants, clinical staff and the public. One of the complexities of CHIS is the large number of stakeholders and the dependency on each other, designed around the potentially infectious volunteer. Communication, flexibility as well as prior experience are therefore major requirements that cannot be underestimated.
6. Roadmap for a pandemic human challenge model

The global threat of infectious disease outbreaks – including pandemics - is increasing as a consequence of a growing world population, intensive livestock farming, urbanization and globalization. The COVID-19 pandemic has had a huge impact on human health, disrupted society and came with huge economic costs. The unprecedented rapid availability of COVID-19 vaccines substantially reduced adverse outcomes of coronavirus infection and was crucial for reducing the impact on society. **A key lesson from the COVID-19 pandemic is that the development and clinical evaluation of new products may be done in a much shorter time frame than was previously thought possible.**

Controlled human infection models have the potential to play a key role in accelerating the clinical development of vaccines, drugs and biologicals, including during a pandemic. As the specific nature of the next pandemic threat is not known, it is uncertain whether knowledge on potential vaccine or drug targets exists, and it should therefore be considered that future first-generation interventions may not be as effective as they were for e.g. COVID-19. In such a case, CHIS may offer a means towards development and efficacy testing of product candidates. From a regulatory point of view, CHIS are not normally considered an acceptable replacement for large field studies, particularly when disease incidence is high as would be expected during a pandemic. Nevertheless, CHIS can support product development in multiple other ways. For instance, early demonstration of proof-of-concept in small-scale studies may allow down-selection of potential candidates for larger field studies. In the case of potential vaccine failure, CHIS may help to identify mechanisms of vaccine failure. A pandemic CHIS can also provide crucial information about pathogenesis, including pathogen replication, shedding and transmission, and assess the efficacy of transmission reducing measures, which may be used to guide public health policies. As mentioned above, CHIS should always be considered alongside other possible means by which similar results can be obtained, for instance through animal or epidemiological studies. At the same time, it must be noted that such studies also cost money, time and effort and may not address all questions.

The ability to rapidly and successfully establish a pandemic CHIS heavily depends on a country's research ecosystem, with prior experience in conducting CHIS, national and international collaboration and available capacity key factors for success. To ensure meaningful impact of a pandemic CHIS in accelerating licensure of new medicinal products and/or address key public health questions in the shortest possible timeframe possible, a number of key activities need to be undertaken, as outlined in this roadmap (see Figure 1). A key recommendation is to establish a working group, including relevant stakeholders, to follow up on these activities.
Vision

Controlled human infection models play an important role in reducing the impact of infectious disease outbreaks.

Strategic goal

To identify the priority approaches and associated key activities that are needed to perform controlled human infection studies in the Netherlands that will help accelerate clinical development and licensure of novel infectious disease products and/or address key public health questions in the context of a pandemic.

To specifically address the use of controlled human infection models in the context of a pandemic the following four priority approaches are identified:

1. Research ecosystem and clinical trial capacity
2. Legal, ethical and regulatory framework
3. Public engagement and open science
4. Funding path

Roadmap pandemic controlled human infection model

Figure 1. Roadmap for the establishment of a pandemic controlled human infection model
Research ecosystem and clinical trial capacity

Research ecosystem

Consolidation of existing expertise on controlled human infection studies in the Netherlands, a prerequisite to set up a pandemic CHIS, will increase the quality of studies and maximize their impact. To establish a robust ecosystem for controlled human infection studies it is essential that collaboration between institutes and investigators, as well as other relevant stakeholders is intensified, with open sharing of information and best practices. National collaboration may be stimulated by e.g. making it conditional for multiple parties to co-apply in order to apply for public funding (ZonMw, NWO). An advantage of a more formal collaboration structure is that it may promote higher quality, improve cost-effectiveness and increase (inter)national competitiveness for funding. Such a collaboration network should also seek to establish relationships with other international actors in this field of research, e.g. hVivo in the UK, and SGS and Vaccinopolis in Belgium.

Key activity:

→ Establish a formal working group (WG) of academic stakeholders to explore the formation of a Dutch national collaboration structure for controlled human infection studies, including a platform for sharing of protocols, results, best practices and procedures, and for training of personnel (core WG)

Clinical trial capacity

During a pandemic, it is crucial that existing clinical trial capacity is used in an optimal manner. Pandemics can have a major impact on health care systems due to the high volume of patients, and staff and hospital beds may be needed for essential clinical care to patients. The study’s operational needs will therefore need to be planned in such a way that the treatment of patients during a pandemic is not negatively affected. A pandemic CHIS will likely be performed in an inpatient setting for safety reasons and to reduce risk of transmission. The Imperial College-led COVID-19 challenge study was performed in individual negative pressure rooms in an in-patient quarantine unit at the Royal Free London NHS Foundation Trust, with 24-hour medical monitoring and access to higher-level clinical support. A physical department will therefore need to be dedicated for the study, for instance in a dedicated isolation unit. In addition, a dedicated team of staff (clinical, laboratory and supportive), will need to be available to run the study. Standard operating procedures will need to be developed specific for CHIS in a pandemic setting. Laboratory facilities will need to be able to prepare the challenge agent and rapidly assess the immunological and microbiological outcomes. They will need to have quality assessment procedures and containment levels appropriate for the challenge agent. As a point of reference, COVID-19 has been classified as a category 3 pathogen, which requires BSL-3 level containment facilities. A clear organizational and governance structure will need to be developed for a
pandemic human challenge study, describing the roles and responsibilities of involved parties such as the sponsor, the principal investigator(s) and the funder, as well as financial liability. Effective project management with proven, senior leadership will be crucial for setting up a pandemic CHIS in the shortest possible timeframe.

When considering financial investment in clinical trial capacity for human challenge studies, including the possible establishment of (a) quarantine unit(s), a business model must be developed based on sustainable financing. Given that financial investment in clinical trial capacity solely for a pandemic CHIS is unlikely to return on investment, a financially more viable option will be to explore a business model in which clinical trial capacity is used for both academic activities as well as for economic, industry-sponsored activities during inter-pandemic periods. The establishment of an academic contract research organization (CRO) may be considered that is embedded in the Dutch academic medical centers. ZonMw and FAST have been searching for possibilities for financial investment in clinical trial capacity24. FAST is the centre for Future Affordable and Sustainable Therapy development, commissioned by the Dutch Ministries of Economic Affairs and Climate (EZK) and Health, Welfare and Sport (VWS) 25 and focused on accelerating clinical translation of new and affordable medicinal products. It should be noted that governmental funding for activities outlined in this roadmap must adhere to strict national and EU rules.

Key activities:

→ Develop a sustainable value proposition and business model for clinical trial capacity for conducting human challenge studies in the Netherlands, including in the context of a pandemic (core WG, together with VWS/EKZ/ZonMw)
→ Increase clinical trial capacity for controlled human challenge studies, including in-patient facilities (VWS, ZonMw, together with core WG)
→ Define a governance and management structure for carrying out a pandemic CHIS (core WG)

Legal and ethical framework

Ethical review of a pandemic CHIS

At an early point of a pandemic, there will be significant uncertainty with regards to the risk factors of developing severe disease and long-term sequelae. As the risk to participants cannot be evaluated until there is a robust knowledge base about risk factors, as well as best practices for clinical management including possible therapeutic options, a pandemic CHIS may not be possible in the first few months of a new pandemic. In the UK, the COVID-19 human challenge study began recruiting healthy, naïve volunteers from March 2021 onwards, mainly due to the time needed to produce the challenge agent and perform quality assurance (QA).
As a consequence, the risk assessment for volunteers was more robust with additional clinical and epidemiological data becoming available about COVID-19.

Although the LUMC COVID-19 CHIS clinical study protocol was never formally evaluated by an ethics committee, the complexity of the study and potential impact of public opinion resulted in the Dutch Central Committee on Research Involving Human Subjects (CCMO) taking the lead as the designated evaluating ethical committee. In the UK, a decision was made to establish a specialist ad-hoc ethics committee to evaluate the COVID-19 human challenge study. This committee reviewed the clinical protocol, with particular attention being paid to the informed consent process and risk assessment of potential volunteers. Prior to the study protocol being approved, several review rounds involving various experts in the field were conducted. A key consideration is whether it will be more effective to establish an ad-hoc committee, or to use existing structures for ethical evaluation that have experience with these kind of studies, possibly involving additional experts on relevant topics such as public health, outbreak management and psychology.

A major challenge for evaluating the risks vs the social and scientific value of a pandemic CHIS is that this balance can rapidly change during the course of a pandemic due to emerging information from real world data, as well as increasing availability of effective pharmaceutical interventions, including vaccines, antiviral drugs, etc. During a pandemic, a process of continuous re-evaluation of public health needs in relation to newly emerging (live) data is therefore needed to amend the study design, the protocol and the added value of the study. Close collaboration is needed between the outbreak management team (OMT), the funder, public health authorities and researchers working on the pandemic CHIS through a scientific and ethical advisory board.

Finally, as outlined in section 3.5, volunteers participating in a pandemic CHIS may not be fully covered by participant insurance for sequelae that occur after challenge, in case such sequelae are a known complication of infection. In the case of pandemic human challenge studies, where volunteers serve a major societal interest, the funder should set up a special fund for the compensation of volunteers in the event of possible sequelae after CHIS, similar to the UK, as these financial risks cannot be carried by the individual UMC that is sponsor to the study.

Priority access to pandemic CHIS

The relationship between public and private parties in the context of a pandemic CHIS needs to be carefully considered. Ideally, the initial development of a pandemic human challenge model is funded by the Dutch government, with no direct involvement of industry. Once such a model has been successfully established, subsequent application and valorisation may be done in partnership. Given that capacity and resources for CHIS will likely be limited during a pandemic, priorities must be considered regarding access to the model, i.e. regarding studies aimed at addressing critical questions with high public health relevance vs studies by commercial parties aimed at clinical development of new products.
in public-private partnership. Priority access rules should be discussed and agreed following discussion with a core group of stakeholders, representing investigators, policy makers, government, industry representatives, etc.

Key activities:

→ Discuss the possibility and requirements (i.e. pre-defined safety criteria) for a fast-track ethical review process for pandemic CHIS (core WG, CCMO)
→ Discuss and ensure access to relevant Dutch national and international epidemiological data during a pandemic for risk assessment (core WG, RIVM, GGD, outbreak management team)
→ Define stakeholders and roles for a scientific and ethical advisory board for a pandemic human challenge model (core WG)
→ Set up a special fund for compensation of participants in the event of sequelae of a pandemic human challenge model (ZonMw, VWS)
→ Define priority access rules to clinical trial capacity during a pandemic (core WG, ZonMw, VWS, RIVM, GGD, industry)

Regulatory aspects – challenge agent

Once human-to-human transmission of potential pandemic threats is confirmed and a pandemic is anticipated, it is crucial to select appropriate clinical isolate(s) as the challenge agent. Clinical isolates can be obtained via microbiology laboratories from hospitalized patients or from national surveillance programs. To use a clinical isolate as a challenge agent, it may be necessary to obtain informed consent from patients from whom the pathogen was isolated. Candidate challenge agents should be representative of circulating pandemic isolates. Seed stocks should be produced as candidate challenge agents, characterized in detail and include clinical, pathophysiological, genomic and epidemiological data. Seed stocks should be tested in fully qualified GMP cell lines in order to prepare and optimize production conditions of the challenge agent. Capacity for the production of the challenge agent should be planned early, and quality assurance and release criteria for the challenge agent should be defined. The UK challenge study used the ancestral SARS-CoV-1 strain (Wuhan-Hu-1) as the challenge agent, even though other variants had already become dominant at that time. This highlights one of the main complexities of performing a pandemic CHIS, i.e. the rapidly changing environment. It may take several months to produce and formally release a new challenge agent batch, and GMP-production is associated with significant costs. Shortening the time until a representative challenge agent becomes available for use will therefore be crucial to ensure meaningful impact of a pandemic CHIS. Capacity for production of a challenge agent according to GMP standards is essential, as production slots in GMP-licensed commercial production facilities commercial may not be available due to prior or other commitments, as was the case in the UK. As viruses are typically considered the major pandemic threat, prior experience in producing viral challenge agents by production facilities will be essential. Alternative, faster analytical tests should be evaluated for assessment of critical quality attributes. For example, for
purity/identity testing, deep sequencing may be an acceptable alternative instead of multiple rounds of passaging of the challenge agent to detect contaminants. Similarly, \textit{in vitro} assays may be more predictive and faster for potency of the challenge agent than animal studies. After production, QA should be finalized and the challenge agent can be formally released for use in a CHIS with associated documentation.

**Key activities:**

→ Establish a dedicated WG to define selection criteria for representative challenge agents and engage with regulatory authorities to establish clear guidelines for production and fast-track release of challenge agents (challenge agent WG)

→ Identify and select potential sites in the Netherlands for GMP production of the CA and secure production slots in the context of a pandemic (ZonMw/VWS, in consultation with challenge agent WG)

→ Define fair access to the CA (core WG)

**Public engagement and open science**

A human challenge study performed during a pandemic raises complex questions about the social and ethical acceptability of risk to individuals. As such, a CHIS during a pandemic cannot/should not be done without public involvement\(^{26,27}\). A structured public consultation strategy should be developed and in place for a next pandemic. The results of public consultation will help to improve the protocol and participant information folder and prioritize research questions and improve public support. Researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results\(^{28}\). Given the public relevance of a pandemic CHIS, open science standards should be required and FAIR access to data and biological specimens should be ensured.

**Key activities:**

→ Establish a communication working group to develop a structured public consultation strategy and communication strategy (communication WG)

→ Promote open science of controlled human infection studies, including FAIR access to data and biological specimens (ZonMw/VWS, together with communication WG)

**Funding path for pandemic CHIS**

in the Netherlands is therefore needed, with a step-up approach that outlines specific stages in the development and execution of a challenge study with associated go/no-go decision rules. For instance, production of seed stocks of candidate challenge agents will likely require minimal funding, but is essential in case the decision is made to continue with the development of a pandemic human challenge model. Taking into account the benefits for the society performing a CHIS should be funded by the government. This includes funding needs to cover early steps, including stockpiling of seed stocks for use as potential challenge agent, until the final step that includes challenge agent manufacturing, and starting the study. Clear decision rules should be made to make the funding available for the next phase, with possible stakeholders involved in making such decisions: the Ministry of Health, Welfare and Sports, ZonMw, the RIVM and the GGD.

Key activities:

→ Define a step-up funding plan for the development of a pandemic human challenge model (VWS/ZonMw, with input from core WG)
→ Arrange funding base for the development of a pandemic human challenge model (VWS, ZonMw)
→ Define concrete activities and timelines for preparations during an early stage of a pandemic (core WG)
References


25. www.fast.nl
Vooruitgang vraagt om onderzoek en ontwikkeling. ZonMw financiert gezondheidsonderzoek én stimuleert het gebruik van de ontwikkelde kennis – om daarmee de zorg en gezondheid te verbeteren.

ZonMw heeft als hoofdopdrachtgevers het ministerie van VWS en NWO.